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# Drug Discovery and Clinical Research



Institute of
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***Dedicated to***

*My Family,*
*Research Associates*
*and*
*Students*

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# Preface

The pharmaceutical industry is one of the largest and most rapidly expanding industries in the world. In recent years there has been a radical shift in the attitude and policies of pharmaceutical industry and the focus has been on new and sustainable drug development strategies. Innovations are not only desirable but mandatory to meet the constantly evolving challenges in this highly competitive field. Numerous novel drugs including vaccines, biosimilars, herbal medicines, new chemical entities, etc. are in the pipeline, which are expected to revolutionize current treatment protocols.

The *Drug Discovery and Clinical Research* bandwagon has been joined by scientists and researchers from all fields including basic sciences, medical sciences, biophysicists, biotechnologists, statisticians, regulatory officials and many more. The joint effort and contribution from all is translating into the fast development of this multi-faceted field. At the same time, it has become challenging for all stakeholders to keep abreast with the explosion in information. The race for the finish-line leaves very little time for the researchers to update themselves and keep tabs on the latest developments in the industry.

To meet these challenges, this book entitled *Drug Discovery and Clinical Research* has been compiled. All chapters have been written by stalwarts of the field who have their finger on the pulse of the industry. The aim of the book is to provide succinctly within one cover, an update on all aspects of this wide area. Although each of the chapter dealt here starting from drug discovery and development, clinical development, bioethics, medical devices, pharmacovigilance, data management, safety monitoring, patient recruitment, etc. are topics for full-fledged book in themselves, an effort has been made via this book to provide a bird's eye view to readers and help them to keep abreast with the latest development despite constraints of time. It is hoped that the book will contribute to the growth of readers, which should translate into drug discovery and clinical research industry's growth.

**SK Gupta**

# Acknowledgments

I first congratulate all the contributors for being a part of this launch venture, and secondly, thank them for their outstanding contributions. Despite their busy schedule and pressing commitments, the authors have put their best effort to give shape to this textbook. The practicalities and nuances that they have gained as experience by way of being in the field for decades have been succinctly described here. My earnest thanks to GJ Samathanam, Advisor, Department of Science and Technology (DPRP) Programme of the Government of India who has been constant source of inspiration and help for providing financial support for this publication, which has been the part of proceedings of the national conference.

I would like to place on record the constant encouragement and support provided by Shiv Raman Dugal, Chairman of the ICRI in completing this task.

I wish to acknowledge the exemplary editorial assistance rendered by Sushma Srivastava for bringing the book in its present form. The publisher M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India has been associated with me for long and has once again given justice to the contents. Lastly, I pay special thanks to my colleagues and students at ICRI and DIPSAR for their valuable help in editorial assistance, without which this task would have been meaningless.

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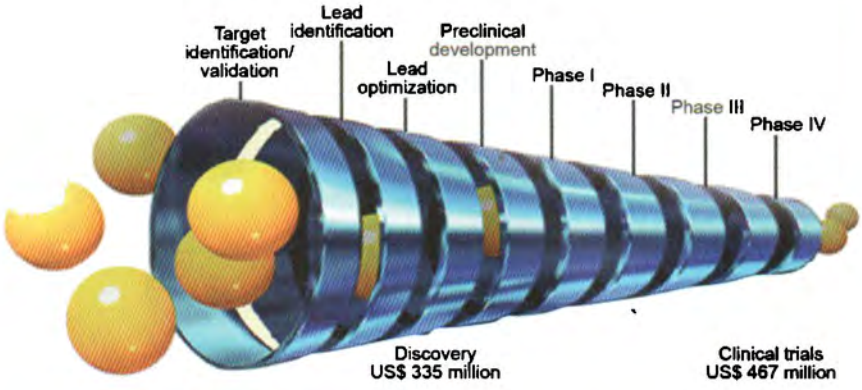
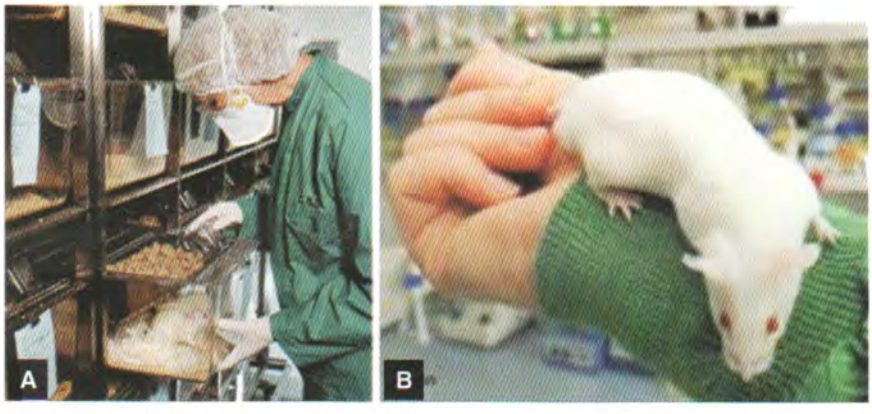



**Fig. 1.1:** Steps in new drug development

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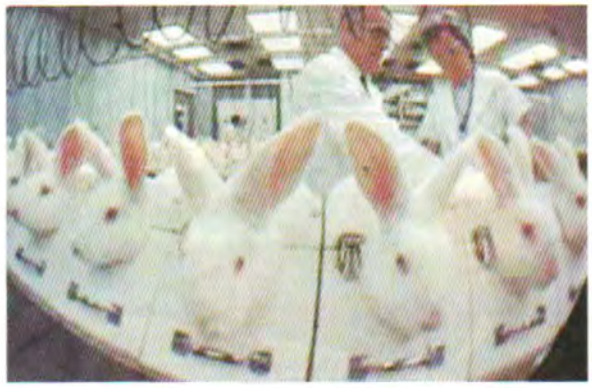

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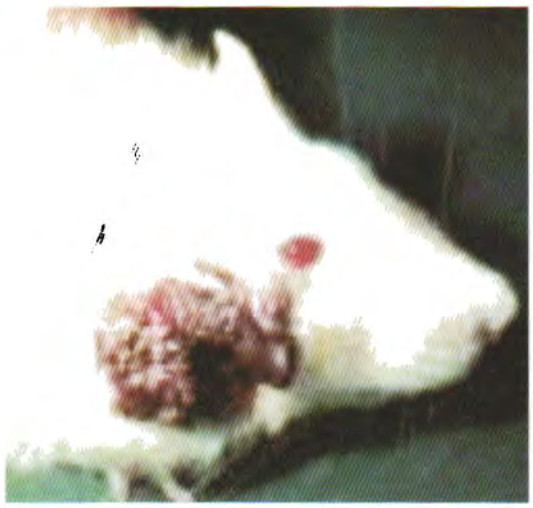

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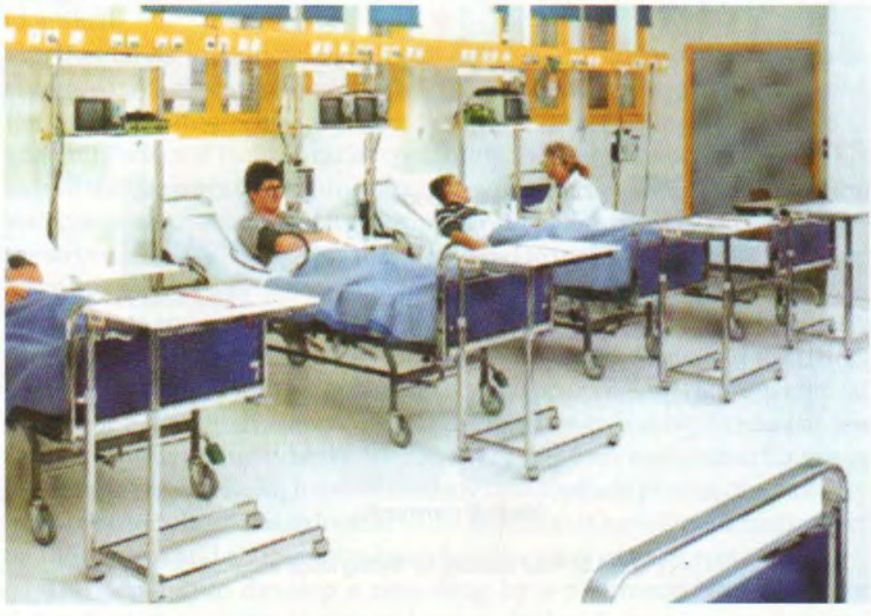

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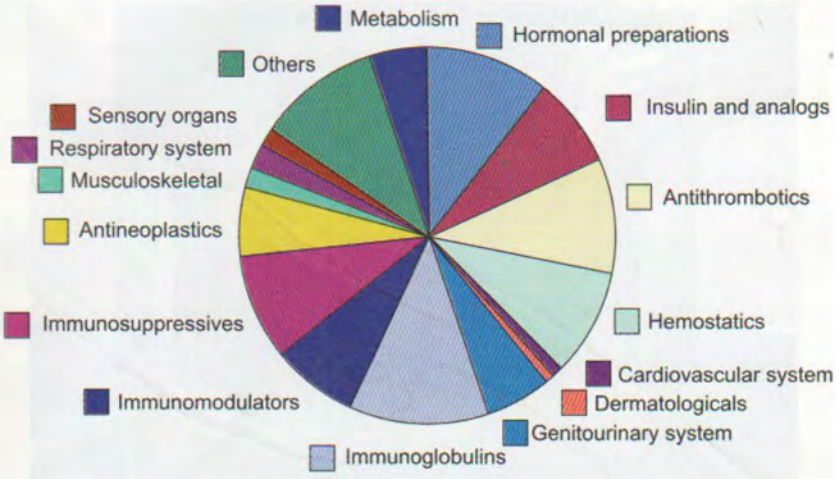
## PLATE 4

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# CHAPTER 1

# New Drug Development

## INTRODUCTION TO DRUG DEVELOPMENT

Drug development is a scientific endeavor which is highly regulated due to public health concern. A promising new molecule identified in drug discovery has to go through the complex and time-consuming process of drug development before it becomes available to patients.

The discovery process begins with an understanding of the disease mechanism(s) or cause of the disease and discovery (or identification) of genes and/or proteins involved in causing certain diseases. The identification of genes/proteins responsible for the disease condition is referred to as target identification. These identified targets (gene/proteins) are the potential targets for drugs to interact and to bring about a beneficial effect in a patient. Next step is target validation, where certain studies are performed to confirm that targets (genes/proteins) are actually involved in the disease. In this stage, along with validation of the target, ability of the target to bind to a drug is identified.

After target identification and validation, a lead compound needs to be identified. A lead compound is a substance which has the greatest potential for successful interaction with the identified target. A lead compound is generally selected from libraries containing thousands of compounds. This step of the drug discovery process is known as lead identification. After the lead compound is identified it goes through an optimization process wherein the structure of the compound may be altered to make it safe and efficacious. Once this process is completed the compound is tested first in animal models (such as rats and mice), then in humans to further ascertain its properties.

It takes about ten to twelve years to develop a new drug and the cost is over •800 million, about 60% of which is spent on necessary rigorous clinical trials. For a variety of reasons, fewer than one or two compounds per ten thousand tested actually make it to the market and are authorized for use in patients. In view of the high cost of the drug development process, the industry has to be careful and has to look in to the factors that have significant impact on the process and should form basis for allocation of resources.

The decision to develop a new drug by a pharmaceutical company depends on the various factors and one of the key factors is to review and find out the unmet medical needs in the specific therapeutic area in which the company is interested due to strategic reasons. In some cases there may

**Table 1.1:** Cost and time involved in drug discovery

| |
|---|
| **Target Discovery** |
| 2.5 years ↓ 4% |
| **Lead generation and lead optimization** |
| 3.0 years ↓ 15% |
| **Preclinical development** |
| 1.0 year ↓ 10% |
| **Phase I, II and III clinical trials** |
| 6.0 years ↓ 68% |
| **FDA review and approval** |
| 1.5 years ↓ 3% |
| **Drug to the market 14 years ↓** |
| • 880 million |

*Source:* PAREXEL. Parexel's Pharmaceutical R & D Statistical Sourcebook, 2001; p.96

be industry – university or industry – government scientific institutes collaboration that may help to develop a new molecule. New and interesting findings may also come from university, institutes and the lead may be taken over by the pharmaceutical companies for further research.

The drug discovery and development process is designed to ensure that only those pharmaceutical products that are both safe and effective are brought to market for the benefit of the patients (Table 1.1).

## DRUG DISCOVERY PROCESS

### Overview of Drug Discovery Process

During the last 50 years the philosophy of valuable drugs discovery has evolved from one that was mostly based around chemistry to one that has more biological approach to treat a disease. These changes were not only driven by strategic imperative, but are enabled also by the significant changes in technology that has occurred during the past half century.

#### *Historical Background*

Before the existence of pharmaceutical industry, medicines were discovered by accident, and their use was passed down by written and verbal tradition. For example, digitalis is an active principal of a natural product, namely foxglove leaf, used to treat dropsy or edema in which liquids accumulate in the body and causes swelling of tissues and body cavities.

This remedy was described and used some hundred(s) of years before the isolation of the active components. In 1776, William Withering, a physician in England treated a lady who was dying of dropsy. He left her, expecting her to die shortly, but he later learned that she had recovered after taking an old cure of a *garden plant* called foxglove. For ten years, Withering conducted experiments to demonstrate the uses of foxglove and discovered that dropsy is actually a symptom of heart disease in which the heart does not pump

hard enough to get rid of urine. He showed that foxglove stimulated urination by pumping more liquids to the kidneys. He published his results in 1785, but it was not until the 20th century that the cardiac glycosides, the component of the foxglove plant, were structurally and pharmacologically described.

In 1950s and 1960s, pharmaceutical industries' success in drug discovery had their origins in serendipity, i.e. discovery by accident/chance. Lead molecules were found by chance or from screening the chemical diversity available. These were then optimized by medicinal chemists to produce candidates, which were passed to development and eventually into the market. This method led to discovery of drugs such as chlorpromazine, meprobamate, and benzodiazepines (chlordiazepoxide, diazepam) all of which have gone on to become successful medicines.

However, this approach suffered from lack of sufficient molecules with high enough structural diversity, and the common use of animal models meant that other factors such as absorption, metabolism, brain penetration, and pharmacokinetics had profound effects on the number of active molecules found. In addition, many molecules that showed activity in the models were of unknown mechanism. This greatly impeded the development of back-ups when the lead failed due to toxicity or poor pharmacokinetics.

To combat these problems, a more rational approach was developed based around the structure of the agonist (i.e. hormones and neurotransmitters) and its receptor. This was set against a background of studying biological/physiological systems in animal tissues. Thus, knowledge around molecular determinants that contribute to affinity and efficacy enabled a generation of specific and potent agonists and antagonists to be developed.

## Steps in Drug Discovery

The advent of molecular biology, coupled with advances in screening and synthetic chemistry technologies, has allowed a combination of both knowledge around the receptor and random screening to be used for drug discovery.

The process of drug development is divided into two stages: New lead discovery and new product development (clinical development) (Fig. 1.1).

### *Target Identification*

Before any potential new medicine is discovered, the disease to be treated needs to be understood, to unravel the underlying cause of the condition. Even with new tools and insights, research on disease mechanism takes many years of work and, too often, leads to frustrating dead ends. And even if the research is successful, it takes many more years of work to turn this basic understanding of what causes a disease into a new treatment.

The disease mechanism defines the possible cause or causes of a particular disorder, as well as the path or phenotype of the disease. Understanding the disease mechanism directs research and formulates a


**Fig. 1.1:** Steps in new drug development *(For color version, see Plate 1)*

possible treatment to slow or reverse the disease process. It also predicts a change of the disease pattern and its implications.

Disease mechanisms can be broadly classified into the following groups:

- Defects in distinct genes—genetic disorders
- Infection by bacteria, fungi, viruses, protozoa or worms
- Immune/autoimmune disease
- Trauma and acute disease based on injury or organ failure
- Multicausal disease

The identification of new and clinically relevant molecular targets for drug intervention is of outstanding importance to the discovery of innovative drugs.

It is estimated that up to 10 genes contribute to multifactorial diseases, which are linked to another 5 to 10 gene products in physiological and pathophysiological circuits which are also suitable for intervention with drugs. Environmental factors such as diet, exposure to toxins, trauma, stress, and other life experiences are assumed to interact with genetic susceptible factors to result in disease. Thus, drug targets may include molecular pathways related to environmental factors.

Current drug therapy is based on less than 500 molecular targets with potential to exploit at least 10 times the number of targets in the future. Targets for therapeutic intervention can be broadly classified into these categories:

- Receptors
- Proteins and enzymes
- DNA
- RNA and ribosomal targets.

Methods used for target identification include classical methods such as cellular and molecular biology and newer technique such as genomics and proteomics.

In the classical method, animal and human cell lines are used to identify the potential target of drug action. Two key research avenues involve the enzymes that metabolize the molecules (drugs) and proteins that act as receptors.

The newer methods like genomics and proteomics along with bioinformatics are aimed at discovering new genes and proteins and quantifying and analyzing gene and protein expression between diseased and normal cells.

### *Target Validation*

Target validation requires a demonstration that a molecular target (such as an enzyme, gene or protein) is actually involved in a disease process, and that binding of a drug to the target is likely to have a curative effect.

The validation of a molecular target *in vitro* (in an artificial environment) usually precedes the validation of the therapeutic concept *in vivo* (in a living organism); together this defines its clinical potential. Validation involves studies in intact animals or disease-related cell-based models that can provide information about the integrative response of an organism to a pharmacological intervention and thereby help to predict the possible profile of new drugs in patients.

Targets are validated with:

- *In vitro models*: RNA and protein expression analysis and cell based assays for inhibitors, agonists (substances which activate the target) and antagonists (counteracts the effect of a target). *In vitro* assays are more robust and cost-effective, and have fewer ethical implications than whole-animal experiments. For these reasons they are usually chosen for high-throughput screening, a process through which active compounds, antibodies or genes which modify a particular biomolecular pathway can be identified rapidly.
- *In vivo models*: *In vivo* testing involves testing in whole animals. It assesses both pharmacology and biological efficacy in parallel. Animal models that are capable of mimicking the disease state (e.g. animals mimicking diabetes), by adding/ modifying or deleting certain genes are used. These animal models are referred to as knock-in and knock-out animal models.

Along with validation of the target it is essential to predict the "druggability" of the target. The "druggability" of a given target is defined by how well a therapeutic agent, such as small drug molecule or antibody, can access the target (i.e. ability of a target to bind to drug).

Knowledge of three-dimensional structure will help to unravel the physiological roles of target proteins and contribute to "chemical" target validation and also enable the prediction of "druggability" of the protein. One of the successfully targeted targets is G-protein coupled receptors (GPCRs), and a sizable number of drugs prescribed today hit this particular class. Therefore, the GPCR target type is considered druggable.

In summary, target validation is one of the bottlenecks in drug discovery, as this phase is less adaptable to automation. Careful validation of target not only with respect to relevance to disease but also druggability will reduce the failure rate and increase the efficiency of drug discovery.

### *Lead Identification*

In this phase, compounds which interact with the target protein and modulate its activity are identified.

The lead identification process starts with the development of an assay which will be followed by screening of compound libraries. The quality of an assay determines the quality of data. The assay used should fulfill these criteria: relevance, reliability, practicability, feasibility, automation and cost-effectiveness.

Primary screens will identify hits. Subsequently, confirmation screens and counter screens will identify leads out of the pool of hits. This winnowing process is commonly referred to as "hits-to-leads."

The success of screening depends on the availability of compounds, as well as their quality and diversity. Efforts to synthesize, collect, and characterize compounds are an essential and costly part of drug discovery.

There are several sources for compounds:

- Natural products (NPs) from microbes, plants, or animals. NPs are usually tested as crude extracts first, followed by isolation and identification of active compounds
- Collections (Random) of discreetly synthesized compounds
- Focused libraries around certain pharmacophores
- Random libraries exploring "chemical space"
- Combinatorial libraries.

A primary screen is designed to rapidly identify hits from compound libraries. The goals are to minimize the number of false-positives and to maximize the number of confirmed hits. Depending on the assay, hit rates typically range between 0.1 and 5 percent. This number also depends on the cutoff parameters set by the researchers, as well as the dynamic range of a given assay.

Typically, primary screens are initially run in multiplets of single compound concentrations. Readouts are expressed as percent activity in comparison to a positive (100 %) and a negative (0 %) control. Hits are then retested a second time (or more often, depending on the assays' robustness). The retest is usually run independently of the first assay, on a different day. If a compound exhibits the same activity within a statistically significant range, it is termed a confirmed hit, which can proceed to dose-response screening.

Establishing a dose-response relationship is an important step in hit verification. It typically involves a so-called secondary screen. In the secondary screen, a range of compound concentrations usually prepared by

serial dilution is tested in an assay to assess the concentration or dose dependence of the assay's readout. Typically, this dose-response is expressed as an $IC_{50}$ in enzyme-, protein-, antibody-, or cell based assays or as an $EC_{50}$ in *in vivo* experiments. $IC_{50}$ is a measure of the effectiveness of a compound in inhibiting biological or biochemical function. This quantitative measure indicates how much of a particular drug is needed to inhibit a given biological process by half. $EC_{50}$ (Half maximal effective concentration) refers to the concentration of a drug or antibody which induces a response halfway between the baseline and maximum. The $EC_{50}$ of a graded dose response curve therefore represents the concentration of a compound where 50% of its maximal effect is observed.

Confirmed hits proceed to a series of counterscreens. These assays usually include drug targets of the same protein or receptor family; for example, panels of GPCRs (G-protein coupled receptors,) or kinases. In cases where selectivity between subtypes is important, counterscreens might include a panel of homologous enzymes, different protein complexes, or heterooligomers. Counterscreens profile the action of a confirmed hit on a defined spectrum of biological target classes. The number and stringency of counterscreens can vary widely and depend on the drug target.

One of the goals throughout the discovery of novel drugs is to establish and confirm the mechanism of action (MOA). In an ideal scenario, the MOA remains consistent from the level of molecular interaction of a drug molecule at the target site through the physiological response in a disease model, and ultimately in the patient.

The tools used for lead identification are: High throughput screening, *in-silico*/virtual screening, NMR-based screening and X-ray crystallography.

- High-throughput screening (HTS) aims to rapidly assess the activity of a large number of compounds or extracts on a given target. Entire in-house compound libraries with millions of compounds can be screened with a throughput of 10,000 (HTS) up to 100,000 compounds per day (ultra-HTS) using robust test assays.
- Virtual *(in-silico)* screening sifts through large numbers of compounds based on a user-defined set of selection criteria. Selection criteria can be as simple as a physical molecular property such as molecular weight or charge, a chemical property such as number of heteroatoms, number of hydrogen-bond acceptors or donors. Selection criteria can be as complex as a three-dimensional description of a binding pocket of the target protein, including chemical functionality and solvation parameters. *In-silico* screening can involve simple filtering based on static selection criteria (i.e. molecular weight) or it can involve actual docking of ligands to a target site, which requires computer-intensive algorithms for conformational analysis, as well as binding energies.
- NMR- based screening fills the gap between HTS and virtual screening. This method combines the random screening approach with the rational structure-based approach to lead discovery.

- X-ray crystallography: Uses X-rays to determine the structure and functioning of biological molecules. The point at which X-ray crystallography comes into the drug discovery and development process depends on the purpose for which it is used. X-ray crystallography is being increasingly used to determine the three-dimensional structure of a lead compound. The information accumulated during the process of lead identification by means of X-ray crystallography is essential for the next stage of drug development which is lead optimization.

Following are the criteria for hits to be regarded as leads:

- Pharmacodynamic properties, e.g. efficacy, potency and selectivity *in vitro* and *in vivo*
- Physicochemical properties, e.g. Lipinski's "rule of five"
- Pharmacokinetic properties, e.g. permeability in the Caco-2 assays
- Chemical optimization potential
- Patentability.

### *Lead Optimization*

Lead optimization is a complex, non-linear process of refining the chemical structure of a confirmed hit to improve its drug characteristics with the goal of producing a preclinical drug candidate. This stage constitutes the tightest bottleneck in drug discovery.

Lead optimization employs a combination of empirical, combinatorial, and rational approaches that optimize leads through a continuous, multi-step process based on knowledge gained at each stage. Typically, one or more confirmed hits are evaluated in secondary assays, and a set of related compounds, called analogs, are synthesized and screened.

The testing of analog series results in quantitative information that correlates changes in chemical structure to biological and pharmacological data generated to establish structure activity relationships (SAR).

The lead optimization process is highly iterative. Leads are assessed in pharmacological assays for their "druglikeness." Medicinal chemists change the lead molecules based on these results in order to optimize pharmacological properties such as bioavailability or stability. At that point the new analogs are fed back into the screening hierarchy for the determination of potency, selectivity and mechanism of action.

Pharmacokinetics (PK)/pharmacodynamics (PD)/absorption, distribution, metabolism, Excretion (ADME) studies are an integral part of lead optimization. They feedback into the medicinal chemistry effort aiming to optimize the physicochemical properties of new leads in terms of minimal toxicity and side effects, as well as of maximum efficacy toward disease. PK/PD/ADME studies rely heavily on analytical methods and instrumentation. The recent innovation and progress in mass spectroscopy (whole-body) imaging, and chromatography technology (HPLC, LC-MS, MS) have

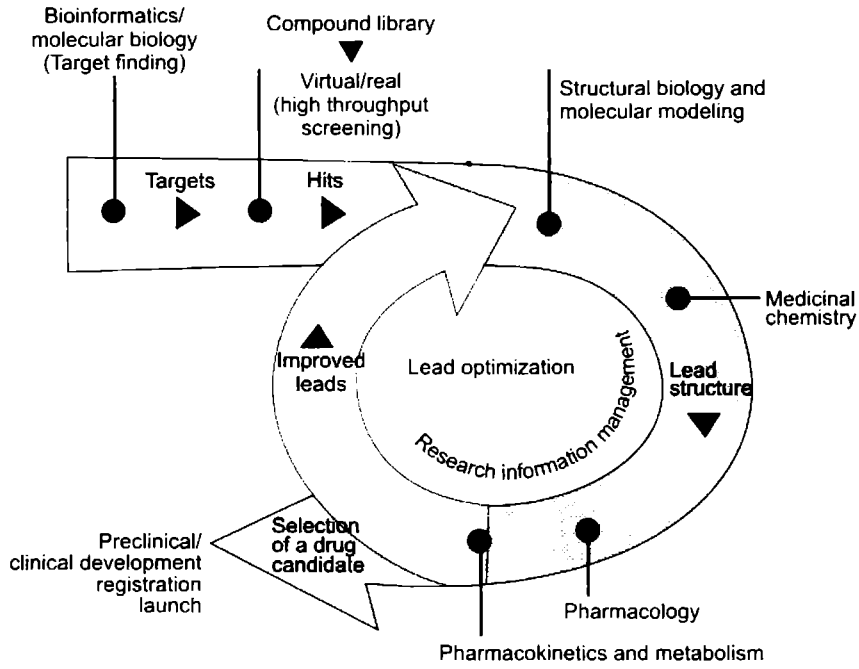



**Fig. 1.2:** Depicts use of *in-silico* technology in various stages of selection of a drug candidate

*Source:* www.scfbio-iitd.res.in/image/insilicodrug.JPG

tremendously increased the quantity and quality of data generated in PK/PD experiments.

These data are then fed into the next optimization cycle. The lead optimization process continues for as long as it takes to achieve a defined drug profile that warrants testing of the new drug in humans (Fig. 1.2).

### *Lead Optimization—Formulation and Delivery*

Formulation development: It is the process of turning an active compound into a form and strength suitable for human use.

Formulation and delivery of drugs is an integral part of the drug discovery and development process. Indeed, formulation problems and solutions influence the design of the lead molecules; they feed back into the iterative lead optimization cycle, as well as the preclinical and clinical evaluations. If formulation substances are not generally recognized as safe (GRAS), they become part of the safety assessment and their PK/PD/ADME behavior, as well as toxicity profile, needs to be documented in the IND (investigational new drug) application. In fact, side effects such as local irritation or allergic reactions are often attributable to drug formulation, not the active pharmaceutical ingredient (API).

Formulation substances might exhibit different biological activity than the actual drug.

Indeed, a sizable number of drug discovery and development programs in the pharmaceutical and biotech industry are centered on new ways of formulating already known and even marketed drugs to increase their efficacy or safety profiles.

### Stakeholders in New Drug Development

Expertise involved to achieve goal of new drug development are numerous. Once the management team sets therapeutic targets, budgets and resources, departments involved in drug discovery include:

- *Research and development:* This department is responsible for finding new compounds and assuring that they are safe enough to test in humans.
- *Medicinal chemists:* Their responsibilities are to prepare new chemical entities which can be screened for biological activity and to prepare compounds which have been found to be active (new leads) in quantities sufficient for advanced testing.
- *Pharmacology/molecular biology/screening:* This department examines each new chemical entity (NCE) in a set of high throughput screens.
- *Safety evaluation:* It demonstrates that the NCE and its metabolites do not accumulate and do not cause harm during short-term administration.
- *Formulations research:* It develops a dosage form that is absorbed into the bloodstream when administered and is stable when stored for long periods of time. The concentration in the blood is an important factor in early development. The potential new drug must reach and maintain a level sufficient to sustain its biological effect; these studies are initially conducted on animals to establish the doses for human studies.
- *Process research:* It manufactures the NCE in sufficient quantity for advanced testing, dosage form development.
- *Legal affairs:* It writes and files the patents necessary to protect a company's inventions.
- *Research administration:* It collects the material generated by all the departments and formats it into a request for exemption so that the NCE can be tested in humans. This submission is the investigational new drug (IND).

### Need for Systematic Approach in New Drug Discovery

The pharmaceutical industry is operating in a world where medicines have to add real value in an environment in which costs are under constant pressure. This high cost is causing the evolution of the drug discovery process so that high percentages of efficient pipeline molecules are delivered to market quickly. The following needs to be considered to have a systematic approach in drug discovery.

### Unmet Medical Needs

A constant driver for developing new medicines has always been the unmet medical need. However, there are now strong pressures to treat the underlying cause of the disease rather than to provide symptomatic relief alone. This is reinventing the biological systems approach, but using humans rather than animals. In order to accomplish this, the investment that has already been initiated in technologies such as noninvasive imaging, clinical genetics and genomics will increase. This is now assured with the publication of the human genome.

The lack of disease models in animals in some therapeutic areas is a major driver to understand the human pathology. This is particularly relevant in the central nervous system (such as depression, bipolar disorder, schizophrenia) area. In these diseases, with no simple ways to validate the targets in the complex intact system, option left is targeting components such as receptor or biochemical systems. In these cases, the scientist is constrained to collecting a logical series of evidence that associates the target with the disease. Along with the existing imaging methods such as PET (Positron emission tomography) and fMRI (Functional magnetic resonance imaging), application of technologies like clinical genetics and genomics will strengthen the understanding of the correlation between disease and specific receptors.

Clinical genetics networks are being put into place to allow sufficient information on probands (proband denotes a particular subject (person or animal) first affected with genetics disorder) to be collected, such that associations between particular gene(s) and disease (target validation) can be made and eventually resulting in identification of a lead compound.

The advent of the human genome's publication now offers a great opportunity for the understanding of the genetic make-up of disease and will furnish specific gene products and/or pathways as new targets that would not have been previously identified. Importantly, they will be born out of human data, so again adding to the level of confidence in the validity of the target.

### Attrition

Attrition is another driver for systematic approach in drug discovery for overall success rate. Attrition has remained static despite the investment in the new technologies. This reflects the fact that good molecules need more than potency and selectivity to be successful, and it is in these areas where technology has been concentrating in the last few years. The challenges ahead lie in reducing the risk of not obtaining efficacy in humans, and in increasing the developability of the molecules.

*Efficacy:* Many new mechanisms fail when they get into humans through lack of efficacy. This is one of the risks that the industry takes when developing

such molecules. One way to diminish risk is to get better validation in humans (proof-of-concept, i.e. proof of efficacy) as soon as possible. The use of imaging, genetics, and genomics has already been discussed earlier as a way to help build early confidence in the target.

It is now recognized that fast decision making saves money and allows resources to be more effectively used. Proof-of-concept is generally obtained in phase III. Killing compounds in phase III is extremely costly; therefore, it is a disadvantage to obtain proof of concept at such a late stage. Thus, simple proof-of-concept studies (POCs) are being sought in phase I or phase II. If POC, were to be obtained during phase I and phase II instead of phase III, it will provide sponsors with sufficient evidence which can be used to assess the clinical and commercial potential of the drug and, in turn, eliminate potential failures from the drug discovery pipeline.

In addition, diagnostics will play a greater role in helping to choose patient populations, at least initially to show that the mechanism works. This will see greater use of imaging, proteomics and genetics in helping to identify the right patient group.

In the meantime, a better balance of novel molecules and those that are precedented will be seen in the drug discovery portfolio. This will mean that a higher proportion of molecules will not fail for efficacy. However, this strategy creates its own problems in that to be successful in the marketplace the molecule will need to be differentiated from those already present. To do this in the clinic will add to the cost and to the overall cycle time, thus these problems will need to be addressed much earlier in the process.

*Developability:* A large proportion of molecules fail due to of lack of developability. Prentis et al suggest that this proportion is as high as 69%, broken down as toxicity (22%), poor biopharmaceutical properties (41%) and market reasons (6%). This is not a new revelation, and efforts have been actively followed to automate and miniaturize methods to measure solubility, stability, pKa (value which describes the acid and basic properties of a substance), bioavailability, brain penetration, and various toxicity. These methods (combinatorial lead optimization) are being applied to leads during optimization, but need to be developed further and applied even earlier to maximize their impact. This is particularly true for toxicity screens, where it can be predicted that a great deal of effort will be done in the next few years.

Great extent of work is being done in the field of predictive algorithms, and Pfizer has developed tool known as the "rule of 5". This is an awareness tool for medicinal chemists that suggests that there will be poor absorption if a molecule has two or more of the following: more than 5 H-bond donors; a molecular weight > 500; c log P > 5; the sum of Ns and Os (a rough measure of H-bond acceptors) >10.

While it is inherently costly to try to fix poor developability by formulation, pharmaceutical development will become more actively engaged in alternative formulations and delivery systems during the lead optimization

phase. The trend towards higher potency compounds, that reduces cost of goods, also allows, due to the smaller dose, alternative delivery systems such as inhalation, nasal, buccal and sublingual absorption.

### *Cycle Times*

The need to speed up the delivery of molecules to the market is another driver to have systematic approach in drug discovery. The regulatory environment and the growing complexity of drug development affect the time taken for a drug to reach the market.

Screening automation and combinatorial chemistry have greatly reduced the time to candidate selection. This will almost certainly decrease again by further application of techniques like chemoinformatics to aid library design, both for those to be used for random screening and those within the process of lead optimization. As mentioned above, continual automation of developability criteria will also speed up the process by selecting compounds with a high probability of succeeding. This raises the concept that speed in each phase should not always be the major driver. A candidate for development goes forward with all of its associated baggage. Fixing problems become costly and may lead to a suboptimal product that cannot fulfill its medical and commercial potential. Thus, spending time choosing the right candidate will have major benefits downstream, both in terms of speed and value. The same concept applies to development candidates in phase III. Differentiation may not be obvious if the mechanism is precedented with another marketed product. Thus, differentiation will become a challenge, which potentially will increase the time in phase III. To aid in this process and help in choosing which differentiators to pursue, this problem will need to be addressed much earlier. This might stimulate automated assays for common side effects of drugs as part of the candidate selection criteria during the lead optimization stage.

### *Economic Value*

There is growing internal pressure to increase productivity while controlling costs. This has led to the drive for high-value molecules in diseases with high unmet need. An extension of this concept is the "blockbuster" approach where projects that deliver medicines with potential peak sales greater than 1 billion pounds are given the highest priority. This means that portfolio management will become even more important with an associated greater interaction between R & D and the commercial functions.

Thus, new portfolio tools will also be major contributors to the future process of drug development. The real value of medicines to the health of society is only now beginning to be recognized. It has taken many years of persuasion that medicines can have profound economic benefit.

The push to raise health, economic and quality-of-life issues has produced a counter response from some regulators that the industry demonstrates

added value in its novel medicines. Thus, committees like National Institute for Clinical Excellence (NICE) in the UK will put pressure on the process to produce medicines that have significant value for society. This will mean that in the future more outcome studies will be needed to demonstrate quality-of-life and economic benefit.

## PRECLINICAL DRUG DEVELOPMENT

### Introduction to Preclinical Drug Development

Preclinical drug development is a stage that begins before clinical trials (testing in humans) during which important safety and pharmacology data are collected. Clinicians and regulators need to be reassured that information concerning all of these different aspects is available to enable clinical trials to progress and ultimately to support regulatory decisions on whether a new drug can be approved for marketing. Most regulatory toxicity studies are conducted in animals to identify possible hazards from which an assessment of risk to humans is made by extrapolation. Regulatory agencies request studies in a rodent (e.g. rat) and a nonrodent (e.g. dog). The choice of animal species is based on the similarities of its metabolism to humans or the applicability of desired pharmacological properties to humans. It is not possible or ethical to use animals in large numbers, to compensate for the same it is assumed that increasing the dose and prolonging the duration of exposure will improve both sensitivity and predictivity of the tests.

Preclinical research includes synthesis, purification and animal testing which is done to measure the biological activity and safety of an investigational drug or device. Preclinical research is conducted by pharmaceutical companies early in the process of new drug development. This research takes place in either the part or whole animal to determine important information, including therapeutic effects the drug may have, potential side effects and toxicities and metabolism and clearance of the drug in the body. Good results in the preclinical or animal stage do not necessarily mean that similar results will be found when the drug is given to healthy volunteers or patients.

The main goals of preclinical studies are to determine a drug's pharmacodynamics (PD), pharmacokinetics (PK) and toxicity through animal testing. These data allow researchers to estimate a safe starting dose of the drug for clinical trials in humans.

The goals of the nonclinical safety evaluation include:

- Categorization of toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility. This information is important for the estimation of an initial safe starting dose for the human trials
- The identification of specific parameters for clinical monitoring for potential adverse effects

- The nonclinical safety studies, although limited at the beginning of clinical development, should be adequate to characterize potential toxic effects.

The need for nonclinical information including toxicology, pharmacology and pharmacokinetics to support clinical trials is addressed in the ICH (International Conference on Harmonization) Safety guidelines. Typically, both *in vitro* and *in vivo* tests will be performed. Studies of a drug's toxicity on organs targeted by that drug, as well as any long-term carcinogenic effects or toxic effects on mammalian reproduction will be estimated in preclinical studies.

## Types of Preclinical Studies

- *In vitro* studies
- *In vivo* studies
- *Ex vivo* studies.

### *In Vitro Studies*

*In vitro* studies are done for testing of a drug or chemical's effect on a specific isolated tissue or organ maintaining its body functions. Basic instruments used for isolated tissue experiments are organ baths, recording devices.

Few examples of *in vitro* studies include:

*Langendroff's heart preparation:* The objective is to study the effect of drugs like noradrenaline, acetylcholine and isoprenaline on the coronary blood flow and heart rate and force of contraction using rat isolated heart.

- *Ileum preparation:* The objective is to record the effect of drugs like histamine and antihistamine by using segment of ileal portion of Guinea pig.
- *Rectus abdominus muscle preparation:* The objective is to record the effect of drugs like d-tubocurarine by using rectus abdominus muscle of frog.

### *In Vivo Studies*

In *in vivo* studies, *in vivo* is a Latin term meaning (with) "in the living". It indicates the use of a whole organism/animals (for an experiment). Researchers use laboratory animals as models of humans or some other target species to achieve long-term objective, such as developing a new drug for a particular disease, screening a particular compound for human toxicity, studying a gene or mutation found in both animals and human; to achieve short-term objective to find out how the animal responds to the treatment. If it is a faithful model of humans, then humans should respond in the same way. Animals and other models, are used because the research cannot be done on humans for practical or ethical reasons.

*Purpose of models:* A specific model is chosen because it is believed to be appropriate to the condition being investigated and is thought likely to respond in the same way as humans to the proposed treatment(s) for the character being investigated.

Having chosen the model it is essential that any experiments in which it is used are well designed, i.e. are capable of demonstrating a response to a treatment. If the model happens to be insensitive or the experiments are badly designed so that they are incapable of distinguishing between treated and control groups, say as a result of using too few animals, then the model is not appropriate to its purpose.

Animal models are used to define a new molecule's:

- Therapeutic potential
- Toxicity potential
- Pharmaceutical properties and metabolic pathways
- Mechanism and specificity of action (lead molecules).

*In vivo* studies are preferred over *in vitro* studies for the following reasons:

- Greater similarity to human studies when compared to *in vitro* screening
- Drug effects modified by physiological mechanisms can be studied
- ADME of drugs that modifies drug effects are also factored
- Most animal systems are similar to human systems
- Effect of drug is studied on complete systems rather than tissues and organs
- Drugs acting on central nervous system, cardiovascular system, gastrointestinal system, and other systems can be studied
- Results easier to interpret and extrapolate.

Some of the examples of *in vivo* studies are:

- Noninvasive method—rat tail cuff method
- Invasive methods—BP recording in anesthetized dog or cat.

*Transgenic animal models:* Partly due to the low speed and high cost of conventional animal models (typically rodents) and the relatively high number of preliminary hits from HTS (high throughput screening), alternative small-animal models have emerged. The small size, high utility, and experimental tractability (i.e. easy to manage) of these animals enable cost-effective and rapid screening of numerous compounds. Technologies for engineering the mouse genome have made it possible to create various disease models for use in screening corresponding therapeutic compounds. Knockout mouse models have been shown to be highly predictive of the effects of drugs that act on target specific gene-sequence alterations or manipulate the levels and patterns of target-gene expression. Using these techniques, researchers can generate specific disease models to validate targets as therapeutic intervention points and screen drug candidates. Transgenic technology represents an attractive approach to reduce the attrition rate of compounds entering clinical trials by increasing the quality of the target and compound combinations making the transition from discovery into development. Some of the transgenic animal models are Obese Zucker rats for testing obesity-related hypertension, genetically epilepsy-prone rats for testing antiepileptic drugs, etc.

### *Ex Vivo Studies*

In *ex vivo*, experiment is performed *in vivo* and then analyzed *in vitro*. The organs of the animals are detached from the body and replaced once an experiment is performed. Then the animals are kept under observation and findings recorded for a set duration.

## General Requirements for Conducting Preclinical Studies

- Toxicity studies should comply with good laboratory practice (GLP).
- These studies should be performed by suitably trained and qualified staff employing properly calibrated and standardized equipment, done as per written protocols.
- Standard operating procedures (SOPs) should be followed.
- Test substances and test systems (*in vitro* or *in vivo*) should be properly characterized and standardized.
- All documents belonging to each study, including its approved protocol, raw data, draft report, final report, and histology slides and paraffin tissue blocks should be preserved for a minimum of 5 years after marketing of the drug.

## Animal Pharmacology Studies

Safety pharmacology studies are studies that investigate potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range or above. Specific pharmacological actions are those which demonstrate the therapeutic potential for humans.

Based on the individual properties and intended uses of an investigational drug, specific studies that need to be conducted and their design will vary. Only scientifically validated methods should be used.

The essential safety pharmacology is to study the effects of the test drug on vital functions. Vital organ systems such as cardiovascular, respiratory and central nervous systems should be studied.

In addition to the essential safety pharmacological studies, additional supplemental and follow-up safety pharmacology studies may need to be conducted as appropriate. These depend on the pharmacological properties or chemical class of the test substance, and the data generated from safety pharmacology studies.

Specific and essential pharmacological studies should be conducted to support use of therapeutics in humans. Essential safety pharmacology studies may be excluded or supplemented based on scientific rationale. Also, the exclusion of certain test(s) or exploration(s) of certain organs, systems or functions should be scientifically justified. Supplemental Safety Pharmacology Studies are required to investigate the possible adverse pharmacological effects that are not assessed in the essential safety pharmacological studies and are a cause for concern.

The following factors are to be considered when specific tests are to be conducted:

- Mechanism of action
- Class-specific effects
- Ligand binding or enzyme assay suggesting a potential for adverse events.

Safety pharmacology studies are usually not required when:

- Product is to be used for local application, e.g. dermal or ocular
- The pharmacology of the investigational drug is well known, and/or
- Systemic absorption from the site of application is low.

Safety pharmacology testing is also not necessary, in case of a new derivative having similar pharmacokinetics and pharmacodynamics. For biotechnology-derived products that achieve highly specific receptor targeting, it is often sufficient to evaluate safety pharmacology end-points as a part of toxicology and/or pharmacodynamic studies; therefore, safety pharmacology studies can be reduced or eliminated for these products. For biotechnology-derived products that represent a novel therapeutic class and/or those products that do not achieve highly specific receptor targeting, a more extensive evaluation by safety pharmacology studies should be considered.

*In vivo* safety pharmacology studies should be designed to define the dose-response relationship of the adverse effect observed. When feasible, the time course (e.g. onset and duration of response) of the adverse effect should be investigated.

*In vitro* studies should be designed to establish a concentration-effect relationship. The range of concentrations used should be selected to increase the likelihood of detecting an effect on the test system. The upper limit of this range may be influenced by physicochemical properties of the test substance and other assay specific factors.

## Animal Toxicity Studies

Toxicokinetic studies should be conducted to assess the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study (Figs 1.3A and B). Other objectives of toxicokinetic studies include:

- To relate the toxicological findings to clinical safety
- To support in selecting species, treatment regimen and designing subsequent nonclinical toxicity studies.

Several toxicity studies need to be done before a drug goes into the clinical phase. They are as follows.

### *Systemic Toxicity Studies*

*Single dose study (Acute toxicity studies):* Single dose studies in animals are essential for any pharmaceutical product intended for human use. The information obtained from these studies is useful in choosing doses for repeat-


**Figs 1.3A and B:** A researcher studies a rat being used in medical experiments
*(For color version, see Plate 1)*

dose studies, providing preliminary identification of target organs of toxicity, and, occasionally, revealing delayed toxicity. Acute toxicity studies may also aid in the selection of starting doses for phase I human studies, and provide information relevant to acute overdosing in humans.

*Repeated-dose systemic toxicity studies:* The primary goal of repeated dose toxicity studies is to characterize the toxicological profile of the test compound following repeated administration. This includes identification of potential target organs of toxicity and exposure/response relationships, and may include the potential reversibility of toxic effects. This information should be part of the safety assessment to support the conduct of human clinical trials and the approval of a marketing authorization.

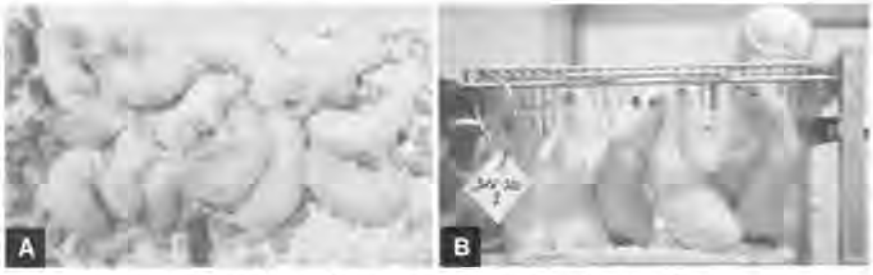
The decision whether a developmental toxicity study needs to be performed should be made on a case-by-case basis taking into consideration historical use, product features, intended target population and intended clinical use.

### *Male Fertility Studies*

Male fertility studies are designed to provide general information concerning the effects of a test substance on male reproductive system such as gonadal function.

### *Female Reproduction and Developmental Toxicity Studies*

Female fertility studies are designed to provide general information concerning the effects of a test substance on female reproductive system such as ovary function and lactation (Figs 1.4A and B). These studies need to be carried out for all drugs proposed to be studied or used in women of childbearing age.




**Figs 1.4A and B:** Reproductive studies done on rats
*(For color version, see Plate 1)*

### *Teratogenicity Study*

The drug should be administered throughout the period of organogenesis in animals if the test drug is intended for women of childbearing age and if women of childbearing age are to be included as subjects in the clinical trial stage.

### *Perinatal Study*

This study is specially recommended if the drug is to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development.

### *Local Toxicity*

These studies are required when the new drug is proposed to be used by some special route (other than oral) in humans. The drug should be applied to an appropriate site (e.g. skin or vaginal mucous membrane) to determine local effects in a suitable species. If the drug is absorbed from the site of application, appropriate systemic toxicity studies will also be required. Examples of local toxicity are dermal toxicity study, vaginal toxicity study, photoallergy, rectal tolerance test, ocular toxicity studies (Fig. 1.5), inhalational toxicity studies, and hypersensitivity.

### *Genotoxicity*

Genotoxicity refers to potentially harmful effects on genetic material (DNA) which may occur directly through the induction of permanent transmissible changes (mutations) in the amount or structure of the DNA within cells. *In vitro* (artificial environment) and *in vivo* (in living organisms) genotoxicity tests are conducted to detect compounds which induce genetic damage directly or indirectly. These tests should enable hazard identification with respect to damage to DNA and its fixation. Damage to DNA can occur at three levels:

1. Point mutations
2. Chromosomal mutations
3. Genomic mutations.

**Fig. 1.5:** Depicts rabbits kept ready for ocular tests *(For color version, see Plate 2)*

The following standard test battery is generally expected to be conducted:

- A test for gene mutation in bacteria (Ames test)
- An *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma assay
- An *in vivo* test for chromosomal damage using rodent hematopoietic cells.

### *Carcinogenicity*

Studies should be performed for all drugs that are expected to be clinically used for six months or more than six months as well as for drugs used frequently in an intermittent manner in the treatment of chronic or recurrent condition (Figs 1.6 and 1.7).

## Limitations of Preclinical Studies

The purpose of preclinical work (animal pharmacology/toxicology testing) is to develop adequate data to undergird a decision that it is reasonably safe to proceed with human trials of the drug. Mice and rats are the most widely used host species for preclinical drug development for a variety of important reasons. First, rodents have a comparatively short life cycle. Rodent research studies can be time-compressed to evaluate disease progression with or without therapeutic intervention. The short life cycle has also lent itself to the development of many unique inbred strains. In addition, rodents, especially mice, have been thoroughly characterized genetically and were the first animal species to be genetically modified by transgenic and gene knock-out methods. The microbiology of rats and mice has been extensively studied. Sophisticated husbandry, biosecurity practices and diagnostic testing effectively control environmental conditions and adventitious infections with pathogenic microorganisms that might cloud the interpretation of experimental findings.

**Fig. 1.6:** Depicts carcinogenicity test done on mice *(For color version, see Plate 2)*

**Fig. 1.7:** Lab mice showing one with a tumor, the other treated with toxin cancer drug *(For color version, see Plate 2)*

Because genetic, environmental, and microbiological variables can be comprehensively defined and carefully controlled, data from studies using rodents are invaluable for characterizing disease conditions and therapies. Also, research reagents are more widely available for biochemical testing of rodents then for testing other laboratory animal species.

However, animal studies have certain limitations:

- Not reliably predictive of human responses due to species variation and extrapolation, poor disease models, confounding effects of laboratory confinement, stress, environment and food
- Repeatability/reproducibility is difficult
- Expensive, time-consuming and not amenable to high throughput. Toxicity studies are costly in terms of animals and resources. For a product

developed for chronic oral therapy approximately 4,000 rats, 1300 mice, 100 rabbits, 50 guinea pigs and 160 dogs, a total of nearly 5,000 animals are used. If the fetus and offspring from the reproductive toxicity studies are included, the number doubles.

- Attempting to translate research from animals to humans not as efficient as studying humans directly—*92% of drugs that pass preclinical testing, almost all in vivo animal-based, fail in clinical trials.*
- Ethical issues in using animal for studies.

Predictive software and advanced *in vitro* technologies, have improved both the efficiency of laboratory animal experiments and the quality of data to make decisions about dosing with NCE. It is very clear that animals are not the way to explore libraries of 1 million or even 25,000 compounds. On the other hand, much can be done when the number that survives the *in silico* and *in vitro* process reaches 1000 or fewer. There are several very compelling new technologies now available that include whole-body imaging, protein biomarkers monitoring by multichannel immunoassays, flow cytometry of blood components, metabonomic component monitoring using *in vivo* micro dialysis and *in vivo* ultrafiltration, automated blood sampling for awake, freely-moving animals [pharmacokinetics (PK) and biomarkers] and parallel monitoring of physiological and electrocardiogram and psychological parameters. While not all of these data sources can be enabled simultaneously, many of them can be accomplished automatically, raising the quality of information available from animal models dramatically.

### FDA Requirements for Preclinical Studies

It is essential to ensure the quality and reliability of safety studies and this can be achieved by adhering to good laboratory practices (GLP). The purpose of GLP is to obtain data on properties and safety of these substances with respect to human health and environment, to promote development of quality test data, such comparable data forms the basis of mutual acceptance across organizations/countries, confidence in and reliability of data from different countries will prevent duplicating tests, saves time, energy and resources.

For every 5000 drug compounds that enter preclinical testing in the United States, only about 5 will eventually be considered acceptable to test in humans. Of those final 5, only 1 drug may actually receive approval for use in patient care.

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies.

Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement:

- Compiling existing nonclinical data from past *in vitro* laboratory or animal studies on the compound

- Compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the US population
- Undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

At the preclinical stage, the FDA will generally ask, at a minimum that sponsors:

- Develop a pharmacological profile of the drug
- Determine the acute toxicity of the drug in at least two species of animals
- Conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

Organization of Economic Cooperation and Development (OECD) framed guidelines known as good laboratory practices (GLP). GLP gives guidelines for animal testing facility (Fig. 1.8), housing the animals, responsibilities and duties of personnel conducting the animal studies, equipment, quality control, etc.

In India, the Committee for the Purpose of Control and Supervision for Experiments on Animals (CPCSEA) ensures that the animal facilities are well-maintained and experiments are conducted as per internationally accepted norms. Organizations or individuals that use animals for research, testing and teaching are required to have a code of ethical conduct which sets out the policies and procedures which must be followed when using animals for research, testing or teaching.

**Fig. 1.8:** Animal testing facility according to GLP requirements
*(For color version, see Plate 3)*

It needs to specify provisions for compliance monitoring, the collection and maintenance of information on projects involving animals and animal management practices and facilities, and allow the fair and prompt handlings of complaints from any member of the animal ethics committee. An institutional animal ethical committee (IAEC) must be established by an institution (or group of organizations) which has an approved code of ethical conduct.

A final report shall be prepared for each nonclinical laboratory study and shall include:

- Name and address of the facility performing the study and the dates on which the study was initiated and completed
- Objectives and procedures stated in the approved protocol, including any changes in the original protocol
- Statistical methods employed for analyzing the data
- The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics
- Stability of the test and control articles under the conditions of administration
- A description of the methods used
- A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and sub strain, age, and procedure used for identification
- A description of the dosage, dosage regimen, route of administration, and duration
- A description of all circumstances that may have affected the quality or integrity of the data
- The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study
- A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis
- The signed and dated reports of each of the individual scientists or other professionals involved in the study
- The locations where all specimens, raw data and the final report are to be stored
- A statement prepared and signed by the quality assurance unit and the final report signed and dated by the study director.

## Conclusion

Drug discovery and drug development is being revolutionized due to changes in technology. Technologies like genomics, proteomics, high throughput

screening and structure-based design have enabled the process of drug discovery to evolve into a system where new lead molecules can be rapidly found against novel, and difficult targets. Preclinical testing of pharmaceuticals in animals has been instrumental in the development of modern therapeutic regimens. Unquestionably, human quality of life (and life expectancy) has flourished as a result of preclinical testing of drugs in animals. However, drug development remains extremely challenging, with numerous obstacles to overcome. The transition from activity *in vitro* (cell culture) to activity *in vivo* (animal model) can be especially challenging. Obtaining pharmacokinetic behavior consistent with the desired reactivity can be very difficult and the use of animals in toxicity testing has not progressed without controversy. Objections to animal testing have emphasized that the results obtained from animal tests do not always correlate well with human experience.

Attrition rates remain high, and generally only one out of ten thousand drugs tested will enter clinical development and make it all the way to regulatory approval and find a place in the market. Drugs most frequently fail in the clinic because of poor pharmacokinetics or toxicity.

Despite the fact that drug development remains a long and arduous journey, the prospect of genome-targeted individualization of therapy remains an extremely exciting one. The possibility of personalized treatments ("right drug for the right patient") based on the genomic or proteomic readout of the particular patient is now becoming a reality.

It is envisaged that more and more strategic alliances will be formed between biotechnology and small pharmaceutical companies to make the most of all of the opportunities like human genome data.

During a new drug's early preclinical development, the sponsor's primary goal is to determine that the product is reasonably safe for initial use in humans and that compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system (Fig. 1.9).

Before the sponsor proceeds to study a new drug in human, approval has to be obtained by IND application.

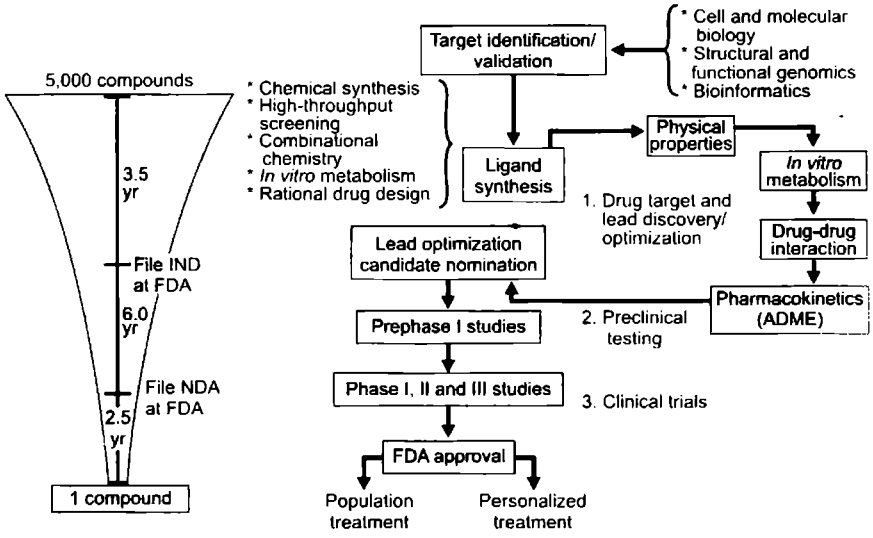



**Fig. 1.9:** The drug discovery process

## Investigational New Drug Application

An investigational new drug (IND) application is to provide the data showing that it is reasonable to begin tests of a new drug on humans. In many ways, the IND application is the result of a successful preclinical development program. The IND application is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials). Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND application is the means through which the sponsor technically obtains this exemption from the FDA. The IND application shows results of previous experiments, how, where and by whom the new studies will be conducted, the chemical structure of the compound; how the compound is manufactured and any toxic effects in the animal studies.

There are two IND application categories:

- Commercial
- Research (noncommercial).

There are three types of IND application:

- An *Investigator IND* application is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND application to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

- *Emergency Use IND* application allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND application. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND application.
- *Treatment IND* application is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place. A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. The purpose is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for treatment use during phase III investigations or after all clinical trials have been completed. In the case of an immediately life-threatening disease, a drug may be made available for treatment use earlier than phase III, but ordinarily not earlier than phase II.

The IND application must contain information in three broad areas:

- *Animal pharmacology and toxicology studies:* Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
- *Manufacturing information:* Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- *Clinical protocols and investigator information:* Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators who oversee the administration of the experimental compound—to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Sponsor files the IND application in Form 1571 to the FDA for review once successful series of preclinical studies are completed.

Along with the IND application, the sponsor submits the statement of the Investigator (Investigator's undertaking) in Form 1572.

Once the IND application is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. If the sponsor hears nothing from CDER (Center for Drug Evaluation and Research), then on Day 31 after submission of IND application, the study may proceed as submitted. The CDER is a division of the FDA that reviews *New Drug Applications* to ensure that the drugs are safe and effective.

During this time, FDA has an opportunity to review the IND application for safety to assure that research subjects will not be subjected to unreasonable risk.

- *Medical review:* During the IND application review process, the medical reviewer evaluates the clinical trial protocol to determine (i) if the participants will be protected from unnecessary risks; and (ii) if the study design will provide data relevant to the safety and effectiveness of the drug. Under Federal regulations, proposed phase I studies are evaluated almost exclusively for safety reasons. Since the late 1980s, FDA reviewers have been instructed to provide drug sponsors with greater freedom during phase I, as long as the investigations do not expose participants to undue risks. In evaluating phase II and III investigations, however, FDA reviewers also must ensure that these studies are of sufficient scientific quality to be capable of yielding data that can support marketing approval
- *Chemistry reviewers:* They address issues related to drug identity, manufacturing control and analysis. The reviewing chemist evaluates the manufacturing and processing procedures for a drug to ensure that the compound is adequately reproducible and stable. At the beginning of the Chemistry and Manufacturing section, the drug sponsor should state whether it believes the chemistry of either the drug substance or the drug product, or the manufacturing of either the drug substance or the drug product, present any signals of potential human risk. If so, these signals should be discussed, with steps proposed to monitor for such risks. In addition, sponsors should describe any chemistry and manufacturing differences between the drug product proposed for clinical use and the drug product used in the animal toxicology trials that formed the basis for the sponsor's conclusion that it was safe to proceed with the proposed clinical study
- *Pharmacology/toxicology review:* This team is staffed by pharmacologists and toxicologists who evaluate the results of animal testing and attempt to relate animal drug effects to potential effects in humans. This section of the application should contain, if known:
  - A description of the pharmacologic effects and mechanism(s) of action of the drug in animals
  - Information on the absorption, distribution, metabolism and excretion of the drug. The regulations do not further describe the presentation of these data, in contrast to the more detailed description of how to submit

toxicology data. A summary report, without individual animal records or individual study results, usually suffices. An integrated summary of the toxicology effects of the drug in animals and *in vitro* the particular studies needed depend on the nature of the drug and the phase of human investigation. When species specificity, immunogenicity, or other considerations appear to make many or all toxicological models irrelevant, sponsors are encouraged to contact the agency to discuss toxicological testing.

- *Statistical analysis:* The purpose of these evaluations is to give the medical officers a better idea of the power of the findings to be extrapolated to the larger patient population in the country
- *Safety review:* Following review of an initial IND application submission, CDER (Center for Drug Evaluation and Research) has 30-calendar-days in which to decide if a clinical hold is necessary (i.e. if patients would be at an unacceptable risk or if CDER doesn't have the data to make such a determination).

Generally, drug review divisions do not contact the sponsor if no concerns arise with drug safety and the proposed clinical trials. If the sponsor hears nothing from CDER, then on day 31 after submission of the IND application, the study may proceed as submitted. The sponsor is notified about the deficiencies through a clinical hold. A clinical hold is issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend a clinical investigation (Flow chart 1.1).

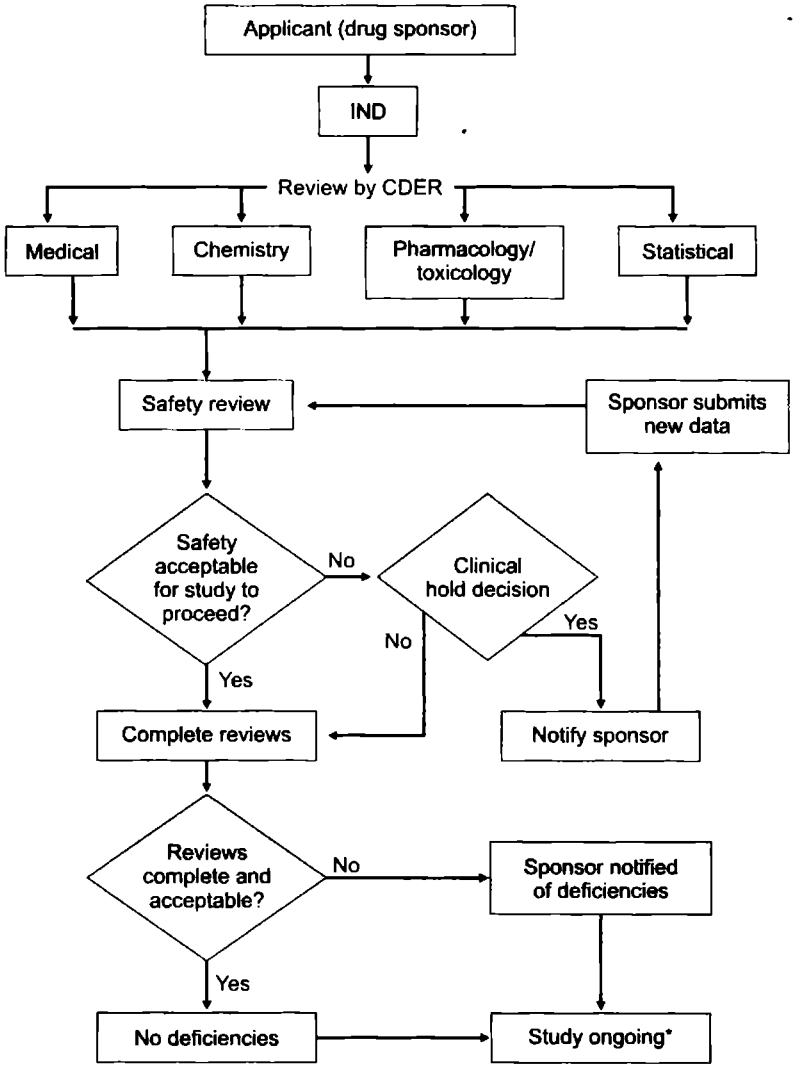
### Sponsor Notification

Once a clinical hold is placed on a commercial IND application, the sponsor will be notified immediately by telephone by the division director. For both individual and commercial IND applications, the division is required to send a letter within five working days following the telephone call. The letter should describe the reasons for the clinical hold and must bear the signature of the division director (or acting division director).

The grounds for imposition of clinical hold are as follows:

- Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury
- Clinical Investigators named in IND application are not qualified
- Investigator Brochure is misleading, erroneous or materially incomplete
- IND does not contain sufficient information to assess risks
- Protocol is deficient to meet objective of trial
- Mechanism that CDER uses when it does not believe, or cannot confirm that the study can be conducted
- CDER will contact sponsor within 30-day initial review period.

**Flow chart 1.1:** IND application review process




* While sponsor answers any deficiencies

The sponsor may then respond to CDER by sending an "IND CLINICAL HOLD RESPONSE" letter to the division. To expedite processing, the letter must be clearly identified as an "IND CLINICAL HOLD RESPONSE" letter.

The division then reviews the sponsor's response and decides within 30 days as to whether the hold should be lifted. If the division does not reply to the clinical hold response within 30 calendar days, the division director will telephone the sponsor and discuss what is being done to facilitate completion of the review.

If it is decided that the hold will not be lifted, the hold decision is automatically sent to the office director for review. The office director must decide within 14 calendar days whether or not to sustain the division's decision to maintain the clinical hold. If the decision is made to lift the hold, the division telephones the sponsor, informs them of the decision and sends a letter confirming that the hold has been lifted. The letter will be sent within 5 working days of the telephone call. However, the trial may begin once the decision has been relayed to the sponsor by telephone.

### *Sponsor will be Notified*

If other deficiencies are found in an IND application that the review division determines are not serious enough to justify delaying clinical studies, the division may either telephone or forward a deficiency letter to the sponsor. In either case, the division informs the sponsor that it may proceed with the planned clinical trials, but that additional information is necessary to complete or correct the IND application file.

### *Study Ongoing*

Once the CDER's 30-day initial review period expires, clinical studies can be initiated, unless a clinical hold has been placed. Beyond the 30-day review period for an IND application, subsequent clinical trials may begin immediately upon submission of the clinical protocol to the IND application (i.e. there is no 30-day waiting period for subsequent clinical trials after the submission of the first clinical trial protocol). If the sponsor was notified of deficiencies that were not serious enough to warrant a clinical hold, the sponsor addresses these deficiencies while the study proceeds.

## Exploratory IND Studies

Exploratory IND studies are intended to provide clinical information for a new drug candidate at a much earlier phase of drug development. These studies help to identify the best candidates for continued development and eliminate those lacking promise. These clinical trials occur very early in phase I, involve very limited human exposure and have no therapeutic intent. Exploratory IND studies are conducted prior to the traditional dose escalation, safety and tolerance studies and provide important information on pharmacokinetics (PK) and bioavailability of a candidate drug.

In April 2005, the FDA released a draft guidance for exploratory IND studies that clarifies preclinical and clinical approaches that should be considered when planning exploratory IND studies in humans. As part of FDA's "Critical Path Initiative", this process is a new tool available to the industry that enables a faster, more cost-effective path to early clinical development.

### *Microdosing (Phase 0 Clinical Trials)*

A primary application of an Exploratory IND study is microdosing or phase 0 clinical trials. Microdosing studies permit collection of human pharmacokinetic (PK) and bioavailability data earlier in the drug development process. This human data is combined with preclinical data to select the best candidates to advance to further, more expensive and extensive clinical development. Distinctive features of phase 0 trials include the administration of single sub-therapeutic doses of the study drug to a small number of subjects (10-15) to gather preliminary data on the agent's pharmacokinetics parameters such as clearance, volume of distribution, $t_{1/2}$ (half-life), etc.

A microdose is defined as less than 1/100th of the dose calculated to yield a pharmacological effect of a test substance and a maximum dose of ≤100 micrograms. Since microdosing studies are designed not to induce pharmacological effects, the potential risk to human subjects is very limited. Therefore, these studies can be initiated with less preclinical safety data (i.e. with single dose study/acute toxicity study), help reduce the number of human subjects needed and require fewer resources for selecting promising drugs candidates for further development.

Microdosing is dependent on the availability of ultrasensitive analytical methods able to measure drug and metabolite concentrations in the low pictogram to femtogram range. Nuclear physics has been applied to conduct analyses at these concentrations, *viz.* Accelerator Mass Spectrometry (AMS) and Positron Emission Tomography (PET). Both techniques rely on the analysis of radioisotopes incorporated into the drugs under study. In the case of AMS, [$^{14}$C] is the most useful isotope for drug metabolism studies whereas for PET [$^{11}$C] is proving to be the most useful isotope.

A typical human microdosing study involves the administration of microgram quantities of drug candidates, lightly-labelled with Carbon-14 ($^{14}$C), to healthy volunteers. Following collection of blood, urine and feces from each subject, samples are analyzed for $^{14}$C content using AMS to determine $C_{max}$, AUC and the terminal half-life of each compound (Fig. 1.10).

If, during the drug discovery process, a number of molecules are identified which have good pharmacological activity but similar or differing animal PK (pharmacokinetic), comparative human microdose studies can be conducted to establish human PK. Armed with this information, the human PK data can then be used to:

- Assist in the candidate selection process
- Determine the first dose for the subsequent phase I study on the selected candidate
- Establish the likely pharmacological dose.

### *Advantages of Microdosing*

- Select the best lead compound supported by clinical data
- Save time: Advance lead candidates to clinical development in months not years

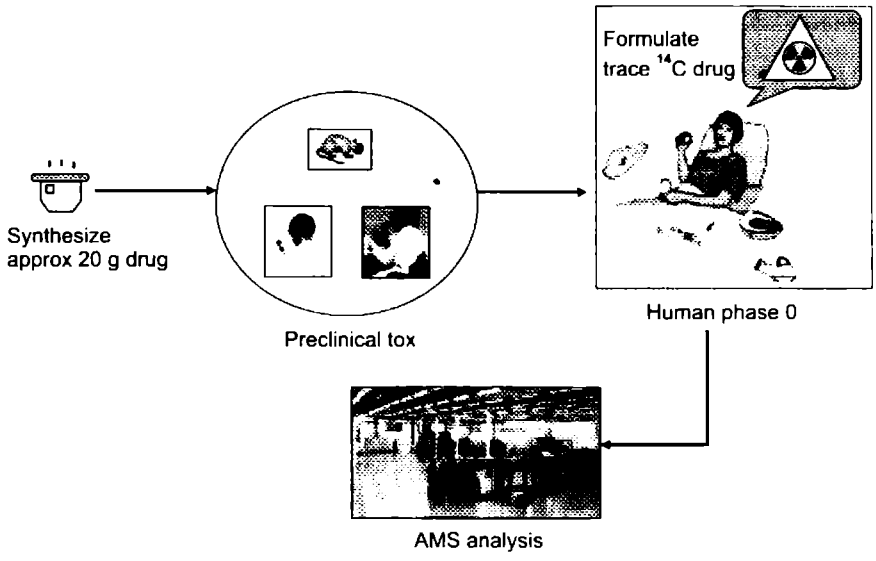



**Fig. 1.10:** Microdosing/phase 0 studies

- Save money: Significantly reduced IND submission requirements and costs
- Cost-effective approach to adding value to lead candidate or drug pipeline.

In conclusion, *Microdosing* is a technique for studying the behavior of compounds *in vivo* through the administration of doses so low they are unlikely to produce whole-body effects, but high enough to allow the cellular response to be studied. This works on the concept that the best model for man is man. This allows studying the pharmacokinetics of the drug with almost no risk of side effects.

Use of the technique has been provisionally endorsed by both the European Medicines Agency and the Food and Drug Administration. It is expected that by 2010, human microdosing will gain a secure foothold at the discovery-preclinical interface driven by early measurement of candidate drug behavior in humans and by irrefutable economic arguments.

## CLINICAL DEVELOPMENT

Clinical trial/study is any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

Clinical trials start after the completion of required preclinical studies and IND application has been filed to the concerned regulatory authority.

The objectives of clinical trials are:

- To identify the relationship between dose and plasma(or other) concentration—Pharmacokinetics
- To define the shape and location of the dose/concentration/response curves for both desired and undesired effects—preliminary assessments of benefit/risk
- On the basis of these curves, to identify the range of dosage/concentrations producing maximum benefit with fewest undesirable effects.

## Key Players in Clinical Research

Clinical research is an integral part of drug development. Unlike in the past, today the process has gained a unique position due to the regulatory requirements and ethical guidelines available globally. Thus designing, conducting, monitoring, appropriate quality assurance and data management determine the success of the clinical research.

Listed below are the players in clinical research who are responsible for these activities:

- Sponsor/clinical research organization
- Medical writing team
- Statistician
- Clinical research associate
- Principal investigator
- Clinical research coordinator
- Data management team
- Ethics committee
- Regulatory authority
- Data safety monitoring board
- Central laboratory.

### *Internal Key Players*

- *Sponsor:* An individual, organization or company, that is responsible for the initiation, management and/or financing of a clinical investigation.

  The sponsor is responsible for the development of the trial protocol and other study documents; selection of qualified investigators, sites and monitors; allocation of duties and responsibilities; study management, data handling and record keeping; supply, storage and handling of pharmaceutical product. It is also the sponsor's responsibility to provide all information needed to conduct investigation, ensure compliance with regulations, inform regulatory authority regarding adverse events and safety reporting, perform data analysis, report findings and submit the IND to the regulatory authority.

- *Contract research organization (CRO):* An organization which is contracted by a sponsor to perform any or all of the activities normally done by the sponsor. The sponsor is required to describe in writing exact responsibilities and obligations transferring to CRO.
- *Medical writing team:* This team is involved in preparing various documents related to clinical trial, viz. protocol, investigator's brochure, clinical study report.
- *Statistician:* The statistician is responsible for activities such as determination of sample size, study design, randomization and analysis of data.
- *Clinical research associate (CRA):* CRA is an individual who works for the sponsor or a CRO. The CRA is responsible for the overall monitoring of the clinical trial at the trial site. The responsibilities of a CRA include evaluation of a site and initiation of the trial; he/she should ensure that regulatory requirements are met and that site personnel are qualified, trained and aware of their obligations. The CRA should monitor data and verify source records or in other words the CRA should oversee the progress of the study at site level.
- *Principal investigator (PI):* According to the FDA, principal investigators should be "qualified by training and experience to be appropriate to serve as PI for a trial". The PI is the individual who conducts, supervises and is responsible for all aspects of a clinical trial. It is the responsibility of the investigator to ensure that regulatory, GCP compliance is maintained during trial conduct. PIs are also involved in the formulation of a recruitment plan, evaluation and treatment of research subjects. The PI should supervise the medical staff participating in the study and perform timely review of all clinical and laboratory data. One of the most important responsibilities of PIs is to ensure proper reporting of all adverse events that takes place.
- *Clinical research coordinator (CRC):* The CRC is a vital link between the all players and the trial site. CRC is placed at the clinical trial site and works directly under trial investigator. The CRC is responsible for coordinating all aspects of the clinical trial and day-to-day operations of the research program.

  The CRC should perform a protocol assessment and maintain adherence to the protocol and document breaches or violations and communicate the same with sponsor and the ethics committee. The CRC should help develop and maintain the study source documents at the trial site. He/she should also document all written and phone correspondence with sponsor, labs, IRB, other regulatory organizations.
- *Data management team:* The data management team is responsible in the management of trial related data obtained from investigative site. Data management related activities include inputs during CRF (case report form) designing, data acquisition, validation, coding, integration and quality assurance.

### External Key Players

For a new drug/device/biologics to be tested in humans, approval from Ethics committee and regulatory authority is required.

*Ethics committee—Institutional Review Board (IRB) or Independent Ethics Committee (IEC):* IRB/IEC is a specially constituted board established to protect rights, safety and well-being of human subjects by providing review and oversight. The ethics committee may be a part of an institution or an independent board. The ethics committee should obtain and review trial documents such as the trial protocol, informed consent document, investigator's brochure, etc.

*Regulatory authority/Licensing authority:* The regulatory authority of each country is responsible for review and approval of drug applications (IND/NDA), dissemination of safety information and conducting audits or inspections of any sector of clinical research including sites, sponsors, or IRBs.

Table 1.2 shows regulatory authorities responsible for approving drug applications of a few countries.

*Data Safety Monitoring Boards (DSMB):* An independent committee, composed of community representatives and clinical research experts, which reviews data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. DSMBs are needed when interim analyses of safety and efficacy are considered essential to ensure the safety of trial participants. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved.

### External Key Players—Others

*Central laboratory:* Instead of using small, localized laboratory facilities or multiple specialty laboratories for multicentric trials, a central laboratory is used to avoid data errors, lengthened study timelines and increased study

**Table 1.2:** Regulatory authorities

| *Countries* | *Regulatory authorities* |
|---|---|
| India | DCGI (Drug Controller General of India) |
| USA | FDA (Food and Drug Administration) |
| European Union | EMEA ( European Medicines Agency) |
| United Kingdom | MHRA (Medicines and Healthcare products Regulatory Agency) |
| Australia | TGA ( Therapeutic Goods Administration) |
| Canada | Health Canada |
| Japan | MHLW (Ministry of Health, Labor and Welfare) |
| China | Ministry of Health of the People's Republic of China |

costs. The concept of a central laboratory is based on the need for homogenous data integration to improve submission quality and reduce the timelines for data submissions. Central laboratories accomplish this by combining the use of high throughput technology with efficient internal systems that make for quick and more combinable collection of lab data.

## Clinical Trial Design

Clinical trial may fail to achieve its aim without a good design. Before a clinical trial may proceed, it will undergo numerous reviews that will include a review of the trial design and applicability of the design to the situation. A good trial design will ensure that the trial is given approval to proceed from regulatory agencies, from ethics committees and from the investigator. A good design will ensure that the trial set-up is achievable, that the investigator will recruit subjects and that the trial will be completed—all within the target timescale. The design of any given clinical trial will depend on many factors. The fundamental factor contributing to the design is the disease for which is drug is to be tested (Target indication). The target indication will influence the objectives of the trial, the options for clinical measurement and the circumstances under which the trial should be carried out.

### *Elements to be Considered During Clinical Trial Design*

*Types of control:* The purpose of the control group is to provide a yardstick against which to measure the efficacy and safety of the drug under investigation and the control may be an untreated group or a group receiving an active treatment or a placebo.

The choice of the comparator is influenced by objective of the study. In cases where efficacy has not yet established (phase I and phase II) it may be that a placebo is the most appropriate comparator. Assuming that the compound has been shown to possess efficacy, the objectives of later studies (phase III onwards) will be to compare the extent of efficacy and safety with that of currently used therapies.

*Volunteer/subjects selection:* It is important to carefully define the patient population from which the study participants will be drawn. In early phase II, the entry criteria for a study may be restrictive and throughout the development program these criteria will evolve as the drug's characteristics are discovered. For example, phase I trials will have healthy volunteers probably with a restricted age range, usually between 18 and 45 years. By the end of phase III the studies should include a population that is representative of the wider patient population who will potentially receive the licensed drug.

*Number of subjects:* The size of a trial is influenced by the disease to be investigated, the objective of the study and the study endpoints.
Statistical assessments of sample size should be based on:

- The expected magnitude of the treatment effect
- The variability of the data

- The specified (small) probability of error
- The desire for information or subsets of the population or secondary endpoints.

*Influence of disease indication on trial design:* The onset and progression of the disease will affect the duration of the trial, the timing of each subject's treatment and the number and timing of assessments.

Acute conditions will require short treatment period and as these types of disease remit spontaneously within certain time, subjects should be entered into the study within one day of onset and assessment to be carried out more frequently to detect early signs of efficacy.

In chronic diseases, signs and symptoms of the disease will be stable for longer periods dictating study of six months or more duration, with monthly assessments carried out for efficacy.

*Randomization:* Randomization is a process that assigns research participants by chance, rather than by choice, to either the investigational group or the control group. In conducting a controlled trial, randomized allocation is the preferred means of assuring comparability of test groups and minimizing the possibility of selection bias. Randomization is done using a computer generated random number table (Fig. 1.11).

Randomization can be simple randomization or stratified randomization. Stratified randomization (stratification) is used when there are differences in the nature of the disease in severity or site and responses to treatment might differ due to this. For example, in analgesic trial, subjects can be stratified according to pain severity into mild, moderate and severe, where the response might differ. Each stratum can be analyzed separately, if required.

### Blinding

Blinding is an important means of reducing the risk of biased study outcomes. A trial where the treatment assignment is not known by the study participant is

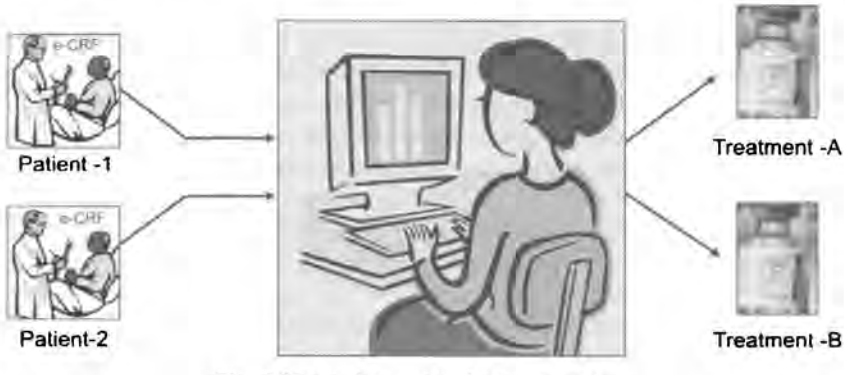



**Fig. 1.11:** Depicts randomization procedure

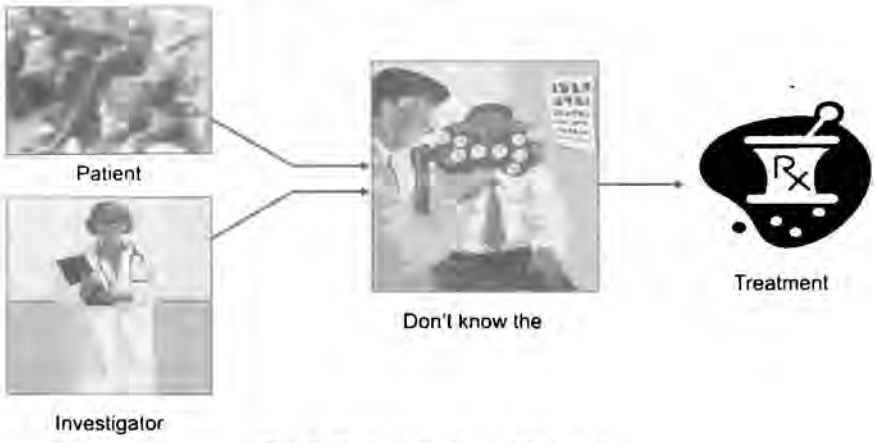



**Fig. 1.12:** Depicts double-blind study

known as single blind study. When both investigator and study participants are unaware of the treatment assignments, the study is double blind. When investigator, study participants and the sponsor staff are unaware of the treatment assignment, study is referred to as triple blind. Studies that do not utilize blinding are referred to as open label studies. Thus, all those concerned with trial are aware of the identity of the investigational medicinal product (Fig. 1.12).

It is essential to maintain blinding throughout the trial to maintain the validity of the trial data. During each monitoring visit, the monitor will verify the maintenance of blind. However, there may be a need for the investigator to know the identity of drugs administered, e.g. during emergency due to adverse event. In such a case, contingency should be provided to know the treatment by unblinding for that specific subject. Another example of requirement of contingency is, in the event of failure of effect (e.g. increased pain); in such a case rescue medication should be specified that is known not to interact with either of the blinded treatments, to avoid breaking the blind.

*Types of trial design:* An appropriate study design should be chosen to provide the desired information in a research study. Examples of study design include parallel group, crossover, factorial and dose escalation.

The most frequently used designs are: Parallel study and cross-over study.

In a parallel study, each subject is assigned to receive one or other treatment and subjects are studied 'in parallel'. In a crossover study each subject will receive a course of each of the treatments under study (Figs 1.13 and 1.14).

The choice of one of these two designs over the other demands careful consideration. Crossover design may be helpful in identifying which treatment is best for a particular patient as each subject acts as his/her own control. However, results from this may not be extrapolated to general population. The choice of comparator for a crossover study must be made carefully to prevent drug interaction and sufficient washout period should be given between two treatment periods so as to avoid carry-over effect of


**Fig. 1.13:** Depicts parallel study


**Fig. 1.14:** Depicts Crossover study

previous treatment. The crossover design will clearly necessitate more subject visits, thus probability of subject dropping out or even not entering into trial increases. The crossover design is appropriate for less prevalent disease, as number of subjects required in crossover design is relatively less and for relatively stable disease, e.g. hypertension.

*Factorial:* When patients are being treated with a combination of drugs, as is current practice for HIV infection, a new drug may be evaluated by testing it in combination with other drugs rather than by itself. A factorial design trial may be used for this purpose. A simple factorial design would have one group testing therapy A, another testing therapy B, a third group testing A and B combined and a control group testing neither A nor B. Factorial designs are considered an efficient way to test medicines in combination.

*Dose escalation:* Also referred to as dose ranging design. The main goal of a dose escalation study is to estimate the response vs. dose given, so as to analyze the efficacy and safety of a drug. Thus, in a dose escalation study, different doses of a drug are tested against each other to establish which dose works best or is least harmful. Dose ranging design is usually chosen for a phase I or early phase II clinical trial. Typically, a dose ranging study,

will include a placebo group of subjects and a few groups that receive different doses of the test drug. Information on the maximum tolerated dose is required to design the groups in a dose escalation study. Therefore, this type of study is usually designed after the availability of maximum tolerated dose information.

*Duration of dosing:* Duration of dosing is determined by factors like pharmacokinetics, mode of action and natural history of the disease being treated. In early phase II clinical trial, available toxicology data may support only a limited duration of dosing. A drug development program will include substantial chronic animal toxicology studies running in parallel with the clinical phases and results from these studies may extend the permissible duration of dosing as they become available.

*Methods of clinical measurement:* The assessment method must be standardized so that results from all subjects can be pooled from all centers and therefore the protocol should describe in depth method of assessments and at what time interval these assessments should be made, to obtain uniformity between centers.

The method chosen must be validated for accuracy and reproducibility. For a quantitative measurement such as blood pressure, the use of standardized equipment, e.g. the sphygmomanometer, is clearly most appropriate. For an assessment of subjective parameter, validated rating scale should be used, e.g. Hamilton Depression Rating Scale for depression.

The timing and circumstances of the assessment should be standardized. Even the quantitative measurement such as blood pressure will be influenced unless a standard procedure is specified. For example, the subject should be sitting for 10 minutes before two blood pressure readings and the mean will be used for analysis. Additionally, the time of day for the measurement may be standardized to avoid diurnal variation.

In summary, elements such as comparator, disease under study, patient population, randomization and blinding, duration of dosing and methods of clinical measurement should be considered while designing clinical study.

## Essential Documents

Essential documents are those documents that individually and collectively evaluate the conduct of a trial and the quality of the data produced. These documents demonstrate the compliance of the investigator and sponsor with the standards of Good Clinical Practice (GCP) and all applicable regulatory requirements.

The GCP guidelines lists essential documents required for a clinical trial. The documents are grouped in three sections according to the stage of the trial:

1. Before the clinical phase of the trial commences
2. During the clinical conduct of the trial
3. After completion or termination of the trial.

### Before the Clinical Phase of the Trial Commences

- *Signed and dated protocol:* A document that describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial
- *Protocol amendments:* The changes in terms of updates or clarifications made in the protocol
- *Sample patient information sheet and informed consent form:* This document provides the subjects with necessary details to participate in the study and their willingness is recorded by means of signing the document
- *Investigator's Brochure:* The IB contains both clinical and nonclinical data pertaining to the description of new drug
- *Sample CRF:* Case report form is the tool (a paper or electronic questionnaire) used by the sponsor of the clinical trial to collect data from each participating trial site
- *Advertisement for subject recruitment (if used):* The advertisement is the proposed method of subject recruitment for the trial. It contains a brief description of the study
- *Financial agreement (where required):* An agreement between the parties who are involved in conducting the clinical trial
- *Insurance/letter of indemnity (where required):* Insurance or a letter guaranteeing that contractual provisions will be met, otherwise financial reparations will be made
- *Research agreement (where required):* Agreement for the research/study to be conducted between the key players who are involved in the trial
- *Communication with sponsor/IRB:* The communication between IRB (Institutional Review Board) and the sponsor should be done before commencing the trial
- *IRB approval:* The IRB or the Ethics Committee is the independent body who approves the trial documents (protocol, CRF, ICF, etc.)
- *IRB composition (if not specified in IRB letter of approval):* Documents containing the information of the details of the ethics committee quorum, name and designations of the ethics committee members
- *Investigators' CVs—signed personally and dated:* The monitor should collect the Curriculum Vitae of the investigator(s) involved in conducting the trial and present to the regulatory body concerned with the trial
- *Signature sheet and authorization sheet:* This document contains the names and signatures of those who are authorized to make changes to the trial documents
- *Reference range of local labs and updates when applicable:* This document will contain the reference (normal) range for various tests which are specific for the instruments available at each lab
- *Certification/accreditation of local lab:* Accreditation/Certification is a process in which the competency, authority or credibility of a laboratory is presented. The accreditation must be a current one. The accreditation

of testing laboratories and certification specialists are permitted to issue official certificates of compliance with established standards, such as physical, chemical, forensic, quality and security standards

- *Study procedures (Site SOPs):* They provide a written set of instructions documenting (normally in a step by step manner) how a procedure should be performed
- *Shipping records for investigational product (IP):* A record or a log is maintained for the shipping/distribution of the IP at various sites where the trial is conducted
- Sample of IP label
- *Sealed envelope of treatment code:* The treatment code is kept in a sealed envelop and should be duly checked by trial monitor for any tampering with the seal that might occur leading to unfair conduct of the trial. This envelope can be opened in case of an emergency
- *Emergency unblinding procedures (if not already described in protocol):* Emergency unblinding/decoding procedure is carried out by the investigator referring the "Treatment decoding log" depending on the occurrence of the serious adverse events during a trial
- *Treatment decoding log (emergency unblinding):* A record, "Treatment decoding log", for the decoding of the code assigned to the subjects in a trial is always kept ready for emergency situation which may arise during a trial
- *Study initiation report:* The study initiation report should be prepared by the monitor after the initiation of a study at a site.

### *During the Clinical Conduct of the Trial*

In addition to all documents listed above, the following documents are also required during the conduct of the trial:

- *Previously-mentioned document:* All previously-mentioned document updates checked before the clinical phase of the trial commences
- *Monitoring visit report:* A written report from the monitor to the sponsor after each site visit. It contains all trial related communications according to the sponsor's SOP
- *Signed and dated informed consent forms:* The informed consent obtained in a form from the subjects should be duly signed and dated by the investigator as well as the patient
- *Source documents:* Original documents, data and records (e.g. hospital records, laboratory notes, subjects' diaries, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, photographic negatives, magnetic media, X-rays and records kept at the pharmacy, laboratories and at medico-technical departments, etc. which are involved in the clinical trial)
- *Signed, dated and completed CRF copy:* The copy of a signed, dated and completely filled case report form (CRF) is also required during the conduct of the trial

- *Documentation of CRF correction:* A documentation of the corrected CRF is required to be maintained if the CRF has undergone correction
- *AE and SAE report:* A report containing all the adverse events and serious adverse events prepared by the investigator should be maintained and presented to the sponsor and the ethics committee/IRB (Investigational Review Board)
- *Sponsor's safety update:* It is a document which provides regular and timely review, appraisal of safety information. Communication of this information is critical to risk management during clinical development of drugs
- *Interim/progress report to IRB/IEC:* It is the progress report of the intermediate results and the evaluation based on analysis performed during the course of a trial
- *Subject screening log/screen failure log:* It will contain all the details of the subjects who have been screened. This log will also contain information regarding the subjects who did not meet the eligibility criteria (Screen Failure Log)
- *Patient identification list:* A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data
- *Subject enrolment log:* This record is maintained to document the identification of the subject who has been enrolled in the trial
- *IP accountability log:* The investigational product usage/accountability should be recorded and maintained properly at the site of the trial conduction
- *Record of retained body fluids/tissue sample:* To document location and identification of retained samples if tests need to be repeated.

### *Completion or Termination of the Trial*

In addition to all documents listed above, the following documents are also required during the conduct of the trial:

- *Audit certificate (if available):* A declaration of confirmation by the auditor that an audit has taken place
- *Documentation of IP destruction:* The accountability of the investigational product (IP) usage is recorded and the left out IP is either returned to the sponsor or destroyed at the site and the process is recorded or documented
- *Study close-out report:* The study close-out report is prepared by the study monitor after the completion of the trial
- *Final report by investigators to IRB:* The investigator prepares the final report to be given to the concerned regulatory body (IRB) involved the trial informing the closing of the trial
- *Clinical study report:* A written description of a trial/study of any therapeutic, prophylactic or diagnostic agent conducted in human

subjects, in which the clinical and statistical description, presentations and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

## Phases of Clinical Trials

- Phase I: Human pharmacology
- Phase II: Therapeutic exploration
- Phase III: Therapeutic confirmation
- Phase IV: Postmarketing studies.

### *Phase I Clinical Trial*

Phase I trials are the first stage of testing in human subjects. phase I studies are also known as Human Pharmacology studies. Normally, a small (20-80) group of healthy volunteers will be selected to participate in these studies. This phase includes trials designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of a drug. Volunteers are paid an inconvenience fee for their time spent in the volunteer center.

*Objectives of phase I studies*

- Safety and tolerability—maximum tolerated dose (the highest dose of a drug that does not cause overt toxicity in humans)
- Pharmacokinetics
- Pharmacodynamics.

*Prerequisites for phase I trials*

- *Preclinical safety data:* Animal toxicity which needs to be completed before start of phase I studies are—single dose toxicity studies, repeated dose, safety pharmacology studies, local tolerance studies, pharmacokinetic studies, mutagenicity studies (*in vitro*), male reproductive system studies
- *Regulatory authority and ethics committee approval:* Ethics committee approval is essential since healthy volunteers are included as subjects in this phase.

*Conduct of the trial*

- *Site:* These trials are often conducted in a specialized inpatient setting called as clinical pharmacological unit/clinical trial unit, where the subject can be observed by full-time staff. The study site should be equipped to monitor all physiological functions, facilities to handle an emergency or a serious unexpected adverse event, facilities for processing blood/plasma, etc. and facilities for estimation of drug levels in biological fluids (Fig. 1.15).

*Players*

- *Investigator:* usually conducted by clinical pharmacologist. The medical staff, paramedical staff should be qualified, skilled to handle emergencies; should be trained in basic life support and also advanced life support
- *Subjects:* Generally healthy volunteer, sometimes patients can be included.

**Fig. 1.15:** Depicts an ideal site for conducting phase I studies
*(For color version, see Plate 3)*

WHO defines healthy subject as 'a person who is free from any abnormality that would complicate interpretation of data or increase the sensitivity of the subject to toxic potential of a drug.' A summary of the main points raised in favor of healthy volunteers is as follows:

1. *Scientific benefits:* In healthy volunteers there are no hurdles such as the unknown parameters of disease condition and concomitant medication.
2. *Practical benefits:* In healthy volunteers, physiological processes are well understood and years of experience in terms of phase I trials has established a strong infrastructure focused on facilities and healthy volunteer databases.
3. *Regulatory benefits:* In terms of regulatory benefits, guidance is well established and dialogue with regulators is simpler.

Healthy volunteer studies are well understood and can act as a reference point to gain an understanding of a test compound.

There are a number of advantages for using healthy volunteers in early phase clinical trials and such studies can often provide excellent data, more quickly and at a lower cost. Healthy volunteers are more accessible, do not have diseases or take medication that needs to be considered and can remain eligible for similar studies in the future. In patient groups, the disease may not be stable over time, there is a spectrum of disease ranging from mild to severe, they are a less accessible group and most patients would prefer to obtain therapeutic benefit which is not normally anticipated in phase I studies. It can also take months to recruit sufficient patients with specific indications. In healthy volunteers, physiological processes are well understood. Healthy volunteers also show an increased acceptance of

frequent or complex sampling as well as stricter controls such as diet and activities and there is a lower drop-out rate as compared to patient groups. Although, not a normal practice, individuals with mild but stable illness, such as hypertension or arthritis, could be considered for phase I studies considering USFDA definition of "normal subject". FDA has defined normal subjects as those "individuals who are free from abnormalities which could complicate the interpretation of the data from the experiment or which might increase the sensitivity of the subject to the toxic potential of the drug". Thus, according to FDA definition, subject/volunteers with mild stable illness are considered healthy if they do not have disease for which drug is being tested and the existing does not complicate with interpretation of data.

For certain disease conditions such as HIV or cancer, real patients who have end-stage disease and lack other treatment options can be included in phase I trials. Also for oncology or HIV trials, inclusion of healthy volunteers is ethically not acceptable, as these drugs are known to have toxic effects.

*Design of phase I studies*

- *Type of control:* Phase I studies generally have placebo as control. Placebo as control is needed to determine variation in adverse event, laboratory value whether due to investigational agent or other influencing factor like—subject psychology (many subjects feel, since they are taking medication they should show some adverse effect), environment (light, temperature, diet, caffeine) and to evaluate common placebo symptoms like headache, dry throat, lethargy, etc.
- *Subject selection:* The healthy subjects are generally recruited based on the following—

  *Inclusion criteria:*
  - Healthy subjects
  - No clinically important abnormal physical findings.
  - Normal clinically acceptable ECG, normal BP/heart rate.
  - Body Mass Index—19 to 29 $kg/m^2$
  - Able to communicate
  - Competent and willing to give informed consent.

  *Exclusion Criteria:*
  - The subjects who have taken investigational drug in 0 to 45 days from the start of study
  - The subjects who have taken any prescribed medicine for 0 to 30 days/ any over-the-counter drugs (0-5 days) from the start of study
  - The subjects who have donated or lost blood, 0 to 12 weeks from the start of study
  - Subjects who are unable to communicate
  - Subjects who are chronic alcoholics and smokers
  - Female subjects especially if pregnant or at risk of pregnancy or lactating

  - Subjects suffering from asthma, neurological, neuromuscular, renal, cardiac, hepatic or psychiatric diseases
  - Subjects who are hypersensitive to drugs
- *Randomization and blinding:* The allocation of subjects to either group is determined by a formal randomization procedure. The level of blinding could be either open labeled, single blinded or double blinded
- *Type of trial design:* Either the parallel or crossover design is used in phase I studies. However, crossover designs are less commonly used, due to carryover effect and need for washout period
- *Dosing:* The first dose to be administered in humans needs to be estimated to safeguard the safety of the volunteers. All available information has to be taken into consideration for the dose selection and this has to be made on a case-by-case basis.

*Estimation of the first dose in humans:* The starting dose will be determined on the basis of data from animals (two species), in particular, NOAEL (No observed adverse effect level) is the highest dose level of drug which does not produce a significant increase in adverse effects). It is determined in nonclinical safety studies performed in the most sensitive and relevant animal species, adjusted with allometric factors (various conversion steps to calculate first human dose, given by FDA) or on the basis of pharmacokinetics which gives the most important information. The relevant dose is then reduced/adjusted by appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials.

For high-risk medicinal products, an additional approach to dose calculation should be taken. The use of 'minimal anticipated biological effect level' (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans. Safety factors are usually applied for the calculation of the first dose in man from MABEL.

The calculation of MABEL should utilize all relevant *in vitro* and *in vivo* available information from pharmacodynamic/pharmacokinetic data such as:

- Receptor binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal(s) species and *in vivo* in the relevant animal species
- Concentration-response curves *in vitro* in target cells from human and the relevant animal(s) species and dose response *in vivo* in the relevant animal species
- Exposures at pharmacological doses in the relevant species
- When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest dose should be used.

*Dose escalation scheme:* Phase I trials include dose-ranging, also called dose escalation studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing.

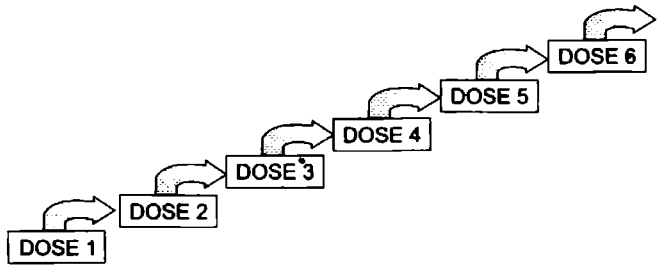



**Fig. 1.16:** Single ascending dose (SAD)

The dose ranging studies in phase I studies include—Single ascending dose and multiple ascending dose ranging studies.

- *Single ascending dose (SAD) studies:* Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. The dose that is considered to be safe is about 1 to 2 percent of the maximum tolerated dose in animals (Fig. 1.16).

  *Procedure:*

  The subjects are screened and selected based on the inclusion/exclusion criteria. The subjects are then hospitalized, their blood and urine samples are analyzed before drug dosing. The samples obtained before dosing are referred to as trough samples. Once the subjects are dosed with the drug, the blood and urine samples are analyzed every four hours from their first dose. ECG is to be monitored for the initial 4 to 6 hours from the first dose administered. Dosing should be done at the same time for each dose increment. The final samples are collected 24 to 48 hours after dosing. The subject's posture should be standardized. The subjects before being discharged would be physically examined, ECGs repeated, blood and urine samples analyzed and asked to report for follow-up after a period of 4 to 7 days from their first dose. If they do not exhibit any adverseside effects and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated and a new group of subjects is then given a higher dose. This is continued until precalculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the maximum tolerated dose)
- *Multiple ascending dose (MAD) studies:* Multiple ascending dose studies start after a successful SAD result is obtained. These studies are done for a period of 14 days; however the time period can vary, some drugs can be tested for a period of 5 days or for 4 weeks depending on the indication of use. The interval between doses would be one half-life.

  *Procedure:*

  The screening and selection of subjects is done based on the inclusion/exclusion criteria and tests conducted are similar to the SAD, but the trough

sample has to be analyzed before the next dose is to be administered. Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics and pharmacodynamics of multiple doses of the drug. In these studies, a group of patients receives multiple low doses of the drug, whilst samples (of blood and other fluids) are collected at various time points and analyzed to understand how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level.

*Pharmacokinetic/Pharmacodynamics:* Clinical pharmacokinetics and pharmacodynamics are indispensable source of information for drug development.

Pharmacokinetics, the study of drug disposition in the body, is an integral part of drug development and rational use. Knowledge and application of pharmacokinetic principles leads to accelerated drug development, cost effective drug use and a reduced frequency of adverse effects and drug interactions. They are essential to establish therapeutic schedules, to evaluate their relevance or to proceed to dosage adjustments in particular patients. This particularly applies to medicinal products with a narrow therapeutic range and to those for which a close relation between plasma concentrations and therapeutic and/or toxic effects can be demonstrated or expected.

In some instances, pharmacokinetic studies may be impossible or limited, e.g. where their provision raises insuperable difficulties or would create risks for test subjects; in these cases, the use of medicinal product is partly or completely based upon pharmacodynamic and clinical studies.

This consists of two sections:

*Pharmacokinetic factors to be studied which deal with:*

- Absorption
- Distribution
- Metabolism
- Elimination, as well as with interactions and adverse reactions.

*Methodology and conditions of study which deals with:*

- Choice of administration (route, dosage, dosage intervals)
- Choice of subject (healthy volunteers, patients with relevant disorders, patients with other interfering conditions)
- Choice of methodology (sampling and analysis, data processing and statistics).

A precise pharmacokinetic analysis of the entire plasma profile, including absorption, distribution and elimination, should be given since these various steps may be interrelated to a great extent. This applies particularly to special dosage forms for which delayed release of the active substance or a prolonged duration of action is claimed. Failing this, at least data on substance concentration at peak ($C_{max}$), time to reach peak ($T_{max}$) and area under the concentration/time curve (AUC) should be provided.

The elimination rate for the parent compound (e.g. total body clearance, elimination half-life) should be studied in volunteers with normal elimination mechanisms. The nature of the main routes of elimination and their relative importance in regard to total elimination should be known.

The pharmacokinetic parameters of most drugs are not expected to change when different doses are administered or when the drug is given through different routes of administration or as single or multiple doses. However, for some drugs the pharmacokinetic parameters change. Hence, in such cases it is essential to determine the nonlinear kinetic properties (i.e. properties that change based on the dose of the drug) of drugs.

Pharmacodynamic studies are done to measure drug concentration related to response: dose-response relationship and also to get an idea of dosage and dosage regimen.

The procedure for conducting phase I studies would be:

- Subject recruitment
- Informed consent
- Screening
- Recording baseline parameters
- Drug administration
- Blood sampling
- Recording post-treatment parameters
- Analysis of biological samples (blood) for drug levels
- Data collection, data analysis, statistical analysis and report generation.

*Outcome from phase I studies:* At the end of phase I studies the sponsor should be ready with:

- Safe dose range (the range which indicates the amount of drug that may be prescribed safely within the framework of usual medicine practice)
- Bioavailability data depending on $C_{max}$ (the maximum concentration of a drug in the body after dosing), $T_{max}$ (the time taken to reach maximum concentration), AUC (area under curve) is a mathematical calculation to evaluate the body's total exposure over time to a given drug. AUCs are used as a guide for dosing schedules and to compare the different drugs' availability in the body), the half-life, metabolic pathway of the drug, metabolites, the route and rate of excretion (Fig. 1.17)
- Nature of adverse drug reactions
- Secondary objectives like drug activity, potential therapeutic benefits.

### *Phase I in India*

Schedule Y requirements to conduct phase I in India:

- Phase I clinical trials are done to determine the maximum tolerated dose in humans; pharmacodynamic effects; adverse reactions, if any, with their nature and intensity; as well as the pharmacokinetic properties of the drug

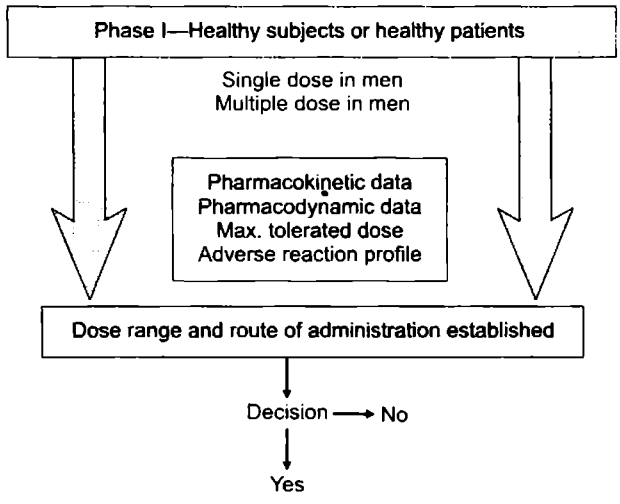



**Fig. 1.17:** Phase I

- At least 2 subjects should be used for each dose. These studies may be carried out in one or two centers
- According to the proposed changes of Schedule Y; apart from Indian companies, foreign companies that share intellectual property rights with an Indian based pharmaceutical company can conduct phase I trials for a new drug.

*Advantages and challenges in conducting phase I clinical trial*
*Advantages:*

- Pharmacokinetic, pharmacodynamic and safety profile of a drug is obtained.

*Challenges:*

- Ethical issues arise due to the inclusion of healthy volunteers as study subjects
- Stringent monitoring of the subjects is required, as it is the first time humans are exposed to the new drug and unexpected drug reactions can occur.

### *Phase II Clinical Trials*

Once the initial safety of the study drug has been confirmed in phase I trials, phase II trials are performed to assess how well the drug works (efficacy), as well as to continue phase I safety assessments in a large group (20-300) of patient volunteers. When the development process for a new drug fails, it is usually during phase II trials when the drug candidate does not work as intended, or has toxic effects. If the failure is due to the toxic effects of the drug, the development of the drug is abandoned. On the other hand, if the

failure is associated with efficacy, the sponsor (R & D department) will perform further research (formulation and basic molecular research) to analyze the unfavorable effects of the drug. The sponsor can reinitiate the trial (from phase I) for the modified drug molecule.

*Objectives of phase II clinical studies:*

- To explore the therapeutic efficacy and safety of the new medicinal product
- Aim at identifying the side effects most commonly associated with the new medicinal product
- Provide essential risk benefit assessment before more new patients are exposed to the new drug.

  Additional objectives are:
  - Evaluation of potential end points
  - Therapeutic regimens
  - Target populations for further studies in phases II and III.

*Prerequisites for phase II trials:*

- *Preclinical safety data:* Animal toxicity which needs to be completed before start of phase II studies along with those completed before phase I are—repeated dose toxicity studies in two species for a period of time equivalent to length of phase II studies, pharmacokinetic studies, mutagenicity studies (*in vitro* and *in vivo*)
- *Early phase clinical trial data:* Outcome of phase I studies (preliminary safety)—generally well tolerated, no significant adverse events
- *Regulatory authority and ethics committee approval.*

*Types of phase II trial:* Phase II studies are sometimes divided into phase IIA and phase IIB. Early phase II trials use a dosage that has been observed to be safe in phase I trials to investigate the pharmacological effects of the new medicinal product and to establish if this is a therapeutically useful intervention or not and may involve only single doses of the drug. Later phase II trials are conducted in patients to establish a safe dose regimen.

Some trials combine phase I and phase II and test both efficacy and toxicity.

*Conduct of the phase II trial and players in phase II:*

- *Site:* Phase II studies are conducted in specialized hospital units and are closely monitored by trained investigator. There should be standard facilities to handle an emergency or a serious unexpected adverse event at the site .The medical staff, paramedical staff should be qualified, skilled to handle emergencies; should be trained in basic life support and also advanced life support. Phase IIa studies are conducted in single site but phase IIb studies are conducted at more than one center hence they are also known as multicentric studies
- *Subjects:* In phase II studies around 50 to 300 participants who are patients will be administered the investigational new drug. Phase II is usually the first time that patients rather than healthy volunteers are exposed to the new drug.

*Trial design:* Some phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other phase II trials are designed as randomized controlled clinical trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized phase II trials have far fewer patients than randomized phase III trials (as it is the first time patients are exposed to new drug in phase II, inclusion criteria will be narrow/stringent, thus the available patient pool meeting this stringent inclusion criteria will be less).

Phase IIa design components are pilot, single centric, open labeled studies conducted on small number of homogenous group of patients. Phase II A is specifically designed to asses dosing regimens, i.e. how much drug should be given.

'Pilot studies' refers to a smaller version of a larger study. Conducting a pilot study does not guarantee success in the main study, but it does increase the likelihood, by providing a range of important functions and valuable insights for other researchers. Thus researchers may start with "qualitative data collection and analysis on a relatively unexplored topic, using the results to design a subsequent quantitative phase of the study".

Phase IIb studies are pivotal, single or double blind, randomized cross over, multicentric studies conducted on heterogeneous population. Phase II b is specifically designed to study efficacy, i.e. how well the drug works at the prescribed doses.

Pivotal studies are those studies which will result in important decisions being made about the medicine and are crucial to draw an inference on efficacy and safety. The results of pivotal studies are identified by the sponsor for regulatory authority to judge the efficacy and safety of the drug.

Phase II studies are comparative studies, where the comparator could be the placebo or the active comparator called the gold standard. Scientifically, comparison to a placebo is required to assess the efficacy of the new drug but a standard drug should be used as comparator if there are ethical issues (e.g. in case of a severe disease condition patient requires a treatment, as placebo has no effect it is not justified).

*Procedure of phase II studies:*

- Pretrial activities are completed to prepare the site to conduct the trial
- Suitable subjects with the target disease are identified
- Informed consent process is completed
- Screening procedures are carried out
- After confirming the eligibility criteria suitable subjects are enrolled into the trial
- Randomization procedures are done
- Subject is given the study drug
- Subject is recalled as per the protocol visit schedule to do the protocol required lab tests
- Data obtained is sent to sponsor entered in Case Report Form
- Data collected are analyzed

- Depending on the data obtained the sponsor decides whether it is worthwhile to proceed further.

A precise pharmacokinetic analysis of the entire plasma profile, including absorption, distribution and elimination would be evaluated. If the results of the phase II trials show that a new treatment may be as good as the existing treatment or better, it then moves on to phase III.

*Outcome of Phase II trial:*

- *Safe dosage schedule:* It can be determined based on the safety (phase I) and efficacy (phase II) results obtained
- *Characterization of dose-response curve:* The graphical representation of the responses to the test drug at different dose levels is obtained
- *Clinical benefit (Placebo/Active control) :* Efficacy of drug is obtained and an initial comparison of the efficacy of test drug with standard marketed drug is obtained
- Pharmacokinetic characteristics of the drug in patients
- *Nature of adverse drug reaction:* Phase II trials subjects have the disease condition that is being treated by the test drug. Therefore in this phase the possible adverse drug reactions that can be experienced by patients are identified (Fig. 1.18).

### *Phase II in India*

Schedule Y requirements to conduct phase II in India:

- Phase II clinical trials are done to determine possible therapeutic use, effective dose range and to further evaluate safety and pharmacokinetics
- Normally, 10 to 12 patients should be studied at each dose level. These studies are usually limited to 3 to 4 centers.
- If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to licensing authority along with the application.

*Advantages and challenges in conducting phase II clinical trial:*
*Advantages:*

- Efficacy of test drug is determined. Only if a positive result is obtained in this phase, the dosing schedule for phase III is designed.

*Challenges:*

- If positive results are not obtained during this phase dosage schedule cannot be determined for phase III. Most often, drug failure is seen in this phase.

### *Phase III Clinical Trials: (Therapeutic Confirmatory Trials)*

Phase III studies are also known as "Therapeutic confirmatory trials". They are performed after preliminary evidence suggesting effectiveness of the drug

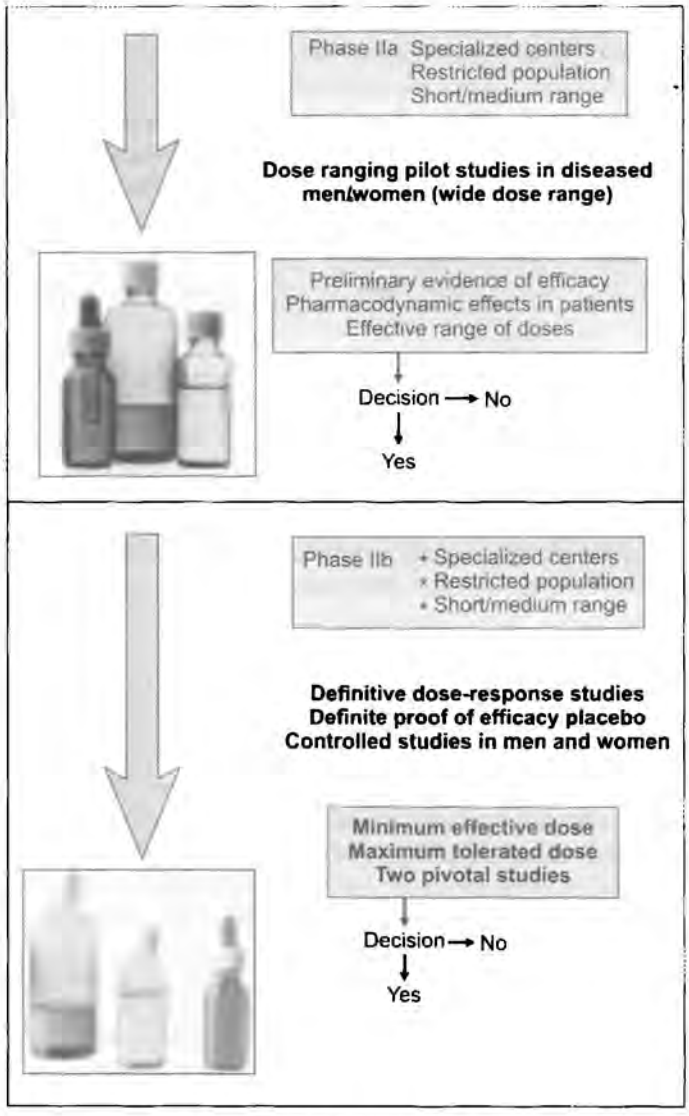



**Fig. 1.18:** Phase II

has been obtained in phase II. They are intended to gather additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase III studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Even at this final stage of drug development, protocol will still exclude many 'real world' patients, e.g. those with other serious medical conditions, women of child bearing age unless using accepted contraceptive precaution.

Phase III studies usually include several hundred to thousand patients. Because of their size and comparatively long duration, phase III trials are the most expensive, time-consuming and difficult trials to design and conduct.

Data obtained from phase III is the major component of New Drug Application. The studies carried out in phase III complete the information needed to support adequate instructions for use of the drug (prescribing information). All features should represent regulatory requirements and proposed clinical use after marketing.

*Objective(s) of phase III clinical trial:* Primary objective of phase III clinical trial is to confirm the therapeutic benefit(s).They are designed to confirm the preliminary evidence accumulated in phase II that a drug is safe and effective for use in the intended indication and recipient population. In this phase, investigational product is generally compared with standard treatment.

The other objectives of phase III trial are to:

- Determine the optimum dosage schedule for general use, safety and efficacy of the investigational product in combination with other drug(s)
- Identification of the disease sub types for which drug is effective
- Study on special population such as renal and hepatic insufficiency, lactating women, elderly population
- Special studies like food/liquid interaction, drug-drug interaction
- Study on patients of different ethnic groups
- Phase III trials can also have HRQL (health related quality of Life) and pharmacoeconomic studies as secondary objective.

In HRQL studies, effect of investigational product on quality of life of individuals can be assessed. Pharmacoeconomic studies involve comparison of cost and outcome of medical intervention.

*Prerequisites for phase III trials:*

- *Preclinical safety data:* Safety data will be collected throughout the development process. In the early stages reliance is placed upon understanding the class effect where other drugs belonging to the same class already exist. As development process progresses specific safety data collection becomes vital. Animal toxicity which needs to be completed before start of phase III studies along with those completed before phases I and II are chronic toxicity, carcinogenicity, *in vivo* genotoxicity, segment II reproductive toxicity study(if female of childbearing age to be involved in the study) and supplemental studies
- *Early phase clinical trial data:* Outcome of phase I studies (preliminary safety)—generally well tolerated, no significant adverse events; outcome of phase II studies (preliminary efficacy)—dose-response relationship, no significant adverse events
- *Regulatory authority and ethics committee approval:* Ethics committee approval may be rate limiting step as approval is required from each of the participating site.

*Types of phase III trials*

- Phase III a—compulsory; regulatory requirement for NDA submission; patient population in large number or in a special category
- Phase III b—Extended trials of IIIa after NDA submission; done before launch as a marketing need. These are conducted predominantly for marketing purposes and are sometimes intended as the main support for the required cost/value arguments. Typically market leader is used as comparator, to achieve a benefit over and above that of the existing drug, thus enabling the marketing and sales groups to maximize performance after launch. Explores—new patient population, new indications, special drug features.

*Conduct of the trial and players in phase III*

- *Site:* Multispeciality hospital with adequate patient attendance and laboratory facilities. Less specialized investigator.
- *Subjects:* Patient population of around 250 to 1000 with broader inclusion criteria are included.

*Clinical trial design:* Common clinical trial design in phase III is "multicentric, randomized, controlled and blinded study".

- Types of control: The objective of phase III will be to compare the extent of efficacy and safety with that of currently used therapies. Placebo can be used as comparator in phase III, if there is no standard treatment for the disease or the standard treatment is ineffective.

  When selecting active/standard comparator, countries where the study is to be carried out, registration status of the potential comparator and dosing regimens of the potential comparator should be considered.

  Control in phase III can also be concurrent control-dose comparison, wherein different dose regimens of same treatment are compared, e.g. comparison of 200 mg and 400 mg of ibuprofen for pain.
- *Patient population:* Patient population included should be representative of general patient population. Factors to be considered for inclusion and exclusion criteria are:

  *Nature and history of the disease:* Inclusion criteria in the protocol should mention clearly patient with which disease and severity of the disease to be included, without which there could be variability in the response to treatment. For example, for an antihypertensive medication trial, inclusion criteria should be expressed in terms of diastolic blood pressure between X mm Hg and Y mm Hg.

  *Concurrent disease and concomitant medication:* Presence of concurrent disease and concomitant medication along with target disease may influence the study drug through metabolic interaction, which might affect the interpretation of results. As the aim of phase III is to evaluate the treatment in a situation approximating real life, inclusion of patient with concurrent disease with/without medication needs to be considered with diligence.

- Influence of disease indication on trial design: The duration of the trial, the timing of each subject's treatment and the number and timing of assessments will depend on whether disease is an acute condition or of chronic type.

  Acute conditions will require a short treatment period and as these types of disease remit spontaneously within certain time; subjects should be entered into the study within one day of onset and assessment to be carried out more frequently to detect early signs of efficacy.

  In chronic diseases, signs and symptoms of the disease will be stable for long periods dictating study of six months or more duration, with monthly assessments carried out for efficacy. If patients are already receiving treatment, withdrawal of current therapy must be carefully considered so as not to destabilize the subject without justification. If it, is justified, adequate wash out period must be provided to remove the effect of the previous therapy and to prevent drug-drug interaction.

  When withdrawal of current therapy is not justifiable, subjects who are newly diagnosed with the condition can be included. However, number of subjects available will be considerably less as compared to total population suffering from the disease requiring longer time to recruit the subjects.

  Need to withdraw current treatment can be avoided by designing a trial where test treatment is added to the current treatment (add-on trial). This implies that current therapy is inadequate and that measurable improvement can be gained, either in terms efficacy or safety by new drug.
- *Randomization and blinding:* In phase III trial, each center acts as strata and within each center randomization like simple randomization or stratification is used. Stratification is used when there are differences in the nature of the disease in severity or site and responses to treatment might differ due to this. For example, in an analgesic trial, subjects can be stratified according to pain severity into mild, moderate and severe, where the response might differ. Each stratum can be analyzed separately if required.

  Double-blind is the preferable design in phase III trial. However, single blinding or open-label design can be used if it is appropriate.

*Types of trial design:* Either parallel, crossover, or factorial design

*Duration of dosing: Duration of dosing is determined by factors like pharmacokinetics, mode of action and natural history of the disease being treated.* The results from phase II will be the guiding factor in deciding the dosing schedule.

*Methods of clinical measurement* (refer page 42)

A central laboratory should be used in order to prevent variable results that may arise due to differences in lab procedures, for studies which have a laboratory parameter as the main efficacy assessment.

*Procedure of phase III studies:*

- Pretrial activities are completed to prepare the site to conduct the trial
- Suitable subjects with the target disease are identified
- Informed consent process is completed
- Screening procedures are carried out
- After confirming the eligibility criteria, suitable subjects are enrolled into the trial
- Subjects are randomly allocated to different groups
- Subjects are given the study/comparator drug
- Individual patient in clinical trial is monitored by the investigator which may be equal to or greater than standard of care
- Subject is recalled as per the protocol visit schedule to do the protocol required lab tests
- Periodic monitoring from sponsor's personnel (frequency of which depends on the trial duration)
- Data obtained is sent to sponsor in the form of completed Case Report Form
- Depending on risk involved in the trial there can be interval protocol monitoring by independent monitoring committee
- Data collected are analyzed.

If the results of the phase III trials show that a new treatment may be as good as the existing treatment or better, the sponsor can apply for marketing approval.

*Outcome from phase III trial:*

- The efficacy of the test drug is confirmed in a more realistic population (Fig. 1.19)
- The efficacy of test drug in special population (such as children or pregnant women) is obtained

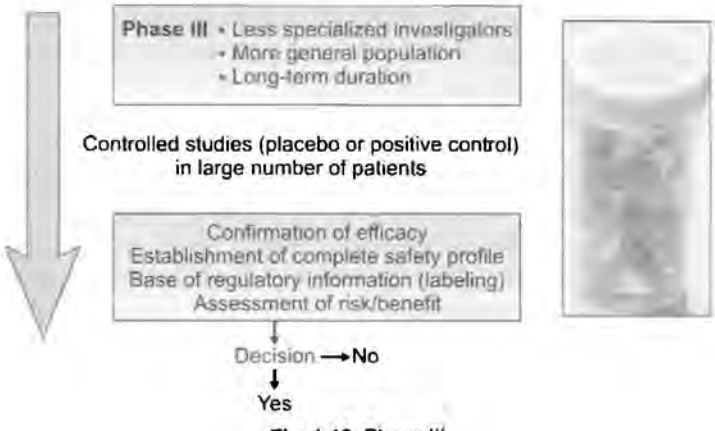



**Fig. 1.19:** Phase III

- Tolerability and safety: In this phase the preliminary results pertaining to safety, efficacy and dosage schedule obtained during phase I and II are confirmed
- Advantages/disadvantages over standard treatment are obtained.

*Phase III in India*

Schedule Y requirements to conduct phase III in India:

- Phase III clinical trials are done to obtain sufficient evidence about the efficacy and safety of the drug in a large number of patients generally in comparison with a standard drug and/or placebo
- If the drug is a new drug discovered in India and/or not marketed in any other country, data should be generated on at least 500 patients distributed over 10 to 15 centers. In addition, postmarketing surveillance on large number of patients is a must for detecting adverse drug reactions
- For new drugs approved outside India, phase III studies need to be carried out primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Data should be generated in at least 100 patients over 3 to 4 centers
- Prior to conduct of phase III studies in Indian subjects, licensing authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad
- If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to Licensing Authority along with the application.

**Advantages and challenges in conducting phase III clinical trial**

*Advantages*

- Therapeutic confirmation of the investigational product
- Due to less stringent inclusion and exclusion criteria, recruitment of subject is relatively easy
- Simultaneous generation of large data
- Results from phase III trial are generalizable.

*Challenges:* Phase III trial is conducted at multiple centers with a single protocol. Thus, the protocol needs to be designed accordingly. Following are the challenges faced during conduct of phase III trial:

- IEC/IRB approval should be obtained for each site/center involved, which might lead to unexpected delay
- Patient recruitment—requires large and heterogeneous population, leading to longer duration and greater cost
- Arranging investigators' meet
- Training of staff and monitoring the trial

- Clinical trial supplies—to be supplied on time to all centers taking into consideration the expiry date and stability data of the new drug
- Central laboratory—sample supply to laboratory
- Centralized data management and analysis
- Different study outcomes—difficult to interpret
- Drafting of a common final report and publication issues.

Once a drug has proven to be satisfactory, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details and shelf-life. This collection of information makes-up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries so they can then grant the sponsor approval to market the drug.

## NDA Application

### *New Drug Application (NDA) Review Process*

The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the US. The data gathered during animal studies and human clinical trials of an investigational new drug (IND) becomes part of the NDA. Once the sponsor has completed phase IIIa successfully and is ready with the clinical study report the application to market drugs can be filed through an NDA application. Following the completion of all three phases of clinical trials, the company analyses all the data and files an NDA with FDA in the form of a dossier.

The clinical study report is a document containing the description of the trial, this when submitted as part of the NDA must comply with requirements as given in ICH E3 when sponsor has to make the submission to USFDA, EMEA, MHLW. The sponsor has to follow the requirements listed in Appendix II of Schedule Y to submit the clinical study reports to the regulatory authority of India. The NDA must contain all the scientific information, safety and efficacy data collected during the trials. The NDAs typically run 100,000 pages or more. By law, FDA is allowed to take around six months to review an NDA.

The ICH M4 guideline is for the organization of Common technical document (CTD) which refers to the application format—a dossier/research binder for regulatory submission for marketing approval of a drug. CTD helps the sponsor as it provides a common format for the preparation of technical documentation to support a NDA that will be submitted to the regulatory authorities. CTD also reduces time and resources needed to compile the dossier for different regulatory submissions.

CTD has 5 modules which are as follows:

1. Administrative and prescribing information
2. Overview and summary of modules 3 to 5

3. Quality (pharmaceutical documentation)
4. Safety (toxicology studies)
5. Efficacy (clinical studies).

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s) and whether the benefits of the drug outweigh the risks
- Whether the drugs proposed labeling (package insert) is appropriate and what it should contain
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality and purity.

### *NDA Content and Format Requirements*

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body and how it is manufactured, processed and packaged. The following resources provide summaries on NDA content, format and classification, plus the NDA review process.

As outlined in Form FDA-356h, *Application to Market a New Drug for Human Use or as an Antibiotic Drug for Human Use*, NDAs consist of as many as 15 different sections:

1. Index
2. Summary
3. Chemistry, manufacturing and control
4. Samples, methods validation package and labeling
5. Nonclinical pharmacology and toxicology
6. Human pharmacokinetics and bioavailability
7. Microbiology (for antimicrobial drugs only)
8. Clinical data
9. Safety update report (typically submitted 120 days after the NDA's submission)
10. Statistics
11. Case report tabulations
12. Case report forms
13. Patent information
14. Patent certification
15. Other information.

Although the exact requirements are a function of the nature of a specific drug, the NDA must provide all relevant data and information that a sponsor has collected during the product's research and development.

CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses. The numbers 1 through 7 are used to describe the type of drug:

3. Quality (pharmaceutical documentation)
4. Safety (toxicology studies)
5. Efficacy (clinical studies).

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CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses. The numbers 1 through 7 are used to describe the type of drug:

1. New molecular entity
2. New salt of previously approved drug (not a new molecular entity)
3. New formulation of previously approved drug (not a new salt OR a new molecular entity)
4. New vombination of two or more drugs
5. Already marketed drug product-duplication (i.e. new manufacturer)
6. New indication (claim) for already marketed drug (includes switch in marketing status from prescription to OTC)
7. Already marketed drug product—no previously approved NDA

The following letter codes describe the review priority of the drug:

S—Standard review for drugs similar to currently available drugs.

P—Priority review for drugs that represent significant advances over existing treatments.

After a NDA is received by the agency, it undergoes a technical screening generally referred to as a completeness review. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application, i.e. justifying initiating CDER's formal review of the NDA.

NDA's that are incomplete become the subject of a formal "refuse-to-file" action. In such cases, the applicant receives a letter detailing the decision and the deficiencies that form its basis. This decision must be forwarded to the sponsor within 60 calendar days after the NDA is initially received by CDER.

Medical reviewers are responsible for evaluating the clinical sections of submissions, such as the safety of the clinical protocols in an IND or the results of this testing as submitted in the NDA.

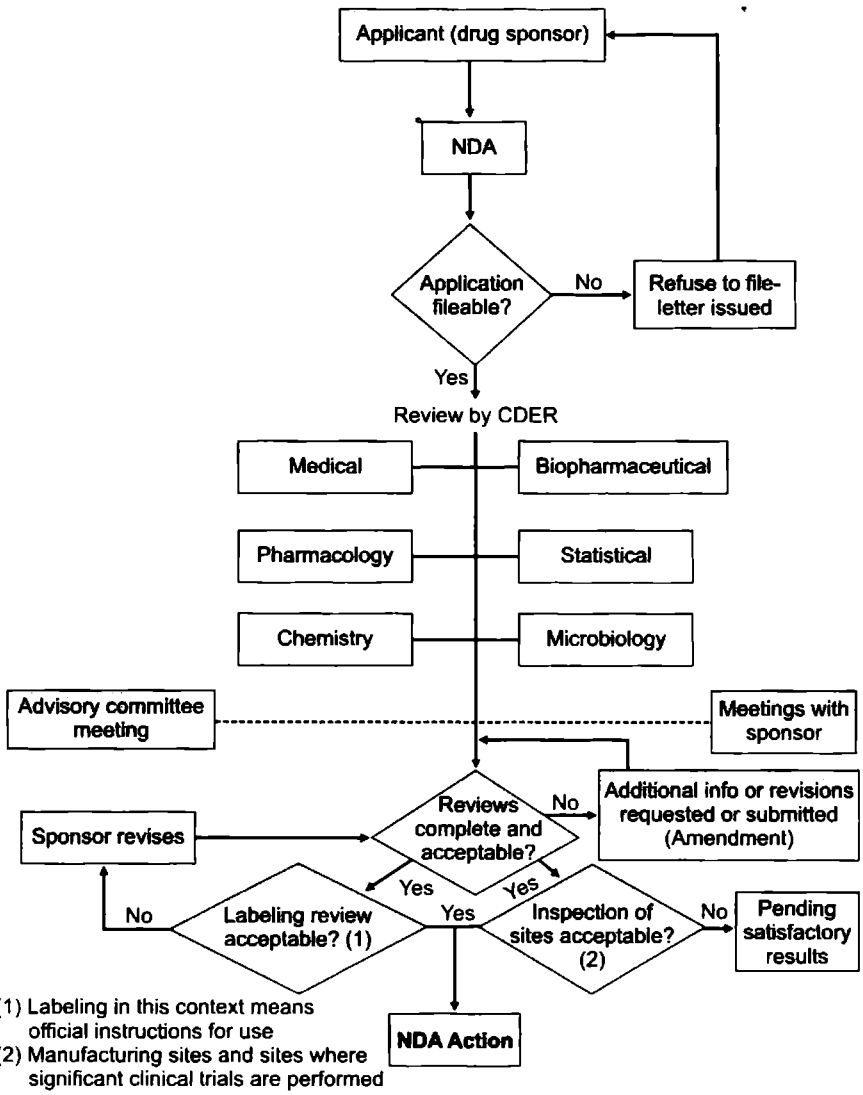
Biopharmaceutical reviewers evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed in, metabolized by and eliminated from the human body.
Statisticians evaluate the statistical relevance of the data in the NDA with the main tasks of evaluating the methods used to conduct studies and the various methods used to analyze the data.

Each review division employs a team of chemists responsible for reviewing the chemistry and manufacturing control sections of drug applications related to drug identity, manufacturing control and analysis.

The clinical microbiology information is required only in NDAs for anti-infective drugs. Since these drugs affect microbial, rather than human physiology, reports on the drug's *in vivo* and *in vitro* effects on the target microorganisms are critical for establishing product effectiveness.

CDER uses advisory committees to obtain outside advice and opinions from expert advisors so that final agency decisions will have the benefit of wider national expert input. Committee recommendations are not binding on CDER, but the agency considers them carefully when deciding drug issues. During the course of reviewing an application, CDER usually communicates often with sponsors about scientific, medical and procedural issues that arise during the review process. Communications may take the form of

**Flow chart 1.2:** NDA review process




*Source*: http://www.washingtonlifescience.com/patient/drug_develop/nda.htm

telephone conversations, letters, faxes or meetings (either face-to-face or via video conferencing) (Flow chart 1.2).

### *Notification of Easily Correctable Deficiencies*

CDER makes every effort to communicate promptly to applicants easily correctable deficiencies found during the review of an application. CDER also informs applicants of the need for more data or information, or for

technical changes in the application needed to facilitate the agency's review. This type of early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application by agency final decision makers as well as by reviewing staff. Instead, major scientific issues are usually addressed in an action letter at the end of the initial review process.

### *End of Review Conference*

At the conclusion of CDER's review of an application, there are three possible action letters that can be sent to the sponsor:

1. *Not approvable letter:* lists the deficiencies in the application and explains why the application cannot be approved.
2. *Approvable letter:* signals that, ultimately, the drug can be approved. It lists minor deficiencies that can be corrected, often involves labeling changes, and possibly requests commitment to do postapproval studies.
3. *Approval letter:* states that the drug is approved. It may follow an approvable letter, but can also be issued directly.

In some cases, an applicant may seek to augment the information provided in the original NDA during the review process. For example, the applicant may submit a new analysis of previously submitted data or information needed to address a deficiency in the drug application. Any such information provided for an unapproved application is considered an NDA amendment. The submission of a significant amendment may result in an extension of FDA's time line for application review.

When an NDA nears approval, agency reviewers evaluate draft package labeling for accuracy and consistency with the regulatory requirements for applicable prescription or over-the-counter drugs. Each element of the proposed labeling, including indications, use instructions, and warnings, is evaluated in terms of conclusions drawn from animal and human testing. All claims, instructions, and precautions must accurately reflect submitted clinical results. The labeling "negotiation process," through which a drug's final approved labeling is agreed upon, can take a few weeks to many months. The length of the process depends upon the number of agency comments and an applicant's willingness to reach agreement.

There is also extensive communication between review team members. If a medical reviewer's reanalysis of clinical data produces results different from those of the sponsor, e.g. the reviewer is likely to forward this information to the statistical reviewer with a request for a statistical reanalysis of the data. Likewise, the pharmacology reviewer may work closely with the statistical reviewer in evaluating the statistical significance of potential cancer-causing effects of the drug in long-term animal studies.

When the technical reviews are completed, each reviewer develops a written evaluation of the NDA that presents their conclusions and their recommendations on the application. The division director or office director

**Table 1.3:** Labeling requirement to be met for approved product

| | |
|---|---|
| Description | : Proprietary and established name of drug, dosage form, ingredients, chemical name, and structural formula. |
| Clinical pharmacology | : Summary of the actions of the drug in humans, *in vitro* and *in vivo* actions in animals if pertinent to human therapeutics, pharmacokinetics. |
| Indications and usage | : Description of use of drug in the treatment, prevention or diagnosis of a recognized disease or condition. |
| Contraindications | : Description of situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. |
| Warnings | : Description of serious adverse reactions and potential safety hazards, subsequent limitation in use and steps that should be taken, if they occur. |
| Precautions | : Information regarding any special care to be exercised for the safe and effective use of the drug. Includes general precautions and information for patients on drug interactions, carcinogenesis/mutagenesis, pregnancy rating, labor and delivery, nursing mothers, and pediatric use. |
| Adverse reactions | : Description of undesirable effect(s) reasonably associated with the proper use of the drug. |
| Drug abuse/dependence | : Description of types of abuse that can occur with the drug and the adverse reactions pertinent to them. |
| Over dosage | : Description of the signs, symptoms and laboratory findings of acute overdosage and the general principles of treatment. |
| Dosage/administration | : Recommendation for usage dose, usual dosage range, and, if appropriate, upper limit beyond which safety and effectiveness have not been established. |
| How supplied? | : Information on the available dosage forms to which the labeling applies. |

then evaluates the reviews and recommendations and decides the action that the division will take on the application. The result is an action letter that provides an approval, approvable or non-approvable decision and a justification for that recommendation. Once the FDA approves the NDA, the new medicine becomes available for physicians to prescribe. The company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality control records. The FDA requires additional studies (phase IV) to evaluate long-term effects (Table 1.3).

*Electronic Records for NDA*

Regulatory agencies are rapidly moving toward requiring submissions in electronic format because electronic submissions allow regulatory reviewers to rapidly and efficiently search and navigate marketing applications and other submissions, facilitating and potentially shortening the time to approval.

An electronic application for a new chemical entity, i.e. NDA, is submitted as an archival copy.

The archival copy is divided into five or six sections containing technical information. Each technical section of the review copy will go to the reviewer in charge of that specific section. Thus, the archival copy is intended to serve as a reference source for FDA reviewers to locate information not contained in the section of the review copy assigned to them. After approval, the archival copy is retained by the FDA and serves as the sole file copy of the approved application.

All documents and datasets for the electronic archival copy should be placed in a main folder using the NDA number (e.g. N123456) as the folder name. Sponsor should obtain the NDA number prior to submission. Inside the main folder, all of the documents and datasets should be organized by the NDA items described on page 2 of FDA form 356h.

The files and folders in folder N123456 contain the following examples:

1. Folder structure for an NDA submission.
2. Table of contents for the NDA.
3. Table of contents with bookmarks for CMC, nonclinical pharmtox, Clinstat, CRT, CRT datasets, CRT profiles, CRF.
4. Table of contents for Hpbio and micro (no bookmarks).
5. Study report bookmarks (clinstat/pneumo/1234.pdf).
6. Document information fields for labels and CRF, publications (pharmtox and Clinstat).
7. Full text index (crf/crfindex.pdx).
8. Data definition file for nonclinical data (pharmtox/datasets/101/define.pdf).
9. Dataset for tumors from a carcinogenicity study (pharmtox/datasets/101/tumor.xpt).
10. Data definition file for clinical data (crt/datasets/1234/define.pdf).
11. Dataset for efficacy data (crt/datasets/1234/efficacy.xpt).
12. Partial bookmarks for CRF (crf/101/001/112.pdf).

The US FDA and the EMEA currently accept the CTD in electronic format. The table of contents of the eCTD is consistent with that of the CTD. The eCTD is not limited to transfer of information alone, it also has provisions for creation, review, life cycle management and archival of electronic submission.

The eCTD is a message specification for the transfer of files from a submitter to a receiver. The primary technical components are:

- A high level folder structure

- An XML backbone file which consists of a comprehensive table of contents and provides corresponding navigation aid
- PDF files.

The eCTD therefore consists of PDF documents stored in the high level folder structure, which is accessed through the XML backbone.

In summary, NDA includes an integrated summary of efficacy (ISE) and of safety (ISS). When evaluating NDAs, regulatory agencies look at:

- Validity of pivotal studies
- Replicability of pivotal studies (consistency across studies)
- Generalizability across populations (demographic groups, concomitant medications, intercurrent diseases, geographic regions, and even cultural groups)
- Establishment of supportable dosage and dose regimen(s)
- Clinical relevance of efficacy results
- Clinical seriousness of safety profile (in context of seriousness of condition being treated)
- Overall usefulness of drug (risk/benefit ratio).

In the US, the FDA does not actually approve the drug itself for sale. It approves the labeling—the package insert (as given in Figure 1.20, final outcome of a new drug application review is the label-package insert. All the information pertaining to new drug should be reproduced as label/package insert complying with FDA label requirement (refer Table 1.3 for labeling requirement) and this will be reviewed and approved by FDA reviewers so that product will carry the truthfully and accurate information as was submitted along with NDA). United States law requires truth in labeling, and the FDA assures that a drug claimed to be safe and effective for treatment of a specified disease or condition has, in fact, been proven to be so. All prescription drugs must have labeling, and without proof of the truth (Clinical studies data) of its label, a drug may not be sold in the United States.

### *Nonarchivable Electronic Records for New Drug Applications*

Center policy is to encourage the submission and review of electronic NDAs as described in the guidance for industry:

- It is Center's policy to discourage the submission of records in electronic formats that are not archivable. The only electronic records that are archivable are those provided as described in the guidance document *'Providing Regulatory Submissions in Electronic Format - NDA (January 1999)'*.
- In the case when some records are submitted in electronic formats that are not archivable, the submission must still be accompanied by an electronic archivable version containing the same information.
- Requests from center staff for word processing files for the purpose of copying and pasting text, figures or tables on individual pages or portions of pages are not consistent with agency policy. In most instances when

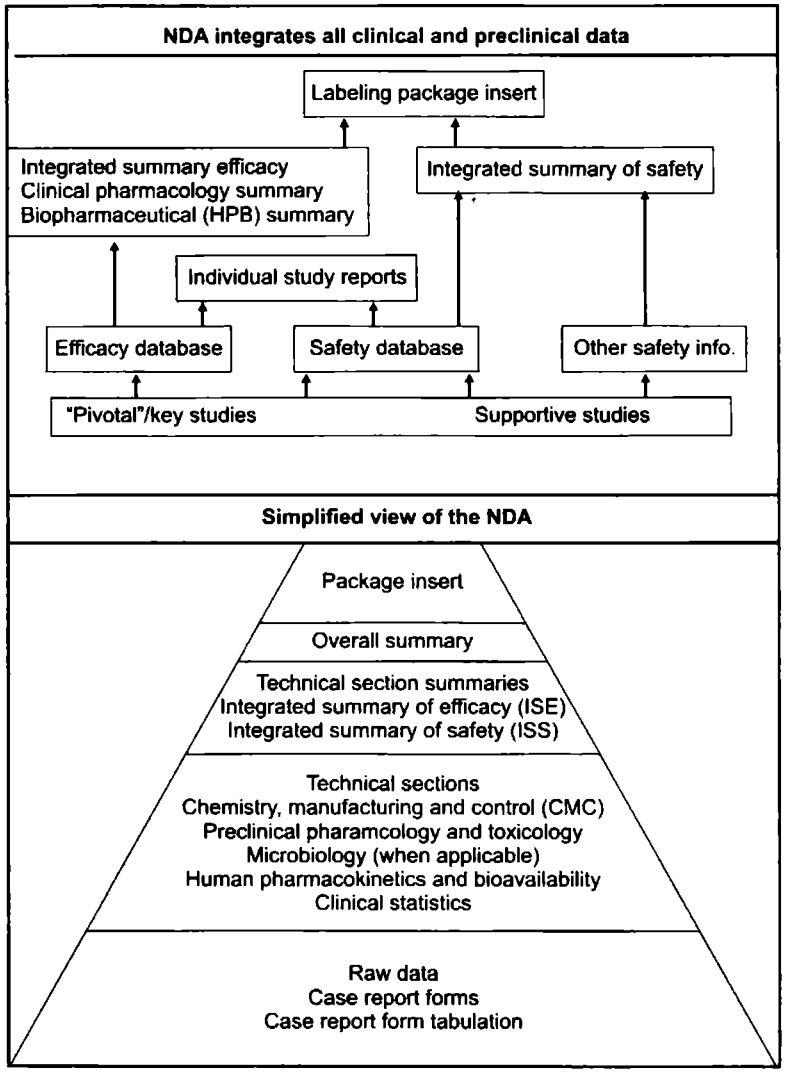



**Fig. 1.20:** NDA review

such functions are needed, they can be adequately performed with archival files.

- If a word processing file is submitted, it cannot be accepted by the Agency in lieu of the archival electronic record as described in the guidance. In other words, the Agency cannot accept a record in a word processing file format unless the record is also provided as recommended by the guidance.
- Requests from Center staff for datasets in formats other than that described in the guidance also are not consistent with Agency policy. In most instances, staff can use the archival dataset to convert data to desired alternative formats.

- If datasets are requested or accepted in a format that is different from that recommended in the guidance, it cannot be accepted *in lieu* of the archivable electronic record as outlined in the guidance. The Agency cannot accept dataset records in a file format not described in the guidance unless the record is also provided as recommended in the guidance. For a transition period beginning in February 1999, the Agency has been making exceptions to its electronic submissions acceptance policy on a case-by-case basis in situations when a sponsor is unable to provide electronic submissions as described in the guidance.
- If a sponsor is asked or offered to provide electronic records that will require the installation of hardware or executable software on any component of the CDER maintained information technology infrastructure, or if the use of the records requires OIT staff support beyond that needed for the electronic submission described in the guidance, advance approval from the Office of Information Technology (OIT) will be needed.

### *Role of Regulatory Bodies*

In order to license/register a new chemical entity (NCE), a pharmaceutical company should develop a dossier that describes the pharmaceutical quality, safety (in animals and humans) and efficacy of the product for a specified indication.

The regulatory requirements for a pharmaceutical product would be evaluation and assessment of the pharmaceutical quality data, including: assessing that the manufacturer(s) of all components, including that of the active pharmaceutical ingredient and the finished product, are certified as meeting the international standards for Good Manufacturing Practices, standard tests for content and impurities, stability, and packaging labeling to ensure that it complies with specified standards.

Evaluation of animal (preclinical) toxicology studies in relation to acute and chronic toxicity, genetic toxicity, teratogenicity, carcinogenicity and others, including whether the studies have been carried out to international standards ICH safety guidelines, national guidelines (like Schedule Y in India) and whether the data and interpretation of the results are valid.

Evaluation of human clinical trials (either placebo or active comparator randomized controlled clinical trials) that have been carried out to define the dose, frequency and duration of treatment that is effective and safe, including assessing that the design and conduct of the trials meets international requirements like ICH GCP, that data are valid and have been interpreted correctly.

*Food and drug administration:* The US Food and Drug Administration (FDA) is an agency of the United States Department of Health and Human Services and is responsible for the safety regulation of drugs, vaccines, biological products and medical devices. New drugs receive extensive scrutiny before

FDA approval in a process called a *New Drug Application* (NDA). The NDA is the vehicle in the United States through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing. Recently, the FDA has mandated that NDAs submitted electronically should be done in the eCTD format.

*European Medicines Agency:* The European Medicines Agency (EMEA) is the regulatory agency for the evaluation of medicinal products in European Union. EMEA operates as a decentralized scientific agency. For products eligible for or requiring central approval, a pharmaceutical company submits an application for marketing authorization to the EMEA. A single evaluation is carried out through the Committee for Medicinal Products for Human Use (CHMP) if the Committee concludes that quality, safety and efficacy of the medicinal product is sufficiently proven, it adopts a positive opinion. This is sent to the *European Commission* to be transformed into a marketing authorization valid for the whole of the European Union. The EMEA's Committee on Orphan Medicinal Products (COMP) administers the granting of *orphan drug* status.

*Drugs Controller General of India:* The Drugs Controller General of India (DCGI) is responsible for regulatory approvals of clinical trials in India. This central authority reviews NDAs (form 44) as per the guidelines of Schedule Y. The DCGI has now classified clinical trials into two categories—A and B. Category A comprises of clinical trials for which a protocol has already been approved in specific countries such as the US, UK, Japan, Australia. The time frames for clearance of these applications are 2 to 4 weeks. All other application fall under category B. Their review will take at least 8 to 12 weeks. The DCGI has yet to set up an e-submission procedure.

*Therapeutic Goods Administration:* Therapeutic Goods Administration (TGA) is the regulatory authority which carries out a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard. Medicines are evaluated by one of three regulatory units of the TGA. Prescription and other specified medicines are evaluated by the Drug Safety and Evaluation Branch (DSEB), OTC Medicines by the OTC Medicines Section (OTC), and complementary medicines by the Office of Complementary Medicines (OCM). One of these regulatory units evaluates the application submitted and forwards its recommendation to the Australian Drug Evaluation Committee (ADEC). The ADEC forwards its recommendation for approval or rejection to the Minister for Health.

### *ANDA Process*

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provide for the review and ultimate approval of a generic

drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the public.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*).

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e. performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Waxman-Hatch Act. This Act expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without conducting costly and duplicative clinical trials. At the same time, the brand-name companies can apply for up to five additional years longer patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process. Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation.

An application must contain sufficient information to allow a review to be conducted in an efficient and timely manner. Upon receipt of the application a pre-filing assessment of its completeness and acceptability is performed by a project manager within the Regulatory Support Branch, Office of Generic Drugs. If this initial review documents that the application contains all the necessary components, an "acknowledgment letter" is sent to the applicant indicating its acceptability for review and confirming its filing date.

Once the application has been determined to be acceptable for filing, the Bioequivalence, Chemistry/Microbiology and Labeling reviews may begin. If the application is missing one or more essential components, a "Refuse to File" letter is sent to the applicant. The letter documents the missing component(s) and informs the applicant that the application will not be filed until it is complete. No further review of the application occurs until the

applicant provides the requested data and the application is found acceptable and complete.

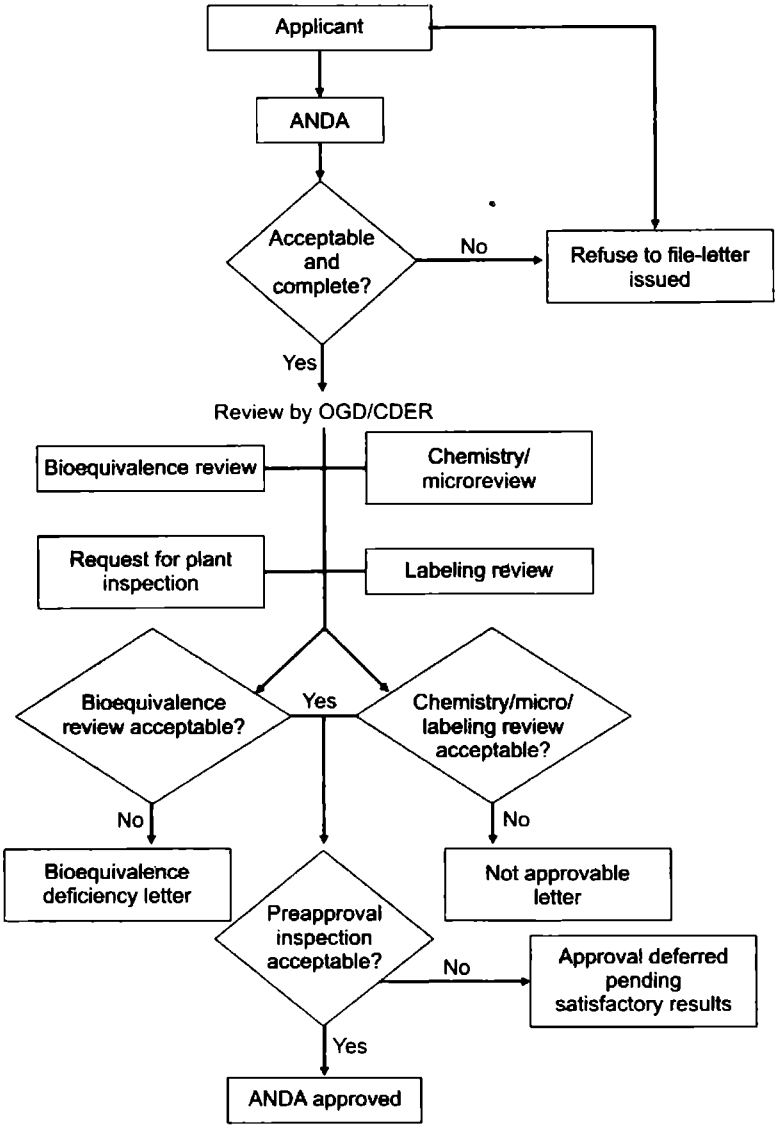
The FDA requires an applicant to provide detailed information on a product to establish bioequivalency. Applicants may request a waiver from performing *in vivo* (testing done in humans) bioequivalence studies for certain drug products where bioavailability (the rate and extent to which the active ingredient or active moiety is absorbed from the drug product and becomes available at the site of action) may be demonstrated by submitting data such as (i) a formulation comparison for products whose bioavailability is self evident, for example, oral solutions, injectables or ophthalmic solutions where the formulations are identical, or (ii) comparative dissolution. Alternatively, *in vivo* bioequivalence testing comparing the rate and extent of absorption of the generic vs the reference product is required for most tablet and capsule dosage forms.

The Chemistry/Microbiology review process provides assurance that the generic drug will be manufactured in a reproducible manner under controlled conditions. Areas such as the applicant's manufacturing procedures, raw material specifications and controls, sterilization process, container and closure systems and accelerated and room temperature stability data are reviewed to assure that the drug will perform in an acceptable manner. Upon filing an ANDA an establishment evaluation request is forwarded to the Office of Compliance to determine whether or not the product manufacturer, the bulk drug substance manufacturer and any of the outside testing or packaging facilities are operating in compliance with current Good Manufacturing Practice (cGMP) regulations. Each facility listed on the evaluation request is evaluated individually and an overall evaluation for the entire application is made by the Office of Compliance. Furthermore, a preapproval product specific inspection may be performed on to assure data integrity of the application (Flow chart 1.3).

The Labeling review process ensures that the proposed generic drug labeling (package insert, container, package label and patient information) is identical to that of the reference listed drug except for differences due to changes in the manufacturer, distributor, pending exclusivity issues or other characteristics inherent to the generic drug product (tablet size, shape or color, etc.). Furthermore, the labeling review serves to identify and resolve issues that may contribute to medication errors such as similar sounding or appearing drug names, and the legibility or prominence of the drug name or strength.

If there are deficiencies involved in the Chemistry/Manufacturing/Controls, Microbiology or Labeling portions of the application, these deficiencies are communicated to the applicant in a facsimile. The facsimile instructs the applicant to provide information and data to address the deficiencies and provides regulatory direction on how to amend the application. Once the above sections are found to be acceptable, as well as,

**Flow chart 1.3:** ANDA review process




*Source:* https://secure.pharmacytimes.com/lessons/200205-01.asp

the preapproval inspection and bioequivalence portion of the application, then the application moves toward approval.

After all components of the application are found to be acceptable an approval or tentative approval letter is issued to the applicant to market the generic drug product. If the approval occurs prior to the expiration of any patents or exclusivities accorded to the reference listed drug product, a tentative approval letter is issued to the applicant which details the

circumstances associated with the tentative approval of the generic drug product and delays final approval until all patent/exclusivity issues have expired. A tentative approval does not allow the applicant to market the generic drug product.

### *Drug Application Regulatory Compliance*

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and drug sponsors to provide guidelines for the processing, content, and evaluation of applications, and for the design, production, manufacturing, and testing of regulated products. They also provide consistency in the Agency's regulation, inspection and enforcement procedures.

Following are the guidance documents available:

- *Current Good Manufacturing Practice (cGMP) regulations:* The cGMP regulations for drugs contain minimum requirements for the methods, facilities and controls used in manufacturing, processing, and packing of a drug product. FDA can issue a warning letter or initiate other regulatory actions against a company that fails to comply with Current Good Manufacturing Practice regulations.
- *Code of Federal Regulations (CFR):* The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the *CFR*. The *CFR* is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the *CFR* interprets the *Federal Food, Drug and Cosmetic Act* and related statutes. Section 21 of the *CFR* contains most regulations pertaining to food and drugs. The regulations document the actions of drug sponsors that are required under Federal law.
- MaPPs (Manual of Policies and Procedures) are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MaPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures.
- *Compliance Policy Programs and Guidelines*
  - *Compliance References:* This web site from the Office of Regulatory Affairs provides links to compliance policy guides, regulatory procedures manuals, and other compliance related information.
  - *Compliance Program Guidance Manual:* These programs and instructions are for FDA field inspectors.

### *Post-drug Approval Activities*

A vital part of CDER's mission is to monitor the safety and effectiveness of drugs that are currently available to the American people. FDA has in place

postmarketing programs that monitor marketed human medical products for unexpected adverse events. These programs alert the Agency to potential threats to public health. Agency experts then identify the need for preventive actions, such as changes in product labeling information and, rarely, re-evaluation of an approval decision.

*Post-marketing programs:* FDA maintains a system of post-marketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug approval process. FDA monitors adverse events such as adverse reactions and poisonings. The Agency uses this information to update drug labeling, and, on rare occasions, to re-evaluate the approval or marketing decision.

- The adverse event reporting system (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The ultimate goal of AERS is to improve public health by providing the best available tools for storing and analyzing safety reports. The reports in AERS are evaluated by multi disciplinary staff safety evaluators, epidemiologists and other scientists in the Center for Drug Evaluation and Research's (CDER) Office of Drug Safety.
- The MedWatch program is for health professionals and the public to voluntarily report serious reactions and problems with medical products, such as drugs and medical devices. It also ensures that new safety information is rapidly communicated to the medical community thereby improving patient care. All data contained on the MedWatch form will be entered into the AERS database.
- The prescription drug advertising and promotional labeling webpage provides links to an interactive chart illustrating CDER's process for reviewing and monitoring prescription drug advertising and promotional labeling.
- Pharmaceutical industry surveillance: After a drug is approved and marketed, the FDA uses different mechanisms to assure that (i) firms adhere to the terms and conditions of approval described in the application and (ii) the drug is manufactured in a consistent and controlled manner. This is done by periodic, unannounced inspections of drug production and control facilities by FDA's field investigators and analysts. Manufacturers of prescription medical products are required by regulation to submit adverse event reports to the FDA. The Med Watch website provides information on mandatory reporting by manufacturers. In addition, drug manufacturers must submit either error and accident reports or drug quality reports when deviation from current good manufacturing practice regulations occurs.
- FDA receives medication error reports on marketed human drugs (including prescription drugs, generic drugs and over-the-counter drugs) and nonvaccine biological products and devices. A medication error is

"any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."

- Drug shortages: It is FDA's policy to attempt to prevent or alleviate shortages of medically necessary products. Drug shortages may arise from varying causes, such as the unavailability of raw materials or packaging components, marketing decisions and enforcement issues.
- Therapeutic inequivalence reporting: In the past 10 years, FDA's Center for Drug Evaluation and Research has received an increase of reports of drug products that fail to work in patients because the product simply has no effect or is toxic. These problems are usually attributed to switching brands of drugs.

The following regulations apply to adverse drug event reporting.

21*CFR*310.305 : Records and reports concerning adverse drug experiences of marketed prescription drugs for human use without approved new drug applications

- 21*CFR*312.32: Investigational new drug safety reports
- 21*CFR*314.80: Post-marketing reporting of adverse drug experiences.

There are guidance documents for: Postmarketing Reporting of Adverse Drug Experiences, Enforcement of the Postmarketing Adverse Drug Reporting Regulation, Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products and the Guidance document for CDER staff is CDER's Manual of Policies and Procedures (MaPPs).

Even when an NDA is approved unconditionally, regulatory scrutiny of a drug does not end. In most countries, yearly safety reports must be filed with the applicable regulatory agencies as long as a drug remains on the market, and these agencies independently monitor drug safety.

### *Post-marketing Surveillance*

New drugs should be closely monitored for their safety once they are marketed. Thus post-marketing surveillance (PMS), which is systematic detection and evaluation of adverse reactions, is required for a newly marketed drug when used in clinical practice. The sponsor should furnish Periodic Safety Update Report (PSUR) by conducting PMS.

- *Periodic safety update report (PSUR):* A PSUR is intended to provide an update of the worldwide safety experience of a medicinal product to competent authorities at defined time points post-authorization. Marketing authorization (MA) holders are expected to provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new or changing information. This evaluation

should ascertain whether further investigations need to be carried out and whether changes should be made to the marketing authorization and product information.

PSURs must be submitted for all registered products regardless of marketing status. A single report may cover all products containing the same active substance licensed by one MA holder. The report will usually include all dosage forms and formulations, as well as all indications, associated with such an active moiety. Within the PSUR, separate presentations of data for different dosage forms, indications or populations (for example, children vs. adults) may be appropriate, however an overview of the combined data should also be provided.

- *PSUR reporting cycle in INDIA, EU and USA*
  - *India:* Schedule Y recommends that for all new products, PSURs should be submitted every 6 months for the initial 2 years and thereafter annually for the next 2 years to the Drugs Controller General of India. The reporting cycle requirements in India are similar to that of the requirements of European Union (EU).
  - *European Union:* PSURs are required to be submitted every 6 months for the first 2 years, annually for the three following years and every 3 years, thereafter. In EU, it is generally acceptable to the regulators that the generic companies skip the 6 monthly cycles of initial 2 years and submit the PSURs every 3 years from the date of marketing approval.
  - *United States of America:* Reporting requirements of US FDA are different. The US regulations require quarterly reports during the first 3 years and annual reports, thereafter.

### *Phase IV Clinical Trial*

Phase IV clinical studies are defined as those studies performed with drugs that have been granted marketing authorization. The term "phase IV" is fairly standard and covers the vast majority of postregistration clinical study. Phase IV studies are not considered necessary for the granting of a marketing authorization but they are often important for optimizing the drug's use.

Phase IV studies are also referred to as "marketing studies" or "experience studies" to emphasize that they are conducted once the drug is marketed, rather than prior to its approval by the regulatory authorities. Some other terms, such as "seeding trials" or "observational studies", have also been used, but they usually denote efforts made by marketing departments to encourage physicians to prescribe the new drug, rather than proper trials.

Phase IV studies differ from post-marketing surveillance which is observational and interventional intended mainly to monitor the safety of a marketed drug. Phase IV studies are, in fact, part of this process, but their objectives include efficacy or effectiveness in addition to safety.

*Purposes:* The role of Phase IV clinical trials are to extend knowledge about drug efficacy and to confirm the safety of a new drug in a wider patient

population treated in regular medical care after the drug has been approved for marketing.

- *Effectiveness:* While the efficacy of the drug has been demonstrated in a restricted patient population in phase II and III clinical trials, its effectiveness in a wider population is still largely unknown when the drug comes to the market.

  Phase III clinical trials performed for regulatory purposes usually include highly selected patients, and the results obtained do not automatically translate to the population at large. Phase IV clinical studies, in contrast, include broader patient populations which more closely reflect the reality of medical practice. A case in point is the elderly population, which has historically tended to be excluded from preregistration clinical trial programs and yet account for a substantial proportion of the patient population that consume medicines.
- *Comparison with available treatment:* A second purpose of phase IV studies is to investigate the relative merit of a newly marketed drug as compared to other available treatments. The role of phase I-III trials is to demonstrate that the drug has biological activity and clinical efficacy, hence, the need to compare it, to the extent possible, to a placebo or an untreated control group. In contrast, the role of phase IV studies is to demonstrate that the drug is effective, hence, the need to compare it to alternative treatments for the disease under consideration. Examples of such comparative studies are comparing different chemical entities (e.g. methyldopa versus propranolol for hypertension), medicines within the same pharmaceutical class (e.g. captopril versus enalapril) and demonstration of efficacy in different patient groups (e.g. treatment of systolic hypertension in elderly patient).
- *Test new hypothesis:* A third purpose of phase IV studies is to focus on hypotheses and questions which could not be tested and answered in preregistration trials due to the small number of patients and limited time available before filing for marketing authorization. Questions still unanswered at the phase IV stage can include the following:
  - Long-term benefit or harm of the drug
  - Impact of the drug on secondary endpoints
  - Details of drug administration schedules (such as dose fractionations),
  - Combinations with other drugs, the effect of concomitant medications or supportive care
  - Overall cost-effectiveness in routine medical practice
  - Quality of life
  - Compliance in routine medical practice.

Phase IV studies can also explore:

- New indication for a product: Example, benefits of beta-blockers in heart failure was identified in a phase IV study (CIBIS II trial)

  - New dosage regimen: Example, phenytoin was initially given three times a day for epilepsy management but subsequent studies demonstrated once-daily dosing to be sufficient.
  - New formulations: Example, dry powder inhaler for asthma management instead of metered-dose inhalers.
- *Introduce drug into clinical practice:* Perhaps the more important purpose of phase IV studies is to introduce a new drug into routine clinical practice. The motivation for doing so is not only commercial, it also has a sound scientific and ethical basis. Indeed, valuable drugs may be underused, if clinicians are unconvinced of their merit.

  Phase IV studies provide the ideal setting to further document the safety of a newly marketed drug. Because they are properly controlled (generally, phase IV studies are compared with the existing treatment or with current best practice, they are said to be controlled trial) and closely watched, such studies yield a more reliable safety profile than any method of spontaneous reporting of adverse drug reactions (ADRs), such as Yellow Cards, case reports, literature screening and so forth. In particular, the denominator is known in a prospective trial and therefore, the true incidence of ADRs can be estimated accurately. This is especially useful to study unpredictable ADRs. Phase IV trials should aim at the detection of unpredictable ADRs and should not focus on predictable, non serious adverse events or abnormal laboratory data that are not clinically important, since these add no value to what is already known from the pharmacology of the product and from preregistration trials.

  While relatively common adverse events are well documented at the end of phases I-IV, rare ADRs will require the treatment of a larger number of patients to be detected.

### *Design Considerations*

Approach in designing phase IV studies should be to minimize the risk of performing unnecessary trials and to ensure that trial has pragmatic and correctly balanced objectives that meet both company and external needs. It must be thoughtfully designed to properly address a serious question of interest to those health care professional who will be using and paying for the drug.

*Randomization:* The most crucial aspect of phase IV trials is that they should be based on a sound statistical design. Claims of effectiveness and/or efficiency can rarely be made on the basis of nonrandomized studies. Properly randomized studies of sufficient size yield a reliable and definitive answer, even if they are ultra-simple. Publication of their results may have a major impact on medical practice.

One objective of phase IV studies is to study the effectiveness of a drug in current clinical practice. This implies that the number of patients entered in such studies be large enough so as to answer the questions of interest with

reasonable certainty. In fact, the efficacy of a new drug may be expected to be lower in phase IV studies than in phase III trials, because less responsive patients may be included in the trial, the conditions in which the patients are treated may be less tightly controlled, less experienced clinical investigators may be involved, and so on. The sample size of a phase IV study should take all these factors into account.

*Broad eligibility criteria:* One of the main objectives of phase IV studies is to study the drug in wide patient populations. This implies that the eligibility criteria in such studies be relaxed as compared to those of preregistration trials. Several authors have discussed the relative merits of strict versus broad eligibility criteria. As a general rule, strict criteria seem appropriate for preregistration clinical trials and broad criteria for phase IV studies. No patients should be excluded from phase IV studies except, if:

- There is a safety concern if they receive the drug or
- There is a sound basis for targeting certain subpopulation of patients.

The decision to enroll a patient in phase IV study is best left to the discretion of the attending physician, rather than regulating the process by means of lengthy lists of inclusion and exclusion criteria. All patients should be included unless the physician is uncertain about the benefit of either of the treatments to the patient, only then can the patient can be excluded.

*Active control and equivalence trials:* Many new drugs have to be compared to placebo to be granted marketing authorization even though an active treatment is known for the disease considered. Yet, the relevant medical question is not to show that the drug is biologically active as compared to placebo, but rather to prove that the drug has medical or economical benefits over the currently available treatment(s). Thus, there is an important place for phase IV studies with "active controls," which are not required for regulatory reasons yet are essential for medical practice.

When studies use an active control group, it is often of interest to show that the new drug has the same efficacy as the control group (rather than higher efficacy), in which case these studies are called "equivalence" studies (or "active control equivalence" studies). Such trials are needed when a new drug is not expected to have better efficacy than the standard therapy, but offers a better safety profile, is more practicable, or is less expensive than the standard therapy, and should, therefore, be substituted for it in routine clinical practice. There is also an important place for phase IV "equivalence" trials with such new drugs.

### *GCP Standards*

ICH-GCP is the standard applied by the vast majority of pharmaceutical companies for phase I- IV clinical trial programs, without distinction of phase or purpose of the trials.

*Simplified standards:* The spirit of GCP can be maintained even if its implementation is adapted to the post registration setting. First, the intensive monitoring and site visit frequencies recommended by the GCP guidelines fall far beyond the budget of most post-registration programs. Monitoring is among the most costly aspects of trial management, and if it is required to validate data submitted to regulatory agencies, it may not be needed for studies to yield informative answers. If intensive monitoring is imposed on all trials, a well-intended sponsor might be tempted to reduce the number of patients required by a phase IV project (or perhaps to drop the project altogether) rather than to relax the GCP requirements so as to keep the budget within reasonable limits. In phase IV studies, monitoring could well be limited to an initiation and close out visit, or even in some cases to no visit at all. Second, the collection and filing of essential documents can be considerably reduced in phase IV clinical trials.

Third, quality control, which also needs to be highly detailed in a new drug application, may receive much less attention in the post-registration setting without impairing the scientific validity of the trial. For example, checking patient compliance through pill counts would be unfeasible, but also pointless in most situations of public health relevance. No measure of compliance is needed when the purpose of the study is to investigate the effect of a drug as actually taken by the patient rather than as intended by the investigator. Since in phase IV settings the drugs are used as recommended in the summary of the product characteristics, no special safety by the investigator concern should arise from their use.

Phase IV trials must aim at confirming the clinical benefit of a new product in a wide patient population and this is best achieved through large, simple, randomized clinical studies with realistic rather than exhaustive quality control.

Phase IV studies have been accepted by many companies as a part of the drug development process. These studies should still comply with ICH GCP. However, the level and nature of safety monitoring may differ compared with pre-authorization studies.

Overview of clinical trial phases is discussed in Table 1.4.

## PHARMACOVIGILANCE

The World Health Organization in 2002 defined pharmacovigilance as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems'. The principle of identifying and responding to drug safety issues apply equally to pre-marketing period but the term 'Pharmacovigilance' originated in the post-marketing arena. Pharmacovigilance is seen as a specialist discipline within the industry and most large pharmaceutical companies have sizable pharmacovigilance departments. Pharmacovigilance is a shared responsibility that is performed by doctors, pharmacists and pharmaceutical

**Table 1.4:** Overview of clinical trial phases

| | | | | *Phase IV* |
|---|---|---|---|---|
| Objectives | Determine the metabolic and pharmacological actions and the maximally tolerated dose | Evaluate effectiveness, determine the short-term side effects and identify common risks for a specific population and disease | Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risk-benefit ratio in a demographical diverse sample | Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the FDA |
| Factors to be identified | • Bioavailability<br>• Bioequivalence<br>• Dose proportionality<br>• Metabolism<br>• Pharmacodynamics<br>• Pharmacokinetics | • Bioavailability<br>• Drug-disease interactions<br>• Drug-drug interactions<br>• Efficacy at various doses<br>• Pharmacodynamics<br>• Pharmacokinetics<br>• Patient safety | • Drug-disease interactions<br>• Drug-drug interactions<br>• Dosage intervals<br>• Risk-benefit information<br>• Efficacy and safety for subgroups | • Epidemiological data<br>• Efficacy and safety within large, diverse populations<br>• Pharmacoeconomics |
| Data focus | • Vital signs<br>• Plasma and serum levels<br>• Adverse events | • Dose response and tolerance<br>• Adverse events<br>• Efficacy | • Laboratory data<br>• Efficacy<br>• Adverse events | • Efficacy<br>• Pharmacoeconomics<br>• Epidemiology<br>• Adverse events |
| Design features | • Single, ascending dose tiers<br>• Unblinded<br>• Uncontrolled | • Placebo-controlled comparisons<br>• Active controlled comparisons<br>• Well-defined entry criteria | • Randomized<br>• Controlled<br>• 2-3 treatment arms<br>• Broader eligibility criteria | • Uncontrolled<br>• Observational |
| Duration | Up to 1 month | Several months | Several years | Ongoing (following FDA approval) |

*Contd...*

*Contd...*

| | *Phase I* | *Phase II* | *Phase III* | *Phase IV* |
|---|---|---|---|---|
| Population | Healthy volunteers or individuals with the target disease (such as cancer or HIV) | Individuals with target disease | Individuals with target disease | Individuals with target disease as well as new age groups, genders, etc. |
| Sample size | 20 to 80 | 200 to 300 | Hundreds to thousands | Thousands |
| Example | Study of a single dose of drug X in normal subjects | Double-blind study evaluating safety and efficacy of drug X vs. placebo in patients with hypertension | Study of drug X vs. standard treatment in hypertension study | Study of economic benefit of newly-approved drug X vs. standard treatment for hypertension |

companies throughout the product life cycle. However, post-marketing surveillance is solely a sponsor initiated activity. Post-marketing surveillance is a component of pharmacovigilance.

### Terminology

- *Adverse drug reaction (ADR):* An unintended reaction to a drug taken at doses normally used in man.
- *Adverse event (AE):* A negative experience encountered by an individual during the course of a clinical trial, which may or may not be associated with a drug. If an association between an AE and a drug is established the event is referred to as an adverse drug reaction.
- *Serious adverse event (SAE):* Any adverse event is referred to as a serious adverse event when the event is fatal, life-threatening, permanently disabling, or which results in hospitalization.

### Rationale and Aims of Pharmacovigilance

Events such as the thalidomide tragedy, which was caused by the drug thalidomide, taken by mothers during their pregnancy leading to limb deformities in newborns highlighted the importance of the need for a pharmacovigilance system. However, the need for a pharmacovigilance system in all countries was highlighted by the exclusive adverse reaction occurrence to the drug clioquinol in Japan.

The main reason to monitor ADR for an approved product is due to limitation of pre-marketing clinical studies to identify safety issues. Following are the reasons why pre-marketing studies are inadequate to cover all aspects of drug safety:

- Relatively small number of patients studied as compared to large number of patients exposed after marketing.
- The frequent exclusion of individuals who may be at greater risk of ADRs e.g. the elderly, children, pregnant women and patients with significant, concurrent disease and taking other medications.
- The structured nature of clinical studies where drugs are given at specific doses for limited period with careful monitoring by experienced investigators. In clinical practice, a drug is unlikely to be used according to the instruction and there is less monitoring.
- Duration of clinical studies is limited and there could be long latent period between starting the drug and the development of ADR which may not be detected in clinical studies.

Based on these observations the primary aims of pharmacovigilance programs are as follows:

- To improve patient care and safety in relation to the use of medicines, and all medical and paramedical interventions
- To improve public health and safety in relation to the use of medicines

- To contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use
- To promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.

## Pharmacovigilance Process

In many countries, pharmacovigilance is part of governmental drug regulation. In several countries, it has become mandatory for pharmaceutical companies to assess case causality in case reports of adverse reactions to their own drugs.

The pharmacovigilance process includes the following steps:

- Detecting and reporting an adverse drug reaction
- Data collection and capture
- Data storage and maintenance
- Data selection, retrieval and manipulation

Pharmacovigilance relies on information gathered from the collection of individual case safety reports and other pharmacoepidemiological data. For the detection of new adverse reaction, post-marketing reports by alert individuals is the main source of information.

- *Reporting of an adverse drug reaction:* A paper based, ADR (adverse drug reaction) form is filled out with patient and reaction details. Such data recorded on a paper form is later the basis for data entry into a computerized system. ADR reporting is of two types—spontaneous reporting and mandatory reporting.
  - *Spontaneous reporting:* This is the most common form of ADR reporting where in healthcare professionals identify and report any suspected adverse drug reaction to their national pharmacovigilance centre or to the manufacturer. Spontaneous reports are almost always submitted voluntarily.
  - *Mandatory reporting:* Manufacturers are required to submit reports they receive from healthcare providers to the national authority, in the form of a PSUR (Periodic Safety Update Report).
- *Data collection and capture:* Data collection and capture in a database management system involves creation, update and transformation of information.
- *Data storage and maintenance:* Once data have been entered into a database, it could be assumed to be a static system, in which nothing can change. However, maintaining the quality of data that has been stored poses its own challenges. The data must be secured against partial and complete loss. The integrity of the data must be protected.

- *Data selection, retrieval and manipulation:* The production of useful output involves the transformation of raw data into a refined representation which should remain truthful to the source of information and be appropriate for analysis. The common technique for selection, retrieval and aggregation of data in a database involves the use of query languages. Query commands can be executed through specially designed search interfaces.

Once the ADR data are obtained the data are sent to the WHO Uppsala Monitoring Centre where the data are stored in the central database. Based on the information in the central database a signal can be generated. The WHO definition of a pharmacovigilance signal is "reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously". Signal detection is one of the most important objectives of pharmacovigilance. The whole process of risk/benefit evaluation depends on effective detection of signals.

The process of signal detection is done by collection of adverse event reports followed by assessment of individual reports or clusters of reports in spontaneous reporting systems, observational databases and clinical trials. The detection of signals requires clinical assessment assisted by epidemiological and statistical analyses.

### WHO and Uppsala Monitoring Centre (UMC)

The Uppsala Monitoring Centre is the field-name of the WHO Collaborating Centre for International Drug Monitoring. The UMC is responsible for the management of the WHO program for international drug monitoring.

The WHO Program for international drug monitoring provides a forum for WHO member states to collaborate in the monitoring of drug safety. Within the program, individual case reports of suspected adverse drug reactions are collected and stored in a common database.

Functions of the WHO Program for international drug monitoring include:

- Identification and analysis of new adverse reaction signals from the case report information submitted to the National Centres and from them to the WHO database. A data-mining approach is used at the UMC to support the clinical analysis made by a panel of signal reviewers
- Information exchange between WHO and National Centres, mainly through 'Vigimed', an e-mail information exchange system
- Publication of periodical newsletters, guidelines and books in the pharmacovigilance and risk management area
- Supply of tools for management of clinical information including adverse drug reaction case reports. The main products are the WHO Drug Dictionary and the WHO Adverse Reaction Terminology

- Provision of training and consultancy support to National Centres and countries establishing pharmacovigilance systems
- Computer software for case report management designed to suit the needs of National Centres (VigiFlow)
- Annual meetings for representatives of National Centres at which scientific and organizational matters are discussed
- Methodological research for the development of pharmacovigilance as a science.

The functions of the UMC are as follows:

- To co-ordinate the WHO program for international drug monitoring and its more than eighty member countries
- To collect, assess and communicate information from member countries about the benefits, harms and risks of drugs and other substances used in medicine to improve patient therapy and public health worldwide
- To collaborate with member countries in the development and practice of the science of pharmacovigilance.

### Pharmacovigilance in India

The Government of India with the assistance of World Bank initiated the National Pharmacovigilance Programme in 2004. The Central Drugs Standard Control Organization (CDSCO) coordinates this country-wide pharmacovigilance program under the aegis of DGHS, Ministry of Health and Family Welfare.

India did not have a formal pharmacovigilance system in the past to detect adverse reactions of marketed drugs as very few new drugs were discovered in India. However, due to the increase in the number of new drugs being approved for marketing in India, there was a need for a vibrant pharmacovigilance system in the country. The legislative requirements of pharmacovigilance in India are guided by specifications of Schedule Y of the Drugs and Cosmetics Act, 1945. The Schedule Y also deals with regulations relating to preclinical and clinical studies for development of a new drug as well as clinical trial requirements for import, manufacture, and obtaining marketing approval for a new drug in India. The section entitled post-marketing surveillance in this schedule includes the requirement for submission of periodic safety update reports (PSURs), PSUR cycle, template for PSUR, and the timelines and conditions for expedited reporting.

As per the requirements of Schedule Y of the Drugs and Cosmetic Act, 1945, the reporting of adverse events from the clinical trials is mandatory. Schedule Y provides details of timelines for reporting adverse events by sponsor, investigator and ethics committee. These details are listed below (Fig. 1.21).

Any unexpected serious adverse event occurring during a clinical trial should be communicated by the sponsor to the Licensing authority within 14 calendar days.

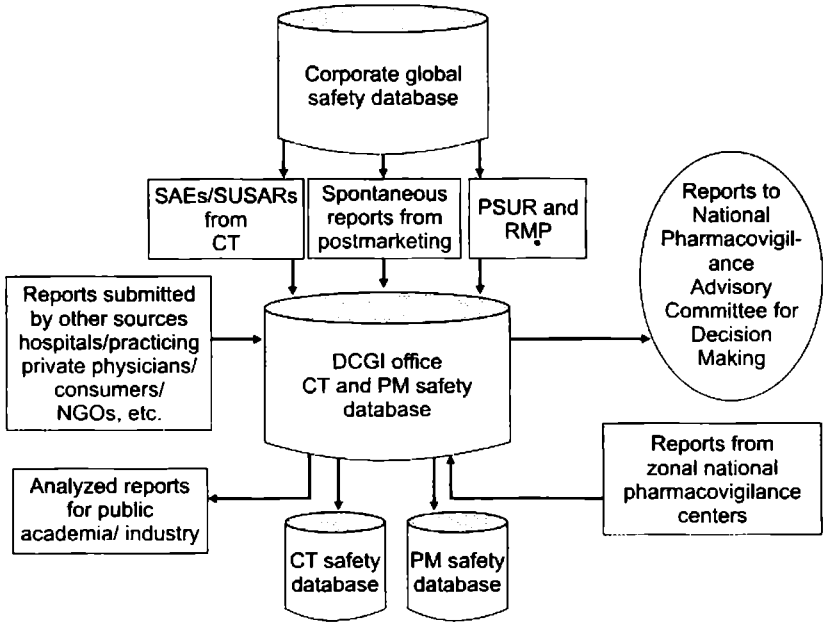



**Fig. 1.21:** Flow of pharmacovigilance data in India

*Source:* http://www.ijp-online.com/temp/IndianJPharmacol393124-6222353-014342.pdf

Any unexpected serious adverse event occurring during a clinical trial should be communicated by the investigator to the sponsor within 24 hours and to the ethics committee within 7 working days.

### Pharmacovigilance in the United Kingdom

The primary system for reporting suspected ADRs in the United Kingdom is the "Yellow Card Scheme" (YCS) which was introduced in 1964 as a result of the thalidomide tragedy. The YCS is a 'spontaneous' reporting system wherein health professionals voluntarily complete a card at the time a patient presents with a potential ADR. Completed Yellow Cards are submitted to the Medicine and Healthcare Products Regulatory Agency. Since 1991, data have been stored on the adverse drug reactions on-line information tracking system (ADROIT).

Until 2002, Yellow Cards were completed by doctors, dentists, coroners and pharmacists who suspected that an adverse event (AE) was related to a particular medication or combination of medications. In 2002, the YCS was extended so that nurses, midwives and health visitors could also report suspected ADRs.

EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorization of medicinal products in the European Economic Area (EEA).

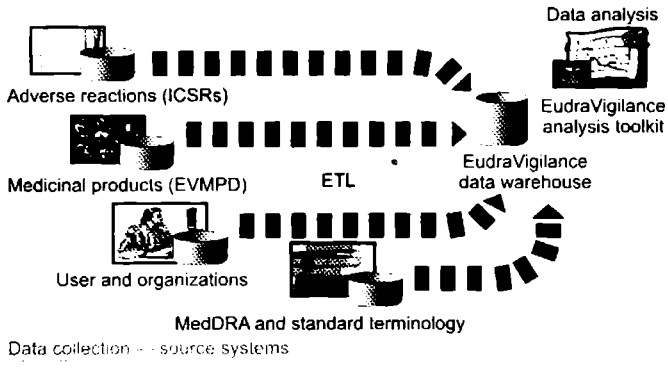



**Fig. 1.22:** Components of Eudravigilance analysis system

*Source:* http://eudravigilance.emea.europa.eu/human/EVComDataAnalysisSystem.asp

EudraVigilance supports in particular (Fig. 1.22):

- Electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between the European Medicines Agency (EMEA), national competent authorities, marketing authorization holders, and sponsors of clinical trials in the EEA
- Early detection of possible safety signals associated with medicinal products for human use
- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions
- Decision making process, based on a broader knowledge of the adverse reaction profile of medicinal products especially in the frame of risk management.

### Pharmacovigilance in the United States of America

MedWatch is the reporting system for adverse events in the USA. This system provides important and timely clinical information about safety issues involving medical products, including prescription and over-the-counter drugs, biologics, medical and radiation-emitting devices, and special nutritional products.

MedWatch allows healthcare professionals and consumers to report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use. Reporting can be done on line, by phone, or by submitting the MedWatch 3500 form by mail or fax.

The FDA Form 3500 are used by healthcare professionals and consumers for voluntary reporting of adverse events noted spontaneously in the course of clinical care, not events that occur during IND clinical trials or other clinical studies. Those mandatory reports are submitted to FDA.

## Pharmacovigilance Software

The fast and reliable reporting of ADR (adverse drug reaction) data is an important task for pharmaceutical companies. In order to comply with regulations, good information management systems are essential. Many of the systems available are client specific.

Drug safety software applications should be simple, easy to use with functionality to comply with ADR reporting requirements, web based to enhance cross-divisional and cross affiliate work flows as well as being able to scale up with increasing demands, company growth and mergers.

Features of good ADR management tool (drug safety software):

- ICH compliance by design including E2B reporting
- Collect and report data to meet all common international regulations including FDA, CIOMS (Council for International Organizations of Medical Sciences), EMEA (European Medicines Agency), and MHRA (Medicines and Healthcare Products Regulatory Agency)
- Code against standard dictionaries including current MedDRA
- Data validation, cross-field validation checks and use of pick lists
- FDA 21 CFR part 11 compliance
- Duplicate check
- Built-in query tool
- Data export function
- Integrated spell-checker
- Full audit trail
- Mandatory fields
- Letter generation using Microsoft Word
- Open database for use of third-party query and reporting tools
- Use of reference dictionaries, e.g. contacts, lab tests.

### *Vigibase*

From the start of the international movement for drug safety it was recognized that pooling data in a central database in order to detect signals early was essential. The creation of the WHO Collaborating Centre for International Drug Monitoring, collecting case information in an internationally agreed format has led to a high-quality, accessible data store for use by researchers from National Centres connected to the WHO Drug Monitoring Program.

Over the years, many technical modifications have been made to the ways in which data held in the WHO database were processed and retrieved. In the mid 1990s, the UMC decided to start work on a new database system for the management of WHO Program case report information. This led to the development of a new web-based database search program called Vigibase which makes use of XML (international computer language understandable in different computer programs). XML makes searching easier and also improves data handling, as data fields and their contents are kept together as part of the structured document.

Remote access to information in the WHO database takes place through internet-based interfaces, a main advantage of this is that the user does not have to install the application interface software on local computers, but can run the program from an internet browser. As new search modules are added or other improvements made, these become instantly accessible for all users, without the need for reinstallation of software.

Vigibase is updated every night, so all correct reports will be entered within 24 hours of receipt by the UMC. Another feature is that technically incomplete reports will be stored as a searchable subset of the database in the same structure as the correct ones. The report handling system has built-in features to speed up corrections, keeping the same high quality standard. For acceptance into the ADR (adverse drug reaction) database, a report has to pass an extensive, error-checking procedure while in a buffer data folder, involving the following:

- Syntax check
- Inter-field coherence check
- Check for duplication
- Check of drug names and adverse reaction terms.

Vigibase includes new features of the WHO Drug Dictionary, for entering more detailed information about each drug name. However, since ICH has declared it mandatory to use MedDRA terms, Vigibase is also compatible with the MedDRA software.

The WHO database, Vigibase, has these main tables:

- *Report:* Case identification, dates, classification
- *Patient:* Identification, age, gender, outcome, causality
- *Background:* Patient's previous illnesses/predisposing conditions
- *Death:* Cause of death, causality, and postmortem information.

### *Total Safety—A Commercially Available Pharmacovigilance Software System*

In order to fulfill the regulatory requirements it is essential for companies to have proactive pharmacovigilance programs that include comprehensive risk management plans and signal detection/analysis throughout a product's life cycle.

To address these needs, Aris Global has developed software known as total safety. Total Safety is an integrated software solution that enables companies to implement effective domestic and global pharmacovigilance, clinical safety and risk management programs.

The Total Safety site comprises of the following industry-leading solutions

- ARISg™ - The world's leading pharmacovigilance and clinical safety system
- ARISj™ - Japanese pharmacovigilance system

- agXchange ESM™ - Modular gateway for extended electronic exchange
- agXchange IRT™ - Inbound receipt and triage of adverse event information
- agConnect™ - Clinical safety reconciliation system
- agComposer™ - Comprehensive periodic and aggregate reporting system
- agSignals™ - Advanced signal detection and data mining system.

Of these solutions agComposer is a comprehensive periodic and aggregate reporting system that schedules, creates and tracks a full range of submission-ready, ICH-approved periodic reports, including PSURs, bridging reports and other annual reports such as the ASR.

agComposer automatically sets deadlines and reminders to ensure reporting obligations are met on time. As a periodic or aggregate report is due, it can only be generated in cooperation with other departments. agComposer fully integrates the required departments and processes—clinical trial, regulatory and medical information—to ensure deadlines are met and reports meet the various regulatory agency requirements.

## REGULATORY APPROVALS FOR REGISTRATION OF DRUGS

### Drug Regulation Scenario

Drug regulation has developed over the past 50 years in response to crises in relation to pharmaceutical products. The initial regulatory standards were primarily related to ensuring the pharmaceutical quality of medicinal products and subsequent developments in the early 1960s led to the development of standards for testing efficacy and safety of new medicines as well.

Despite the existence of standards for drug regulation since 50 years, there are still many problems with the safety and quality of medicines. The primary aim of drug regulation is protection of public health. Medicines are not normal 'commodities'; they should meet health needs, and access to essential medicines is a fundamental human right. Thus, medicines have additional social value. Appropriate use of medicines requires a 'learned intermediary' to prescribe them and a trained person to dispense them appropriately before the consumer takes them.

The market for pharmaceuticals is therefore not a usual market in economic terms, there are major informational asymmetries and monopoly behaviors by suppliers that include patent rights and 'data exclusivity' clauses that further strengthen monopolies. In addition to the quality, safety and efficacy requirements, therefore, these are the arguments for regulating the pharmaceutical industry more generally and controlling what it supplies.

Over the past 10 to 15 years, the balance between controlling pharmaceuticals in the interests of ensuring public health and encouraging the development of the pharmaceutical industry has shifted in favor of the innovative industry. Regulation has been seen as an 'impediment' to profits

and industry development. The resulting pressure on regulators has been to approve new medicines quickly—sometimes on the basis of what can only be described as preliminary data—to remove regulatory 'bottlenecks', to carry out reviews and evaluations of data in the shortest possible time. There has also been pressure from patient groups to speed up access to new, 'breakthrough' medicines, for example in the field of HIV/AIDS.

## Challenges Faced by the Pharmaceutical Industry

The drug development process is known to be complex, costly and time-consuming. The process is also risky in that most compounds that undergo clinical testing are abandoned without obtaining marketing approval. The cost of new drug development is also critically dependent on the proportion of drugs that fail in clinical testing. Given the length and cost of the drug development process, careful consideration of all factors that have a significant impact on the process is needed to appropriately allocate research and development resources.

The pharmaceutical industry is faced with the challenge of surviving and succeeding in an environment that has become more complicated and uncertain, and one that is characterized by rapid developments in science and technology, and organizational change. From the standpoint of the pharmaceutical industry, the drive for change is the result of a combination of political, economic, technological and social factors; all of which have helped redefine the dynamics of this particular industry. If product is to be marketed globally, pharmaceutical industry is burdened with different requirements for registration of product.

Issues and challenges faced by pharmaceutical industry are not restricted during drug development process alone but well beyond this which includes registration of their product and placing their product in highly competitive environment. Following topics discusse few of the issues.

### *Barriers during Drug Development Process*

Most of the tools used by pharmaceutical company for toxicology and human safety testing may fail to predict the specific safety problem that ultimately halts development or that requires post-authorization withdrawal. More generally, there are too few analytic tools (e.g. analytical devices, assay systems, surrogate markers and cell culture methods) to assist in providing medicine safety and effectiveness studies more quickly, with more certainty, and at lower cost. Key enabling technologies involving the use of animals and the use of human tissue in biomedical research are subject to complex regulations which impede drug development.

Regulatory authorities are becoming more risk-averse. This lack of flexibility only entrenches the existing regulatory requirements and perceptions, and often results in the need for expanded studies to quantify potential adverse events. Industry experts feel that alternative approach to

traditional randomized controlled trial should be evaluated that does not compromise safety and efficacy. Such alternative approaches have been successfully used for high risk diseases such as cancer or AIDS where accepting results from limited size studies combined with post-authorization monitoring have allowed products to come to market far more quickly than by conventional approaches.

Poor communication between the industry, physicians and regulators during medicines development results in requests for additional data and regulatory questions following submission, and in turn these requests lead to increasing unpredictability of outcomes and delays in the marketing authorization process.

### *Challenges Related to Cost Factor*

Over the past few years, the growth of the worldwide pharmaceutical industry has been slower than the increases in research and development (R & D) costs, and this has led to a cost-earnings differential that cannot be sustained indefinitely. Firms have found it increasingly difficult to sustain historical levels of growth principally because of two converging factors. First, the earnings of the pharmaceutical industry are being increasingly squeezed between pricing constraints due to government policies and generic competition; and second, through the rising costs of R & D due to increasing legislative requirements and growing technological sophistication.

As a consequence of these pressures on pharmaceutical earnings, combined with that of rising R & D costs, pharmaceutical firms have been forced to adopt a number of cost containment measures in addition to those pertaining to the safety and efficacy of drugs. The need to demonstrate 'value' to the consumer has now become imperative.

Traditionally, the pricing methods adopted in the former producer-driven environment for pharmaceuticals was essentially based on what was considered to be 'fair returns' for the high costs and risks associated with innovation. Today, however, much of that has changed. The deregulation of generic products has helped to bring about a much greater acceptance of product substitution, which in turn has led to changes in consumer choice—an event that has acted as a catalyst for change within the marketplace. Therefore, rather than being producer-driven, the market for pharmaceuticals today is essentially customer-led.

Price has become the key indicator of how the marketplace truly values the products that are discovered, marketed and sold. Consequently, the price that a company charges for a product is the culmination of every decision made along the chain of discovery to marketing. Therefore, in order to be able to survive this challenging environment, pharmaceutical companies can no longer permit their internal processes to determine price levels, as this has now become the privilege of the customer.

The demand for innovation in an increasingly complex, global business environment has necessitated new approaches to organization because the requirements for success in the marketplace have changed in a number of profound ways. In addition to demands for efficiency, quality and flexibility, pharmaceutical companies are also required to simultaneously cut costs, improve standards of quality, shorten product development times, and introduce innovative products that customers value. As a result, companies have been forced to re-examine every aspect of how their businesses are implemented and conducted, and this has given rise to a number of important issues that question the long-held and accepted ways of managing pharmaceuticals.

The discovery, development and marketing of new pharmaceutical products are the essence of the research-based pharmaceutical industry. As a result of the transformation toward a customer-led marketplace, important issues have been raised which present a number of challenges to many pharmaceutical companies. Of greater significance is the issue of cost.

The total cost of bringing a new product to market from discovery through to launch, including the cost of capital with a risk premium and the cost associated with failures, is estimated to be approximately $800 million, over a 10 to 12 years period. Of this total, around 30 percent of the costs are concentrated in exploratory research while the remaining 70 percent are invested in subsequent development phases. At the same time, the percentage of money spent on innovation has been increasing steadily from around 6 percent in the 1960s to approximately 20 percent by the late 1990s.

Both the increased cost together with the growing quantity of resources being invested in pharmaceutical innovation are due to a combination of factors other than inflation. Traditionally, the rate of growth of the firm has been linked to new product introductions, as it was believed that increased investment in innovation generally guaranteed more novel products. Furthermore, the shift from acute to chronic therapy has increased the complexity of research as well as the regulatory approval process. Demands for regulatory data have almost doubled since the mid-1980s thus increasing the time it takes to get a product to market. In addition, companies with low levels of new product innovation have spent vast amounts of capital in an effort to secure future sources of revenue.

Owing to the culmination of these factors pharmaceutical companies face the immediate prospect of lower margins and almost no price flexibility for existing products in the world's largest markets. Therefore, the fundamental question that arises is whether pharmaceutical companies can afford to keep spending on innovation at current industry levels?

### *Challenges to Improve Input/output Ratio*

Regarding the level of research productivity within pharmaceutical firms, two important features have emerged. First, companies have discovered that

as research moves up the technology curve it not only becomes more complex and costly, but that the level of output begins to decline as well. Second, as size and complexity increase, so do organizational inefficiencies. This combination of technological complexity, increase in cost, the effect of diminishing returns, as well as greater bureaucracy have consequently led to growing levels of inefficiency within the innovation process. The implication of this long-term decline in innovative productivity within the pharmaceutical industry suggests that companies are not as successful as they used to be at innovation.

It is universally acknowledged that in customer-led markets the customer's perception of value is paramount. It is for this reason that the products that do not meet the requirements and satisfaction of the customer base will not be able to recoup the investments made. Therefore, this is another challenge faced by pharmaceutical companies to improve the input/output ratio by customizing innovative output to match more closely the needs of sophisticated, cost-conscious and value-driven customer base.

### *Challenges in Producing Unique Product Rapidly*

Historically, the largest pharmaceutical companies have achieved the majority of their sales by developing so-called annuity drugs that treat long-term chronic diseases within the largest number of patients. Because of this, the real strength of all of the pharmaceutical majors is contained in the various therapeutic classes they serve. However, most of these categories are now mature and already have relatively well satisfied patients. With mature products going off patent and with no new major therapies on the immediate horizon, there is the potential for a price ceiling to be placed for large-volume categories experiencing the move to generic status for many of the leading products. Consequently, the move toward organized generic, class and therapeutic substitution is a signal that imitative R & D will be less rewarding in the future. Economic venture into large number of 'me-too' drugs might be a futile.

One of the most important issues facing most pharmaceutical companies at present is the question of whether they have the capacity to convince their customers to pay premium prices to cover production costs, as well as to provide satisfactory returns for the future development of additional undifferentiated drugs. Many of the currently untreatable diseases such as AIDS, cancer, migraine and multiple sclerosis are those that provide the most lucrative business opportunities. At the same time, healthcare providers and insurers within the industrialized nations continue to debate the sensitive issue of whether society can afford the costs of maintaining and extending the quality of life. As a result, an inherent paradox exists.

The challenges pharmaceutical companies are facing is to rapidly produce unique products that are truly successful in treating unconquered diseases, while at the same time obtaining high prices that are required to pay for cutting-edge research.

### *Challenges in Establishing "Value- for- Money"*

One of the most significant developments in the move toward customer-led change is the accelerated search for mechanisms to establish a sense of 'value-for-money'. This has led to the creation of pharmacoeconomics, which encompasses a set of potentially useful approaches for making more rational decisions for selecting drugs. Such approaches include analysis of cost versus benefit ratio, cost effectiveness, cost minimization, cost utility, the quality of adjusted life years and eventual outcomes. Pharmacoeconomics will enable the pharmaceutical companies to demonstrate value in order to support the marketing of products. It could also be used when selecting projects for R & D purposes.

In most instances, however, there are conflicting forces at work. On one hand, healthcare payers as well as providers demand the lowest-cost solution to their healthcare problems while remaining partial to acquisition costs. Conversely, pharmaceutical companies wish to avoid the downward pressure on prices by focusing on product value rather than on the cost of acquisition. Further escalating the value-cost conflict is the fact that there are no global standards for pharamacoeconomic techniques, coupled with a severe lack of conformity on how customers interpret output. When these factors are combined, the use of a particular set of approaches that are based on single cost structures becomes problematic.

### *Challenges in Convincing Customers to Accept the Product*

In order for pharmaceutical companies to be able to reverse the decline of their profit margins, it is important that an atmosphere of acceptance be created among customers concerning the value of drugs rather than of their costs. If customers are not convinced that healthcare costs can only be reduced through integrated approaches and not by ingredient cost management, then this effort will surely fail. Conversely, unless research-based firms can discover a mechanism through which future returns for a successful product can be secured, thereby justifying the significant investment required for high risk, cutting-edge research, there will be a general decline in the number of products offering genuine solutions to healthcare problems.

Another challenge faced by research-based pharmaceutical companies is the need to convince their increasingly cost-conscious customers to look beyond the management of acquisition costs, and to appreciate instead the overall value of a drug in terms of its total savings in overall healthcare costs.

Furthermore, many of the development pipelines are currently saturated with chemical class variations, which will only serve to provide low-grade improvements in efficacy or safety. Such substances only have a limited potential to create meaningful differentiation over existing brands, or cheaper generic or therapeutic substitutes. In addition, the degree of patent protection available no longer provides a safety net over gross profit margins. Thus, the

key issue centers on the extent to which a customer perceives how much a product is worth.

Inevitably, many pharmaceutical companies will have to implement an in-depth review regarding the potential marketability of their product pipelines. Therefore, pharmaceutical companies, need to decide whether they should continue to develop products for which customers are unlikely to pay enough in order that firms may recoup their development costs, or should such projects be abandoned in the first instance?

### *Challenges due to Changing Market Environment*

In the past, it was widely accepted that the more money and effort were put into innovation the greater was the chance of discovering new products. Corresponding to this stream of thought, it was also believed that the greater the number of new products introduced to the market, the greater the prospect of achieving considerable market success and hence competitive advantage. Although somewhat correct, this is no longer the case due to the changes that have occurred in the marketplace. Since much of today's management practice and operating culture in large industrial research laboratories was established prior to 1970, many of the institutions and instincts developed in this early period are now at odds with current realities. A new set of rules has emerged which now governs the market for pharmaceuticals, and as a result, requires re-examination of the assumptions upon which traditional pharmaceutical management is based.

In today's customer-driven market the degree of innovation success is a function of how well a product is perceived to offer new or better solutions to a customer's clinical problems. Companies are forced to make decisions based on resource allocation. They must favor new and better products, select from those considered marginal that will establish clinical and cost value from the customer's perspective, and abandon all products deemed mediocre. Success in the pharmaceutical industry is no longer determined by product innovation alone, but through a combination of value generating factors.

For many years the role of the physician was deemed crucial to ensuring product success. This was most common in instances where physicians had complete freedom of choice with regard to prescribing, or where there was relatively little concern for cost containment measures. However, since the end of the 1980s a rapid change has occurred as both public and private payers have come to realize that a policy of cost containment could only become truly effective if industry-focused supply side controls are effectively linked with physician and patient focused demand side controls. This has resulted in the development of a wide array of containment measures ranging from formularies to prescribing guidelines, mandatory substitution of cheaper products, as well as practice protocols. Therefore, while the physician remains an important constituent in the marketplace, the upstream consolidation of

buyers together with tighter cost control measures has irreversibly changed the balance of power.

In summary, pharmaceutical manufactures should meet the needs of a modern and aggressive market and satisfy the healthcare need of cost-conscious customers rather than just sell pharmaceuticals. Companies need to look beyond "me-too" products and move towards developing innovative targeted therapies that address the underlying molecular mechanisms of disease. Ultimately, keeping both biology and clinical practice in mind throughout the entire drug discovery and development continuum can increase the likelihood that compounds reaching the development-candidate stage will have the safety and tolerability profiles and pharmaceutical characteristics necessary for successful clinical development.

## CLINICAL DATA MANAGEMENT

### Introduction

All clinical trials are performed to answer certain questions about the efficacy and safety of a drug or device. The answers solely depend upon the quality of data, which are collected during the trial and submitted after the trial. The study data are the immense asset for the pharmaceutical and biotech companies. Probability of getting a marketing approval for a drug or device increases if the study data are accurate. Hence, data management plays a crucial role in ensuring the success of a trial. Adopting proper methods to manage the trial data helps in increasing the quality of data. Learning, practicing and improving upon these methods has led to the creation of clinical data management as a specialty.

Drug development encompasses stages such as formulation, toxicology and clinical trials. Clinical trial or a study in turn has various stages as depicted in Figure 1.23. However these may overlap. A study starts with an objective, which gets translated to a protocol, proceeds with identification of

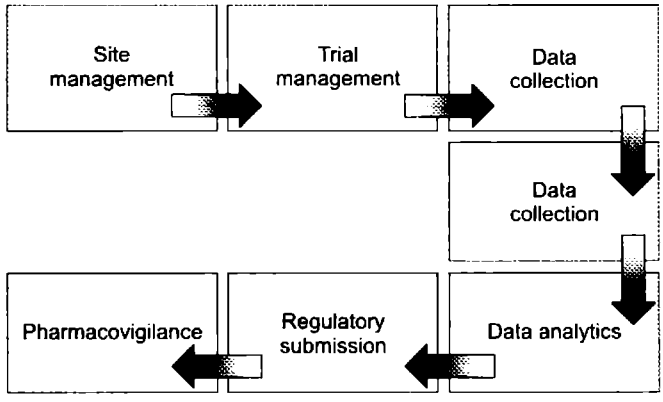



**Fig. 1.23:** Overview of clinical trial processes

sites and management of the trial. Actual process of data management is initiated with the collection of data.

### History of Clinical Data Management

Clinical data management (CDM) has evolved from a data entry process into a diverse process to "provide clean data in a useable format in a timely manner", "provide a database fit for use" or "ensure data are clean and database is ready to lock".

Though clinical data management had to be done with whatever data was collected for clinical trials from its earliest days, the processes were given a major focus in the early 1970s, when the Public Health Service recognized the need for good practices in clinical data management. With the advent of electronically transmitted clinical trial data, standardized practices and procedures developed further. Regulatory requirements have advanced the necessity of clinical data management as a science.

Quality of the trial data is much more critical as pharmaceutical companies invest vast amounts of money in drug research. It is also vital for regulatory submission and approval. Hence, CDM has grown from a mere data entry process to a technology based science.

### Oracle Clinical (OC)

It is a vendor developed data management system and also known as a Relational Database Management System. It is used for managing database design and data acquisition for clinical study.

The global library contained in OC is a central repository for the objects that compose data collection definitions for clinical studies. This allows for objects to be re-used for multiple studies, saves time in study set-up and ensures that there is standardization and consistency of data collection and reporting. OC can be customized to contain "Views" that allow the data to be browsed. System generated error messages are programmed to conduct Data validation. They are called—

*Validations:* Programmatic procedure which checks for illogical or incorrect data, e.g. check AE Start Date is after the Stop Date.

*Derivations*: Programmatic procedure which calculate data based on data that are stored in the database, e.g. Derive Age from Birth date.

The Oracle clinical applications allow electronic data to be created, modified, maintained and transmitted. Therefore, in accordance with 21 CFR Part 11, procedures and controls are established to ensure the authenticity, integrity and when appropriate the confidentiality of electronic records. Such procedures and controls include:

- *Audit trials:* The use of secure, computer-generated, time-stamped audit trials to independently record the date and time of entries and actions that create, modify or delete electronic records

- *Electronic signature certification:* Individuals must be trained to use applicable systems/programs and that training must be documented
- *Electronic signature controls:* Ensure uniqueness
  Two distinct ID components (non-biometric).
  All individuals receive a unique sign-on and password that is considered the electronic signature. Every sign-on ID has assigned security to allow or prevent software access as well as software functionality
  The user sign-on is the legally binding equivalent of the individual's handwritten signature
- *System and data security:* Limits system access to authorized individuals.

### Overview of Clinical Data Management

Clinical data management refers to the management of data capture and data flow processes in conduct of a clinical research. It begins with design of data capture instrument and data collection, continues with data quality control procedures and ends with database finalization. The locked database undergoes a statistical analysis after which it is ready to be submitted to the regulatory authority for approval. Processes used to support the clinical data must be clearly defined and documented. Documents supporting CDM activities include protocol and standard operating procedures (SOPs).

### Data Management Plan

Before starting with the data management processes, a data management plan (DMP) must be put in place. DMP helps to proactively assess and plan for the study-specific data management processes. The DMP serves as the backbone of overall quality system of data management (DM) and outlines:

- How and when each step of the CDM process must be carried out
- What documents are to be created and finalized
- Defines the data management tasks, responsibilities, deliverables and timelines
- Which SOPs or guidelines will apply to the various processes
- What document or output to collect or produce
- What level of quality must be achieved.

Preparation, review and finalization of the DMP involves participation from sponsor, lead data managers, project managers, biostatisticians, database programmers, lead clinical research associates (CRAs), project directors, medical monitors and clinical scientists.

Some of the key elements included in a typical DMP include (Fig. 1.24):

- Trial work flow
- Study set-up/design
- Computing environment
- Database development and testing
- CRF management, including CRF flow and tracking

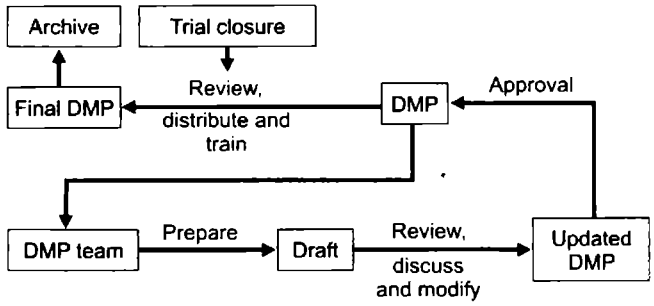



**Fig. 1.24:** An outline of the development and review process of a DMP

- Data capture, data entry and study specific guidelines
- Serious adverse event reconciliation
- Data validation procedures
- Coding procedures
- Lab data management
- Data transfer procedures
- Discrepancy management
- Reporting processes
- Study lock
- Quality audit.

### Data Capture and Collection

Data capture is a key concept in data management. This refers to procedures for gathering and recording data from or related to subjects in the study. It could either be paper-based or through electronic data capture (EDC). Promise of enhanced efficiency has led to increasing movement towards implementation of the electronic medical record and to computerized automation in general.

#### *Paper CRF Based Study*

Trial data are written on paper CRF(s) at the investigator sites. The study coordinator refers to "the source" (patient, patient's chart or other medical records, source document, etc.) and transcribes the data onto the paper CRF. This is just the first of many 'transcription' processes in clinical data management. These CRF(s) are periodically reviewed by CRAs to ensure that the data is valid and complete. A copy of the CRF is retained at the site and additional copies are sent to the sponsor and the data management team where the data is entered into a database. Data can be transferred from the paper CRF to the customized database in different ways.

- One way is to scan the CRF. The scanned images of the CRF(s) are electronically transferred to the database. Data entry is then performed as per the scanned images of CRF(s) into the database

- Image recognition technology includes optical character recognition (OCR) and optical mark recognition (OMR). Here the data is captured from handwritten printed copies. Then the handwritten information is translated into electronic text documents. The image recognition software converts the scanned image to machine-readable and editable text.

Data editors then review the data in the database and identify any discrepancies in the data. These are resolved using a Data clarification form (DCF), which is sent to the investigator at the site. After all the discrepancies are resolved, the data in the database is declared as "clean", at which point the database is locked. These paper CRF(s) have to be retained for up to 15 years at the sponsor and investigator sites.

Paper based trials have their own disadvantages. The cost of printing and distributing CRF(s) is high. Enormous amount of time is spent in resolving simple data entry errors. Study performance information is not available to project managers in time for smooth conduct of trials. Repetition of tasks by different departments in regard to serious adverse event recording and reporting is common.

### *EDC Based Study*

EDC is the capability to collect data electronically, without using paper CRF(s). It could consist of both online and off-line technologies. EDC is defined by the Clinical Data Interchange Standards Consortium (CDISC) as follows:

*"Collecting or acquiring data as a permanent electronic record with or without a human interface (e.g., using data collection systems or applications that are modem-based, web-based, optical mark/character recognition, or involve audio text, interactive voice response, graphical interfaces, clinical laboratory interfaces, or touch screens). Note: 'Permanent' in the context of these definitions implies that any changes made to the electronic data are recorded via an audit trial."*

Interactive voice response system (IVRS) consists of interactive speech or touch-pad menu-driven systems that take the caller through a series of prompts. Responses are entered through a telephonic keypad. This technology is typically used in areas such as patient randomization, adverse event reporting, trial supply management, patient visit tracking, assisting with study startup or collecting subject diary information.

The database designed electronic CRF, (eCRF) is a true replica of the paper CRF in order to store the subject data when viewed on-screen. These eCRF (s) will have built-in real-time data validation checks. The data is entered directly into the interface of the central/global clinical database and immediately available for review to authorized study staff. This technology is also referred to as remote data entry (RDE) or remote data capture (RDC). eCRF(s) have certain advantages over paper CRF(s). They are:

- Facilitates faster and more active management of the data gathering and processing workflow, thereby accelerating the transmission time of data to the sponsor

- Automated data edit checks alert the site to possible errors in data entry
- Ensures faster correction of issues and immediate site education, hence is cost saving
- Ensures immediate viewing and review of the data by the sponsor and data management, hence online feedback is provided to the site immediately.

EDC has its own demerits. Primarily the reluctance of the investigators to use technology is a concern. As use of technology not only involves newer processes but also integration of other systems and groups, it requires higher planning and investment.

### *Data Privacy*

The ICH Guideline for Good Clinical Practice (GCP) states, *"The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirement(s)."*

Adherence to sponsor's privacy policies is essential for maintenance of subject confidentiality. Security of all paper and electronic data has to be maintained. Paper CRF(s) are preferably stored in fireproof vaults with restricted access and all electronic data are protected with a password and firewall. Regulatory issues associated with patient data collection include finalization of error correction rules for CRF(s) using GCP, ensuring computer systems are 21 CFR Part 11 compliant and ensuring that all SOPs related to data management are in place and adhered to.

Investigator's training helps to generate better quality data thereby avoiding the generation of frequent queries. Detection of training issues by study monitors for common problems associated with CRF(s) and looking for recurring types of queries adds to improve the quality of the data.

## CRF Design

CRF(s) are instruments used to collect data from the clinical trials. They are designed to collect all data points specified in the protocol. CRF(s) standardize the collection of study data and also help in meeting the needs of medical, statistical, regulatory and data management personnel. The CRF(s) are filled in by the investigator and then forwarded to the data management unit for entry and review.

In terms of design a well-designed CRF(s) should have the following features:

- Consistency across patients and sites
- Clear, concise and easy to fill questions
- Support data management activities
- Well-designed headers
- Aid computerization of data
- Reliable and clean data for analysis

- Grouping of similar type of data together
- Collect raw data rather than calculated data
- Avoidance of long fields of free text
- Easy access of header information
- Legible font style and size
- Sufficient margins for binding and punching purposes.

Some of the CRF essentials include study name/identifier, unique subject identifier, form name, page number, signature of person completing the form, date of form completion, instructions (when to complete, where to send) and numbering of items for easy reference.

While designing a CRF, there are typically three types of question responses that can be incorporated:

- *Open response:* This typically involves free text, for example, adverse event (AE) text, medication text, medical history details, date/time, numeric lab values
- *Closed response:* This typically consists of check boxes, multiple choice, etc
- *Combination response:* This consists of a combination of both open and closed type responses. For example, on the medical history record, a question asking for specifying if any abnormality present, requires an answer yes or no (closed). If the answer is yes, then one is asked to specify details of the abnormality (open).

Before design finalization, a pilot is carried out with few 'dummy' CRF(s) to identify potential troublesome fields; accordingly training sessions are conducted for investigators and CRAs during study initiation. The CRF design review and finalization involves participation from the project data managers, statisticians, regulatory managers, medical monitors, lead CRAs and clinical scientists.

A set of CRF completion guidelines are finalized and documented in the DMP. This serves as a guideline to the investigators while filling in the CRF(s) and would typically consist of the following instructions:

- Read and follow all instructions carefully
- Write legibly on the form
- Use permanent ink on the forms
- Ensure all questions are answered and complete
- Write answers inside the space provided
- Submit original forms when necessary
- Use appropriate mechanisms for making corrections on the CRF(s)
- Check the forms before submission to the data management unit
- Ensure that patient ID information is correct
- Follow correct schedule/visits for forms submission
- Follow procedures for visits/examinations/tests that are not done and for unscheduled visits

- List abbreviations, if applicable
- Instructions for early terminators/study discontinuation
- Instructions for SAE reporting.

### Clinical Database/Data Management Technology

A comprehensive system is required to manage clinical trial data including database creation and automated data entry screen design, efficient support for double data entry, terminology encoding, data validation, query management, data review and reporting, flexible database import and export.

Such systems are evolved out of the deep rooted knowledge and experience of professionals, the system can then represent an unparalleled level of maturity and a rich understanding of the day-to-day requirements for efficient and effective clinical data management workflow processes — from database set-up, to data quality controls and final export. The system has to be complete, intelligent, easy to learn and use and powerful.

A clinical data management system (CDMS) enhances the efficiency of the clinical trial process. Implementation of the CDMS involves planning and interaction of various teams. Design of CRF data flow into the system either manually or electronically is the first step. Subsequent steps are creating the global database, validation/derivation procedures, data extraction programs and reporting. One can also integrate dictionaries, AE (Adverse Event) reporting systems, EDC/RDC (Electronic Data Capture/Remote Data Capture) and CTMS (Clinical Trial Management System) with CDMS. It is essential to ensure that data is automatically transformed from a collection format to the reporting formats as needed by the sponsor and the regulatory authorities.

The main objective of database design is to capture and store clinical data accurately. The essential features of good design are ease of data capture, efficient creation of analysis data sets and accommodation of source data transfer formats.

### CRF Login and Inventory

The paper CRF(s) from site must be efficiently transmitted to the data management unit for entry and processing. Typical methods include faxing, mailing, scanning and in some cases hand delivered by the site monitor. Once the CRF(s) are received at the data management unit, each CRF page must be logged into the CDMS and each page gets inventoried into the CDMS. Tracking inventories are set-up to detect missing pages and duplicate pages. When the CRF(s) are received as faxes or scanned images, some of the CDMS(s) can automatically store the images in a CRF image database. When paper CRF(s) are manually received, one can scan the CRF pages and store the images in CDMS. Subsequent processing steps may utilize images rather than paper.

### Audit Trial

21 CFR Part 11 compliance requires that all persons accessing the clinical data management system must have electronic signatures of their own. All CDM personnel who access the database must have their unique electronic signature/user IDs. Any modification, change, updation or deletion made in the database will be captured in the 'audit trial'. A well-designed audit trial captures details of the date and time of change, user ID of person making the change, original entry on database, final entry on database (changed value) and the reason for change.

## Data Entry

Data entry refers to the process of transferring data from the paper CRF to the database. This is also referred to as transcribing the data. Data entry results in creation of electronic data, which corresponds to the CRF data. Once data is entered into the database, it is reviewed and validated by the data editor. Emphasis for data entry is on typing speed and typing skills, since this activity requires large amounts of data to be keyed into the database. Data entry consists of both double entry and single entry.

### Double Entry

This involves entry of the same CRF page by two independent data entry personnel. The first data entry personnel keys in the data into the database. Later, a second independent data entry personnel keys in the same data. In case of a difference or discrepancy between the first and second entry, a 'pop up' box throws up, alerting the second data entry personnel to either key in what they see or to accept what the first data entry personnel has entered. Another option is to have a 'third' personnel review the differences/discrepancies and resolve them. Thus double data entry serves as a quality check on the data that is entered into the database.

### Single Entry

This involves entry by single data entry personnel. This process is used when there are sufficient and extensive checks built into the database that would detect certain errors that might be missed out by the data entry personnel. Single data entry is extensively used in EDC and RDC systems, where the investigator and site personnel directly key in the data. This eliminates having data entry personnel within the data management unit. Once the data is keyed in directly at site, it is ready to be reviewed, edited and validated by the data editors.

Data entry could be of two types:

- Data entry is done locally at the site database and then transmitted periodically to the central database via internet or using a dialup line.

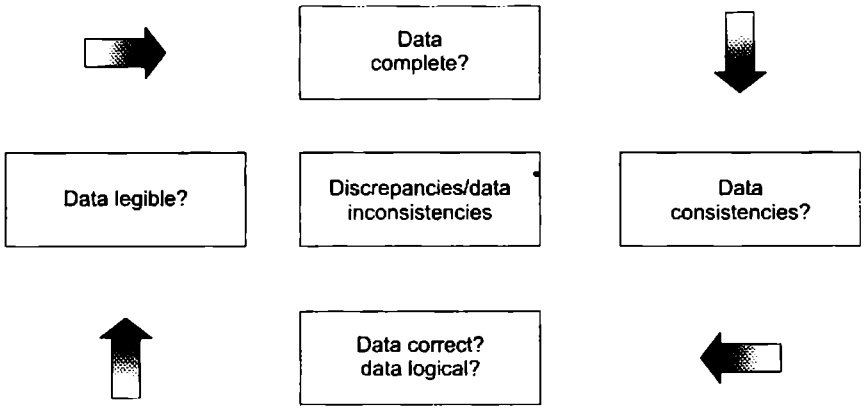



**Fig. 1.25:** Types of data inconsistencies

Sometimes the data is also sent using other electronic media such as a CD, floppy or as a mail attachment

- Data entry is done online directly into the central database via internet. Usually these systems are web-based and the data are available in real time for review.

### Data Review and Validation

Once data entry is complete, the data is ready to be reviewed by the data editor. The data editor ensures that all discrepancies are addressed and resolved and that the database is finally clean and ready to be locked. Discrepancies are any inconsistencies found in the clinical trial data that need to be addressed. Discrepancies include incomplete data, illogical data, incorrect data and illegible data (Fig. 1.25).

Discrepancies could be checked either manually or through computer-generated checks (validations and edit checks) that are programmed into the database. System-programmed validations are designed before start of the data management activities and these serve as checks or alerts to the data editor. The data editor ensures that all discrepancies and validations are addressed and resolved before locking the study.

Data cleaning or validation refers to a collection of activities by data management, used to assure validity and accuracy of the clinical data. It comprises of both logical and statistical checks to detect impossible values due to data entry errors, coding and inconsistent data. The DMP and SOPs clearly defines the tasks, roles and responsibilities involved in cleaning a database.

There are various types of checks that must be performed and various types of data points and discrepancies that must be addressed during the process of review and cleaning (accordingly validations could be programmed for these discrepancies).

### Point-by-Point Checks

This refers to cross checking between the CRF and the database for every data point. If the data editor performs this check, it serves as a second quality check apart from double data entry. Incorrect entries or entries missed out by data entry are corrected during this check. Special emphasis is given to dates, numerical values and header information, where there are likely to be more data entry misses.

### Missing Data or Blank Field Checks

Missing data and blank fields must be queried for, unless indicated by the investigator as 'not done', 'not applicable' or 'not available'. It is better to program validations for missing data fields rather than review them manually. Examples of missing data include missing AE/medication term, missing start/stop dates, completely blank CRF(s) where none of the question responses are provided.

### Data Consistency Checks

Checks are designed to identify potential data errors by checking corresponding events, sequence of dates, missing data (indicated as existing elsewhere) etc. Checks include cross checking between data points both across different CRF(s) and also within the same CRF.

Consider an example of inconsistent data across different CRF records: On the AE record, an AE is reported with action 'concomitant medication'; however on the Concomitant Medication record, there is no appropriate medication administered within the timeframe.

Consider the AE record where fever is reported with action 'concomitant medication':

| *Event* | *Start Date* | *Stop Date* | *Action* | *Outcome* |
|---|---|---|---|---|
| Fever | 13-Jun-2005 | 20-Jun-2005 | Concomitant Medication | Resolved |

Now consider the concomitant medication record where paracetamol is reported as follows:

| *Medication* | *Start Date* | *Stop date* | *Outcome* |
|---|---|---|---|
| Paracetamol | 21-Jun-2005 | 21-Jun-2005 | Stopped |

Here, paracetamol has not been given in the appropriate timeframe and hence this data is considered inconsistent.

Examples of inconsistent data across different fields, but within the same CRF include (a) an AE reported with a 'start date' but the outcome is reported as 'continuing/persisting' (b) stop date of a medication is greater than the visit date.

Consider another example of an antibiotics record versus a trial medication record. Data consistency checks are to be reviewed both within a particular CRF and across different CRFs. Note the two sections/modules in the antibiotics record. The first section is designed to "report doses of antibiotics taken before intake of first dose of trial drug". The second section is designed to "report doses of antibiotics taken after intake of first dose of trial drug".

The first section of the antibiotics record is reported with the following details:

| *Antibiotic* | *Dose* | *Route* | *Start date* | *Stop date* |
|---|---|---|---|---|
| Amoxicillin | 6 mg | Oral | 11-May-2001 | 14-May-2001 |

The second section of the antibiotics record is reported with the following details:

| *Antibiotic* | *Dose* | *Route* | *Start date* | *Stop date* |
|---|---|---|---|---|
| Streptomycin | 7 mg | IV | 16-May-2001 | 17-May-2001 |

The trial medication record where the first dose of trial drug is reported with the following details:

| *Trial medication* | *Dosage* | *Route* | *Dosing dates* |
|---|---|---|---|
| XX | 50 mg | IV | 15-May-2001 |

In this example, a crosscheck of data between the two sections of the same antibiotic record and also between the antibiotic record and trial medication record shows that the data reported is logical and consistent.

### *Laboratory Data and Range Checks*

Laboratory data has to be treated in a special manner, as they are different from all other CRF data. The data have to be interpreted with the help of reference ranges and must be expressed in the specified units for proper interpretation. This is much more important when data are combined from multiple studies. If the units are different they have to be converted to one common unit before interpretation. Hence, the data have to be stored along with the original units in which they were captured. Linking the data with proper normal ranges is critical. Reference ranges may have to be taken from the study specific ranges or standard books when ranges are not available with the data.

Range validations are designed to identify statistical outliners, values that are outside normal variation of population under study and values that are physiologically impossible. An example of an 'out-of range' discrepancy

is the reporting of hemoglobin value as 90 g/L, where the normal specified range as per the protocol is 110 to 160 g/L. While carrying out range checks, data editors need to ensure that appropriate range values and range units are applied for the particular test performed. For example, ranges for WBC types could be applied in units of either 'percentage' or 'absolute'. A granulocyte value could be reported in the unit of percentage, whereas the corresponding range could be applied in the absolute unit, hence the granulocyte value would most definitely be out of range.

Consider the following cross-check between the hematology record and AE record:

*Hematology record:*

| *Hematology test* | *Date* | *Result* | *Normal range* |
|---|---|---|---|
| WBC | 05-Jan-2006 | 13,710 cells/cu mm | 4,300 – 10,800 cells/cu mm |

*AE record:*

| *Event* | *Start date* | *Stop date* | *Outcome* |
|---|---|---|---|
| Streptococcal infection | 04-Jan-2006 | 07-Jan-2006 | Resolved |

In this case, a validation should ideally be programmed to flag a WBC 'out of range' discrepancy. The study guidelines may instruct the data editor to either query the site to confirm the correct value or to accept the discrepancy since an increase in WBC count is justified by streptococcal infection in the same time frame.

### *Discrete Value Group (DVG) Discrepancy Checks*

DVG is a question where there is a fixed or expected set of responses. DVG(s) are built into the database in the form of drop-down options. An example of a DVG is the set of responses for the severity of an AE - 'mild', 'moderate', 'severe' and 'life-threatening'. However, if the severity is reported as 'not known', which is not part of this DVG, it constitutes a DVG discrepancy.

Another type of DVG discrepancy is a 'length' discrepancy. When the database is designed, each free text field is assigned a maximum number of characters that it will be allowed to accept when the data is keyed in. If the text reported exceeds the maximum number of characters, a length discrepancy is created, which needs to be addressed by the data editor.

### *Header Inconsistency Checks*

Examples of discrepancies with the header information include (a) an incorrect visit date like 30-Feb-2005 (b) an incomplete visit date like 12-Jan, whereas the date is expected to be reported in the DD-MM-YYYY format (c) incomplete patient initials.

### Missing Pages Checks and CRF Tracking

Details of transmittals and receipt processes of CRF(s) and DCF(s) are documented and maintained during all stages of the data management process. Missing and expected pages tracking systems are also planned and setup in the DMP. Tracking reports of missing pages have to be maintained to identify CRF(s) misrouted in-house as well as CRF(s) not sent from the site.

### Protocol Violation Checks

Protocol adherence ought to be reviewed at all stages of data management. Violations found have to be queried. Special emphasis is given for reviewing primary safety and efficacy endpoints, adherence to inclusion and exclusion criteria, adherence to trial drug dosing regimen, study or drug termination specifications, etc.

### Dates Out of Sequence Checks

Dates out of sequence, refers to dates either in the header or the body of the CRF being inconsistent and out of sequence. Sequence of visits are reviewed and if found to be out of sequence, will be either queried or corrected. Examples include (a) a record belonging to visit 4 has a visit date belonging to that of visit 2 (b) one of the records within a particular visit has a visit date that is out of sequence with the visit date of the other records of the same visit (c) the trial medication is to be taken on a 'daily' basis as per the protocol, however, the dosing details on one of the dates has not been reported in the trial medication record.

Example where one of the screening records is reported with an incorrect 'year', hence there is a screening visit date out of sequence:

| *Record name* | *Visit date* |
|---|---|
| Demography | 20-Feb-2006 |
| Med. history | 20-Feb-2005 |
| Inclusion criteria | 20-Feb-2006 |
| AE | 20-Feb-2006 |

### Continuity of Data Checks

These are checks performed for ensuring continuity of events (AE(s), medications, treatments/procedures etc.) across the study and across visits. Overlapping start/stop dates are checked across visits.

For example, consider a scenario where the protocol states that AE(s) are to be reported in visits 1, 2 and 3. "Headache" is reported as follows:

| | Start date | Stop date | Outcome |
|---|---|---|---|
| 1 | 01-Jan-2004 | 12-Jan-2004 | Continues |
| 2 | 01-Jan-2004 | 12-Jan-2004 | Resolved |
| 3 | 20-Jan-2004 | 20-Jan-2004 | Resolved |

There is an issue in visit 1 reporting, where the 'stop date' has been reported and the outcome is reported as 'continues'. There is also the issue of overlapping start/stop dates in visits 1 and 2. All such issues are queried and clarified with the investigators.

### *Coding Checks*

All the data such as concomitant medications, adverse events, medical history and diseases have to be substituted with a standard reference terminology. This is known as 'coding'. The reference terminology may come from sponsor specific dictionaries or other published dictionaries. The coding of data helps in grouping them under specific systems. Such groupings are required for summary analysis of these data. Coding is done before the database lock.

As an example, consider medications 'paracetamol' (generic name) and 'Crocin' (trade name) reported on the CRF. Both medications have the same active ingredient 'paracetamol' and hence must be considered as the 'same entity' for analysis purpose. Hence, both terms must be coded to 'paracetamol', so that the safety and efficacy analysis during statistical analysis is not affected.

There are certain terms that cannot be directly coded without further clarification from site. For example, the adverse event "ulcers" requires a 'location' (gastric, duodenal, mouth, foot, etc.) in order to be coded. Hence, this must be queried to the site in order to obtain the location of the ulcer.

Standard global dictionaries having their unique coding structures are used for coding terms collected in clinical trials. Different dictionaries follow different structures and different hierarchies based on the classification levels. However, there are many similarities among the dictionaries. There is a term or text (AE, medication, disease) that is often referred to as the "preferred term" and the related "code". In addition to terms and codes, dictionaries generally have auxiliary tables. For example, AE dictionaries have information on effected body systems and drug dictionaries may have additional information on the key ingredients.

Some of the common standard dictionaries used are:

- MedDRA—Medical Dictionary for Regulatory Activities
- COSTART—Coding Symbols for a Thesaurus of Adverse Reaction Terms
- WHO-DRL—World Health Organization Drug Reference List
- WHO-ART—World Health Organization Adverse Reactions Terminology

- ICD-9-CM—International Classification of Diseases, Ninth Revision, Clinical Modification.

*Auto-encoding:* Most modern and advanced coding dictionaries heavily depend on auto-encoders rather than manual coding. Once data from the case report form has been entered and verified, the process of auto-encoding begins, where the text of the investigator term in the clinical trial database is compared to the text strings stored in the dictionary database. When an exact match occurs, the code from the term in the dictionary database is automatically entered into the clinical trial database and the term is considered auto-encoded.

Auto-encoders help in handling synonyms, misspellings, word variations, etc. Auto-encoders may be built-in with CDMS or as stand-alone systems. Auto-encoders have numerous advantages over manual coding such as the ability to handle large numbers of terms and the ability to facilitate consistent coding, without having to rely on the manual re-evaluation of previously coded terms.

### *External Data Checks*

During the conduct of a clinical trial, some data external to the CRF(s), such as laboratory data, PK/PD data and device data (ECG, images, flowmetry, vital signs) are also collected.

Central labs are used to maintain 'uniformity' across the study and across the sites. External data from all the study sites is directly sent to a central lab, from where the vendors provide electronic transfer of computerized data into the sponsor's database. Electronic transfer of data helps in avoiding the transcription errors. At the time of data transfer one has to take care that all the variables are included and are loaded onto the proper study/visit without affecting the blinding.

Data management tracks loading of incorrect subject number, incorrect visit number, incorrect study number, incorrect date/time of sample collection, incorrect date/time of examination, etc. Missing data such as missing collection date/time of blood sample, missing date/time of ECG, missing location of chest radiograph, missing systolic/diastolic blood pressure, missing microbiological culture transmittal ID, etc. are also tracked by data management. Incorrect and incomplete loading details are communicated to the centralized vendors so that the appropriate data can be subsequently 'reloaded'.

### *Duplicate Data Checks*

This refers to duplicate data entries of a particular data value within a single CRF or across similar CRF(s). Duplicate entries and duplicate records are generally deleted as per guideline specifications. Examples of duplicate data include:

- Treatment 'physiotherapy' on '30-Aug-2001' reported twice on either the same treatment record or across two different treatment records

- Both visit 4 and visit 10-blood chemistry CRF(s) (with different collection dates) are updated with same values for all tests performed. In this case, either the collection date on one of the CRF(s) is incorrect or the reported blood chemistry values in one of the CRF(s) are incorrect
- Both 'primary' and 'additional' medical history CRF(s) at screening are reported with same details of abnormalities.

### *Textual Data Checks*

All textual data are to be proof read and checked for spelling errors. Common examples of textual data include pre-existing conditions in medical history record, adverse events, medications/antibiotics, physical examination findings, etc.

### *SAE Reconciliation Checks*

An adverse event is any undesirable experience associated with the use of a medicinal product in a patient. The event is considered as a serious adverse event (SAE) if it results in any of the following outcomes:

- Death
- Life-threatening illness
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect.

Expedited reports are required by the regulatory agencies for certain SAE(s). Accordingly the investigator submits the SAE report to the sponsor and the SAE details are subsequently maintained in the SAE database. The SAE details from the clinical trials are also reported on the CRF(s) which are sent to data management. Before close of study, the data management staff must compare and reconcile the SAE data in the SAE database with that in the clinical trial database, to ensure that all SAE(s) were collected and reported properly (Fig. 1.26).

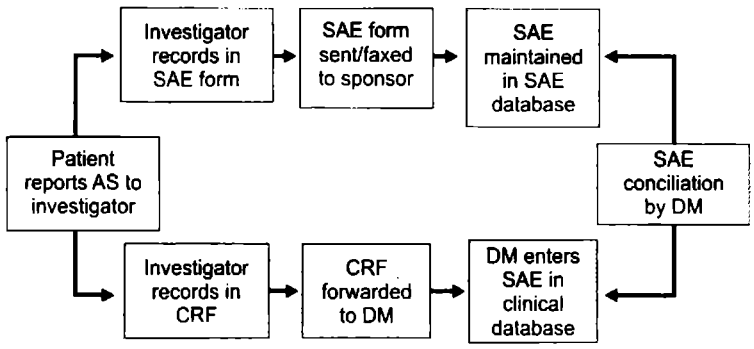



**Fig. 1.26:** Diagrammatic representation of SAE reconciliation

*Discrepancy Management*

A discrepancy is initially in an open or un-reviewed status. The data editor addresses the discrepancy and resolves it, based on the project-specific guidelines or standard guidelines. There are various actions that can be taken to address a discrepancy:

*Closing discrepancy per internal correction*: The data editor can 'internally' resolve and close out the issue without sending a query to the site. This action is applicable when the resolution is fairly 'obvious'. For example,

- A lab value 0.6 is out of range and an 'out of range' validation is generated. The data editor refers to the CRF and notices that the value is actually 6.6 and not 0.6 and that the value was incorrectly entered by data entry. In this case, the data editor could change the value in the database to 6.6
- A medication is reported as 'paracetamol'. This will not code and hence would throw up a coding validation. Since this seems to be very obviously a misspelling, the guidelines may allow the data editor to correct the spelling to 'paracetamol'.

*Closing discrepancy per clinical team:* A discrepancy can sometimes be closed out directly based on instructions from the clinical scientist. Based on an ongoing review, the clinical scientist can instruct the data editor to either create a query to the investigator or provide a resolution for a discrepancy.

*Generating a query to the investigator:* The study guidelines can include instructions to the data editor to query a discrepancy in case it cannot be resolved by internal correction. Queries are generated on data clarification forms [DCF(s)], which are in turn sent to the respective sites. DCF(s) are also referred to as query forms, correction forms or discrepancy forms. DCF drafts can be auto-generated from a discrepancy management system and contain the query text templates.

The process of query management can be broadly classified into five steps.

- *Creating queries:* Queries for discrepancies are entered onto the DCF manually based on reports from the discrepancy management system or the system may create them automatically. A DCF should ideally contain queries belonging to the same patient and to the same site.

  A DCF would typically consist of the following entities:
  - Study number/ID
  - Site number
  - Patient number
  - Investigator name
  - Date of generation
  - Unique DCF ID
  - Query text
  - Space for the query resolution (to be filled by investigator)
  - Date and signature of investigator

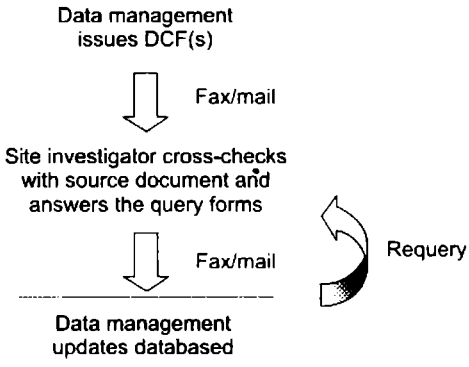



**Fig. 1.27:** Process of discrepancy management

In the case of Remote Data Capture (RDC) systems, queries are entered directly into the database. The investigator answers the queries online and the responses are then available to the data editor

- *Sending queries:* DCF(s) are delivered to site via fax, paper mail, in person or by e-mail. In the case of RDC systems, the queries are immediately accessible to the investigator who can view the queries and provide resolutions online
- *Tracking queries:* The data editor tracks the flow of queries between self and the site. Following up on delayed responses and misrouted DCF(s) is important
- *Resolving queries:* Once the DCF is received from a site, the responses are integrated into the database. Common types of resolutions include retaining the queried value as the correct value, replacing the incorrect value with the correct one provided by the investigator, updating a missing response provided by the investigator
- *Re-querying:* Re-queries are needed when the investigators do not provide a response or provide an incorrect/inconsistent/incomplete response or provide the same response to a query (Fig. 1.27).

### *Query Writing*

Good query writing is extremely important so that the investigator can fully understand the query and hence would in turn provide the correct response. This helps in avoiding re-queries and reduces the turn-around time for query integration into the database.

General tips for query writing include having a thorough understanding of the guidelines and protocol, stating the problem in a simple way, being precise and to the point while wording the query text, using proper punctuation and grammatically correct sentences and avoiding repetition of words in the query text.

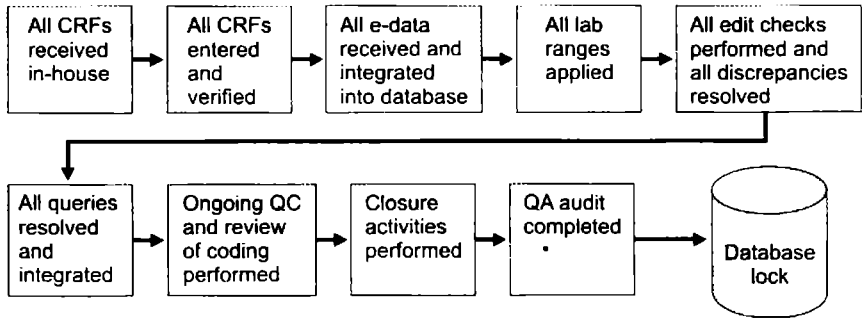



**Fig. 1.28:** Diagrammatic representation of database lock

### Database Closure

Database closure is done to prevent unauthorized or inadvertent changes to the database once the final analysis of the data has begun. This process is referred to as 'soft-locking' the database. This is done after completion of last patient last visit (LPLV).

Database lock is critical in randomized trials to ensure the integrity of the randomization process (as the blind has been broken). Database closure is done when all the discrepancies and validations are resolved, all edit checks are completed, all missing data/external data are in-house, all terms are coded, all lab ranges are applied and SAE(s) reconciled. In other words it is done once the database is cleaned completely (Fig. 1.28).

In order to safeguard the integrity of the data well-defined procedures for the database closure have to be documented and followed. A database can be unlocked with special user access in case there is a necessity of making further updates or modifications to the database. In such cases, the change control procedures must be clearly defined and documented. Change control procedures include notifying the study team, clearly defining the changes being made, specifying the reasons for the changes and documenting the dates when the changes are made. Database closure is followed by final analyses, which lead to conclusions on the trial and for the regulatory submissions.

### Quality Assurance and Quality Control (QA/QC)

QA/QC audits are done periodically—on an ongoing basis as well as at or after the end of the study. QA audits are systematic and independent examinations of trial-related activities and documents to ensure that the CDM related activities and processes were conducted and completed and that the data were accurately recorded, analyzed, documented and reported according to the protocol, SOPs, GCP and applicable regulatory requirements.

Errors or findings are mismatches found between the CRF and the database during a review. They could be due to incorrect transcriptions, incorrect data processing (at the level of data entry or data validation) and incorrect query

integration. The error rate or quality index (QI) is calculated as number of findings against the number of fields in the database. The acceptable error rate is pre-determined by the sponsor and is documented early on in the DMP. For example, a sponsor may require a quality index of 99.9 percent, whereas another sponsor may require a quality index of 99.5 percent.

The sample size for audit should be statistically appropriate and could vary from sponsor to sponsor. For example, some audits could use a 10 percent random sample where the system can randomly auto generate 10 percent of the total enrollment for analysis. Some other audits could involve a 100 percent sampling of all safety and efficacy end points.

*Interim analysis* may be done at regular time intervals for an ongoing study, if specified in the protocol. The analysis may be done monthly, quarterly, biannually, annually, etc. depending on the study duration. The analysis could also be done either on specified modules in the study like safety modules or efficacy modules, or on all modules. Findings from the analysis give a clear picture if the study is on track. Decisions are taken on the proceedings of the trial and if needed, amendments to the protocol are made in order to ensure successful completion of the trial. If major deviations are found against the protocol or the expected results, the data is assessed as a whole to evaluate the quality of the study and decide if the study should proceed as planned. Analyzing findings on a periodic basis helps in making appropriate rectifications to the database early on in the study. Accordingly training is provided to the data management staff so that the findings and errors are not repeated for the rest of the incoming data.

*Final analysis* is done after completion of LPLV. This analysis collates the data from all the interim analyses as well as the data analyzed after the last interim and gives a combined result of all the data modules. The final analysis gives a collective conclusion about the safety and efficacy of the trial drug, which would be part of regulatory submissions (Fig. 1.29).

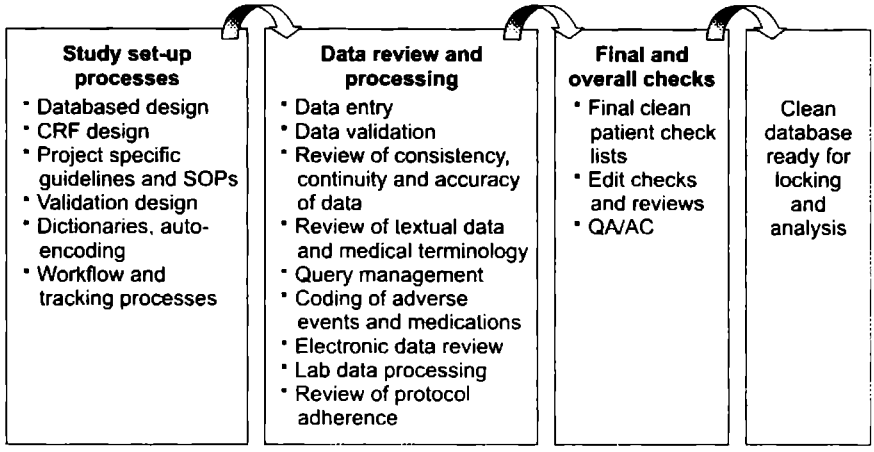



**Fig. 1.29:** Overview of processes in clinical data management

## Data Storage and Archival

All trial related paper documents including CRF(s) and/or electronic files must be stored in a secure and controlled place. It is good to scan all paper documents so that they can be archived in an electronic form. Open formats such as Operational Data Model (ODM) offered by CDISC or PDF are recommended for storage.

Information regarding all clinical data, database design specifications, external data, structural metadata, coding dictionaries, lab ranges, audit trial, listings for edit checks and derived data, discrepancy management logs, queries, program codes, PDF formats of CRF(s), data management plan, validation documentation, regulatory documentation, documentation/memos of deviations from SOPs and other working procedures, are stored in a central document library and should be included in a clinical data archive.

## Clinical Data Management Softwares

Listed below are different software systems categorized as clinical data management systems (designed to capture clinical trial data), drug safety system (designed to capture adverse events), remote data systems (RDC-designed to capture clinical trial data directly into the interface/software application) and data exchange solutions (applications which connect/integrate two different kinds of software applications being used to capture clinical trial data) (Fig. 1.30).

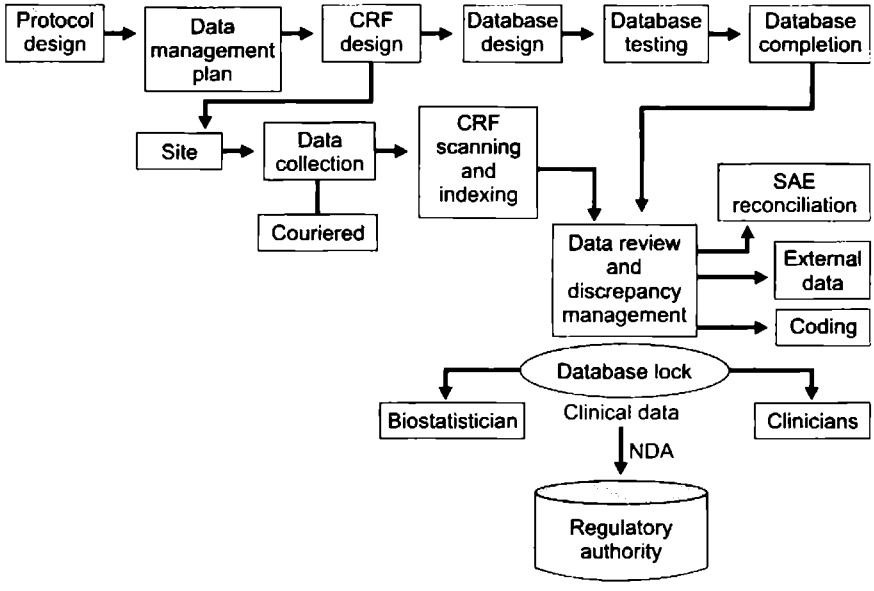



**Fig. 1.30:** Summarized process flow of clinical data management

*Clinical Data Management Systems*

**Oracle Clinical** – Provided by **Oracle**, it is a simple and full-featured interface; investigators, monitors and site coordinators can enter and clean clinical data, monitor trial progress and track source-document verification.

**Clintrial-phase Forward** has provided a clinical data management solution which streamlines data entry and lab loading, discrepancy management, patient and site reporting, data exporting, coding and system administration.

**STARLIMS - LIMS** has provided a web-based laboratory information management system.

**SAS/SHARE** - Application, in which all data are entered, stored, managed, and analyzed as the database server, SAS tables for physical storage, and Microsoft Windows® as the operating system on both the server and desktop.

**WebVDME - Phase forward** has provided a signal detection solution for post-marketing data.

**CTSD - Phase forward** has provided a signal detection solution for data from clinical trials.

**WebSDM - Phase forward** has provided a system for validating and reviewing clinical trial data represented in formats meeting industry standards.

*Drug Safety Systems*

**Clintrace - phase Forward** has provided a solution for monitoring drug safety and reporting adverse events that occur during and after conclusion of the clinical trial process.

**Total safety - Aris Global** has developed a comprehensive suite of integrated software solutions that enable organizations, regardless of status or size, to implement effective domestic and global pharmacovigilance, clinical safety and risk management programs.

**ERT eSafety Net** - this system is designed by **eResearch Technology** to provide a safety data system which utilizes physician front-end support to enable the effective management of global adverse reactions occurring anywhere in the clinical trial process.

*RDC Systems*

**Rave** - Developed by **Medidata**; is the industry-leading system for capturing, managing and reporting clinical research data, designed to help life science companies optimize their research investments by efficiently streamlining the clinical trial process. It is a single platform supporting both electronic data capture (EDC) and clinical data management systems (CDMS) functionality. Medidata Rave has the flexible design to support the breadth of any organization's clinical processes, as well as the unique aspects of individual clinical trials.

**Inform ITM - Phase Forward** has provided an internet-based electronic data capture solution for collection and transmission of patient information in clinical trials.

**MACRO** - It is **InferMed's** electronic data collection solution for clinical trials. MACRO's intitutive drag-and-drop tools for eCRF creation reduce study design time and provide complete control over eCRF layout, ensuring that eCRFs are comparable to paper equivalents.

*Contd...*

*Contd...*

**TrialMax** - CRF Health - TrialMax is the world leader in electronic patient reported outcomes (e-PRO) and wireless data collection solution for the biopharmaceutical industry.

**ERT eData Management** - eDE designed by **eResearchTechnology, Inc.** meets the needs of study investigators and monitors. Specifically, eDE offers a task-and-workflow-driven EDC solution that helps smooth process management by providing organized access to study data. eDE supports sophisticated on-screen validations. eDE's edit check mechanisms include field level validations, which can identify errors at the time of data entry based on values from derived fields or provide conditional navigation throughout a page in addition to consistency checks. eDE allows clients to develop, deploy, manage – and reuse – standards that are drawn from a library that can be maintained at any or all of these levels. Furthermore, eDE is designed so that multiple eDE studies are supported in a single environment. This capability helps clients maintain compliance with internal standards, which provides a method to achieve rapid and consistent study set up every time. It also ensures immediate availability for interim or final analysis.

*Data Exchange Solutions*

**Connect by ClinPhone** - An automated data exchange solution to facilitate seamless sharing of information between independent systems and software. It allows pharmaceutical sponsors to integrate clinical data without having to modify applications on connected systems. Built on revolutionary middleware technology to support two-way, real-time data interchange, Connect enables diverse electronic clinical trial solutions such as IVR (Interactive Voice Response), EDC (Electronic Data Capture), CTMS (Clinical Trial Management System), and DSM (drug supply management) to work together synergistically.

**ClinPhone Combined EDC-IVR** - The combined EDC-IVR solution provides EDC, CDMS, randomization, trial supply management and ePRO, integrated through an innovative Connect software and platform.

**DataLabs by ClinPhone** - Industry's first single data management system that unifies the functionality of paper data entry (PDE) with the flexibility of electronic data capture (EDC) into one, easy-to-use electronic clinical data management platform.

## Recent Advances in CDM

Clinical trial systems to conduct clinical trials electronically have become a necessity today to increase the time to market as well as decrease the cost of trials. The various technologies utilized include EDC systems, adverse event reporting systems (AERS), OCR, OMR, IVRS, etc. These and many other technologies are providing number of benefits in the conduct of the clinical trial. Technology enables advances in trial design, faster data entry, more efficient communications between participants, and improved process management, collection of clinical endpoint data directly from the patients. Technology can also help in the design of a clinical trial especially in the randomization process. It is possible to design a trial that is automatically

modified as it progresses through an adaptive trial design. Continuous monitoring of a critical variable from EDC data can automatically adjust the sample size of a trial for the power that is desired.

EDC decreases paper handling, improves data clarification process, provides validations at the time of data entry, provides realtime access to data, allows for remote monitoring, speeds up regulatory agency submissions and lessens the number of CDM resources required to process the data. EDC data can be integrated by loading of SAS datasets or transport files into a data repository that becomes the source for study analysis and reporting. EDC systems can also be integrated with IVR systems, electronic patient diaries, labs, EKGs and AERS. With lab integration investigators can also look at lab data on-line.

Smart pens are available which enable patients fill out a form, and then use the pen itself to transmit the recorded data via a cradle to the database. Discrepancies in the data are shown to the site, which can correct them against the paper copy. The pen also creates an exact copy of the CRF to be saved online.

Electronic devices such as personal digital assistants [PDA(s)], palm pilots are very efficient in capturing data from subjects. These typically work in an offline mode and are slowly replacing paper-based subject diaries. These devices can also display metrics or tracking status to monitor patient schedules and compliance with alerts to record the data as per the protocol. Some can even help collection of various parameters such as measurement of pain, etc.

Biometric devices provide another way of data collection. Electronic spirometers can record the time, date and measurements of home-administered pulmonary function tests. Some devices can simultaneously record numerous physiological variables.

Data are stored in the memory of the clinical data systems or on paper, microfiche, computer tape, computer disk, optical laser disk or smart cards. Data may be transmitted through hard-wired direct connections, disks, audiotape or videotape broadcast, microwave fiberoptic links. Retrieval of data can be done by automated prompts, query, and search programs. The output may be in a typed format, an audio format or a visual format (e.g. pictures, graphs and tables).

A number of technologies are available to help better communication between sites and sponsors who can help achieve higher quality data in a shorter period of time. Trial portals are available where start-up and other documents can be downloaded, completed and can be shared with the sponsor. In addition, these portals can be used for live investigator training, site personnel training and for investigator meetings. Monitors can send edit checks and protocol changes to the trial sites via the portal. Monitors can conduct protocol-compliance checks by examining the data being collected and fully manage trial processes from their home or office via these web

portals. They can also query sites and generate data-correction forms in realtime. Sites can be graphically shown their recruitment, time from query to response, queries per page, and many other metrics. These reports will allow the site to understand areas that need improvement, or areas in which they excel. Over all, much less efforts are spent reviewing and managing queries which helps to increase study capacities and smooth conduct of multicenter studies.

Desktop productivity tools have been integrated with ERP systems to enable process functions and data to be available through familiar desktop applications. They provide access to tasks such as time management, budget monitoring and organization management from a desktop. Globalization management systems are available to accelerate capturing, authoring, managing and distributing content across multiple formats and languages. To avoid the problem of clinical trials generating mountains of paperwork, FDA is promoting eSourcing. This involves capturing clinical data electronically at the source meaning in the patient diaries and eCRFs. FDA is also encouraging completely paperless submissions of clinical trial results. As a method of eSourcing investigators can record all trial data in their laptops and the same can be synchronized daily with central servers.

Integrated data capture and management systems with lab data integration, integrated dictionary coding and translation tools provide for better reporting. Some systems can help generate the extracts for analysis in analytical tools and also help in generating submission files exactly as requested by FDA. Web-based tools for safety research with search engine, querying, access to information sources—including FDA and WHO datasets, help manage and analyze data efficiently. FDA has collaborated with private vendors for electronic review tools, which provide quicker access to key information.

### Data Standards

Data standards are being developed to overcome the problems of data integration from different systems. Data structure (variable names, variable types and labels), screen layout/paper CRF module, completion instructions, monitoring guidelines, standard reports, tables, listings, laboratory data, global libraries are all being standardized. Clinical data interchange standards consortium (CDISC) is at present leading the way. There are currently over 60 companies that are members of CDISC, and many companies are starting to adopt the CDISC models, even down to the variable name.

Apart from data management personnel, the senior management, clinicians, statisticians, medical writers, auditors, regulatory affairs, IT support and central labs contribute to these data standards development. Standards have become the necessity of the day because of the rapidly increasing number of drugs in development and global submissions.

### CRF Imaging System

Document imaging and workflow systems streamline document handling by eliminating duplication services, reducing hand-offs, simplifying storage, automating process tracking, and speeding distribution. Character recognition software automates data processing so that the staff can focus on data quality instead of data entry.

Case report form (CRF) imaging and workflow application are also sold by Integic by the name "CRF WorkManager" and by ISI as 'CRFTrack".

### Scan, Fax or Import CRFs

Software applications are available to scan locally or remotely and import CRFs quickly and easily. Powerful imaging tools and the ability to fax-in CRFs also help improve the quality and accessibility of documents (Fig. 1.31).

*Quick and easy scanning:* CRFs can be organized into a batch that share common attributes, and assigned keywords to clinical and process information for convenient access. In addition, users can scan documents remotely into a centralized database through remote scan.

*Fax-in capabilities:* Users in remote locations can now be connected in more ways than ever. Regardless of where the user is, CRFs can be faxed into the same database. The process is fast and secure, allowing the user to focus on gathering CRFs for submission.

*Import files:* CRFs in TIFF format can be imported into the application used and included in an existing or new batch. Files can also be replaced or revised, allowing for easy movement and management of pages and versions as they change.

**Fig. 1.31:** CRF import and export system

*Powerful imaging tools:* A palette of imaging tools helps the readability and presentation of scanned CRFs with options to detect and set page orientation automatically, set rotation of pages by reformatting pages or changing the display, and clean pages by removing unwanted holes and scanner marks. In addition, user can set filters to de-skew text, ignore holes, clean edges, remove horizontal and vertical lines and more.

### *Index by OCR or Barcode*

Assign attributes and numbering information to CRFs through a number of different methods: by page template, OCR, barcode or manually. Also, create virtual CRFs for specialized separation.

*Index manually, by OCR or barcode:* There are several options for indexing scanned pages into proper CRFs. If manual indexing is required, helpful page templates can be created to define a page structure for a CRF, so that certain pages that share a common format can be easily identified and indexed (Fig. 1.32).

OCR indexing is a convenient and automatic way of indexing page numbers through specified keywords and "zones" on CRFs. OCR Indexing can also be run in batch mode, allowing multiple batches of scanned files to be indexed at once.

Barcode indexing allows user to gather attribute information automatically and accurately through barcode recognition of protocol, investigator and patient information.

**Fig. 1.32:** OCR indexed scan page

*Create virtual CRFs for specialized separation:* Create a virtual CRF that condenses pages from multiple patients into a single document based on specified criteria. For example, with Virtual CRFs the user can copy Adverse Event pages from patients in a protocol for review, and then convert the Virtual CRF to PDF. The PDF can then be distributed to internal reviewers (Fig. 1.33).


**Fig. 1.33:** Virtual CRF

### *Add Navigation, Ensure Quality and More*

Bookmarks, hyperlinks, annotations and comments can all be added to images and eventual PDFs effortlessly. In addition, QA tools ensure the quality and integrity of pages with a number of options – through searching file size, setting statuses and checking page settings. And with the ability to route pages to be reworked, managing the workflow is easier than ever.

*Create bookmarks and hyperlinks:* Bookmarks and hyperlinks are created easily to ensure submission compliance. In addition, create TOCs that add a structural hierarchy to PDFs that enhance document navigation, and export them as a CSV file for later reference.

*Annotate and comment:* Through a variety of annotations, user can add notes and highlights to CRFs, most of which can also be preserved in PDF. Whether it is notes for clarification or notification, hyperlinks that navigate to predetermined pages, or highlights within CRFs, there are multiple options to choose from. Additional options to lock show and search annotations make it easy to manage comments for team-wide collaboration.

*Perform QA:* Through specialized workflows and QA tools; the application helps ensure the validity and integrity of documents. Search for specified protocols and investigators by file size, as well as for blank pages or specific types of pages, such as DCFs and cover pages. In addition, define the status of a page as "Passed", "Rejected", or "None" during a workflow and then route pages to the appropriate destination. User will be able to ensure quality as the workflow is happening (Fig. 1.34).


**Fig. 1.34:** QA tools

### Review and Manage Globally


**Fig. 1.35:** Automatic PDF conversion

Everything the user needs to manage CRFs better – with an easy-to-view workspace, remote global access, collaborative capabilities and convenient EDMS integration – are conveniently at your fingertips today with the existing software applications.

*Automatic PDF conversion:* With speeds up to 72,000 pages per hour, converting paper CRFs to electronic format has never been quicker and easier. CRFs converted to PDF are ready for submission and can contain bookmarks grouped by Domain and Visit with the proper hyperlinks between DCF and CRF pages. Additional features that prepare CRFs for PDF conversion allow users to create and manage annotations (Fig. 1.35).

*Create workflows and route jobs:* Administrators can also create workflows and route jobs to appropriate departments and keep track of the workflow as it happens. It is easy for administrators to view remaining pages for each job, as well as assign, reject or confirm completion of jobs.

*Remote global access:* CRA's, clinical trial monitors, investigators, and other key team members can fax and view CRFs from remote investigator sites and access the information they need through the CRF web portal.

A collaborative environment is created among clinical trial team members through a secure web interface. Members can download patient PDFs for offline review, assign and restrict access to CRFs for secure document access and ensure the integrity of CRF documents.

*Convenient integration:* Integration with oracle clinical and clintrial allows for faster workflow task processing. To streamline clinical operations as much as possible, split-screen data entry integration allows for greater speed and quality during first and second pass data entry.

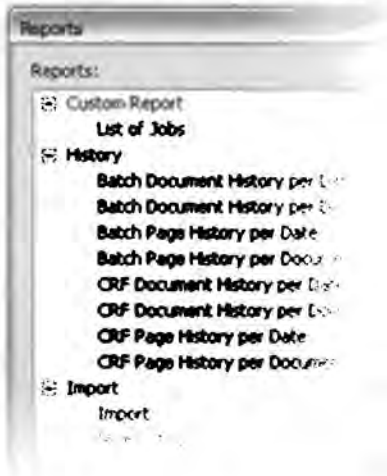



**Fig. 1.36:** Accurate CRF tracking and reporting

### Track and Report

*Accurate CRF tracking and reporting:* In dealing with an overwhelming amount of information, software applications simplify the tedious process of reviewing and verifying CRF collection (Fig. 1.36).

*A simpler, more accurate way to track CRFs:* Maintaining complicated spreadsheets that track CRF information is no more required since a simpler and powerful method is available in the software applications. Users can perform vital QA functions through a host of automated search methods. Users can perform searches to determine missing and contained pages, advanced searches by keyword, drug, investigator, patient and workplace.

*Detailed reporting:* In addition to searching across patients and by keyword, user can also view more detailed tracking, such as page history, user history and audit trail mapping. Print reports for streamlined QC on CRF documents and submission requirements.

### Direct Access Solutions

The means by which a direct connection into sponsors' clinical data management systems can be made. This access ensures that processes and standards are followed, while the sponsor maintains control over data. This is a permission provided to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

### eDiaries

A patient diary is a tool used during a clinical trial or a disease treatment to measure treatment compliance. An electronic patient diary registers the diary in a storage device and allows for monitoring the time the medication was taken, and symptoms or quality of life data were recorded.

Patient diaries are way to find out if a patient takes the medication according to the treatment schedule, which is an important problem during clinical trials and the treatment of degenerative diseases with relatively few symptoms.

### Clinical Trial Portals

Clinical trial portal has been designed as a single entry or a 'one-stop-shop' allowing you to search for comprehensive information on the on-going clinical trials (registry) or results of completed trials (database) conducted by the innovative pharmaceutical industry worldwide.

WHO International Clinical Trials Registry Platform is one of the most valuable sources of evidence about safety and efficacy of health interventions. Extensive media coverage is also done on several cases selective reporting of results. Such trial registration and full reporting of trial results would help ensure a full and unbiased public record on safety and effectiveness public record on safety and effectiveness.

Many journals in addition to International Committee of Medical Journal Editors (ICMJE) now accept only registered trials for potential publication. It is a global, neutral, independent body with convening capacity (i.e. World Health Assembly resolutions). It is authoritative and has an important role in setting norms and standards in research, policy and practice [Good Clinical Practice, Ethics guidelines, Classification standards (e.g., ICD)]. WHO contributes to capacity building (i.e. in developing countries) and has a political legitimacy, accountable to 192 member States. WHO shows commitment to achieving equity in health and has been defined a coordinated global "platform" for trial registration.

The goal is to strengthen public trust in clinical research by promoting transparency and accountability.The objectives are to ensure that all trials worldwide are registered and thus publicly declared and identifiable and ensuring that a minimum set of results are publicly reported for all registered trials and support use of trial registration information for recruitment, research planning, etc.

Some important portals complying with requirements set out by the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the International Committee of Medical Journal Editors (ICMJE) guidelines, and the WHO 20-item Trial Registration Data Set are—

1. International Clinical Trials Registry Platform (ICTRP).
2. Australian New Zealand Clinical Trials Registry (ANZCTR)
3. ClinicalTrials.gov
4. International Standard Randomized Controlled Trial Number Register (ISRCTN).
5. University hospital Medical Information Network- Clinical Trials Registry (UMIN-CTR).
6. Netherland's Trial Register (NTR).

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# CHAPTER 2 Drug Discovery and Development of Biologics

## THE SCIENCE OF DRUG HUNTING

The aim of drug discovery program has always been to use the right science and technology to develop the right products, for the right patients, at the right cost, thereby posing a huge challenge in front of the academia and industry (Lundberg and Reilly, 2009). The drug discovery program has many facets including understanding disease condition, target identification, lead generation, lead optimization and clinical testing.

The task is complicated by looming patent expiries in front of major pharma companies, potentially reducing funds for future investment into R & D and existence of number of good medicines already in the market which shrink the window of opportunity for new discoveries. In addition, the regulatory agencies have set the bar very high and now, require extensive data with proof of safety and efficacy. Even after a new drug has cleared all hurdles for approval, its pricing remains a crucial decision that may be taken only after considering numerous factors such as rise of emerging markets, aging demographics, better disease detection, emergence of new diseases ('diabesity' in the younger population, antibiotic resistance, bacterial and viral infections, etc.) and comorbidities of diseases.

The amalgam of these factors convert the science behind drug discovery program into a drug hunting program, the success-rate of which is as probable as that when looking for a needle in the haystack. The fact is borne out by the low numbers of new molecular entities approved by regulators in recent years.

Till recently, the scientists in the drug discovery program have been either tapping natural products (medicinal plants, microorganisms, marine source, etc.) or synthesizing newer chemical entities. Both the approaches have produced their share of successful molecules. However, the scenario of drug discovery has phenomenally changed with the advent of genomics-based technologies, integrated ultra-high throughput screening based techniques. The emphasis is now on speedy results, and there is immense pressure on traditional approaches to keep pace.

"Biologics" offer solution to the deadlock in the drug discovery program and may help to make it an efficient operation.

## DEFINING BIOLOGICS

Biologicals or "Biologics" can be defined as products of which the active substance is produced by or extracted from a biological source. This is an

all-encompassing definition which includes vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins (RNAi, alternate scaffolds, antisense nucleotides, aptamers, vaccines, monoclonal antibodies, recombinant proteins and peptides, prophylactic vaccines). Consequently, these drugs have been broadly classified into-gene and cell- based biologics. Chemically, biologics can be sugars, proteins, nucleic acids or complex combinations of these substances, or may even be living entities such as cells and tissues. Typical examples of biologic preparations that are available in market are cited in Table 2.1. The biotherapeutic modalities have undergone a sea-change and evolved to a higher platform. They are projected for phenomenal future growth, with biggest players being recombinant proteins and monoclonal antibodies.

The source of biologics is primarily natural vis-à-vis, human, animal, or microorganism. These may be later modified so as to produce on a large scale by biotechnology based techniques. Research on biologics is gaining momentum and they are being tapped to treat a variety of medical conditions for which no other treatments are available. Nearly 200 biologics were approved between January 1995 and June 2007 in the US alone (Giezen et al, 2008). A systematic classification of the approved biologics on the basis of their therapeutic class shows that biologics are proving useful approach in all the major disease conditions (Fig. 2.1).

## MAKING BUSINESS SENSE OUT OF BIOLOGICS

In the United States, the first biological, recombinant insulin, was approved in October 1982. Since then, more than 250 biologics, including recombinant (blood) products, monoclonal antibody-based products, and recombinant vaccines have been approved by regulatory authorities. Between 2003 and 2006, biologics represented over 24%, of all new chemical entities approved by the US. World wide biologics account for about 25% of all new drugs in the market and contribute towards 16% of the total sales. It is being forecasted

**Table 2.1:** Class and examples of the currently marketed biologics

| *Classes* | *Examples* |
|---|---|
| Antibodies | Herceptin, Humira |
| Recombinant proteins | |
| Cytokines | Avonex (IFN-β) |
| Enzymes | Activase (TPA) |
| Receptors | Enbrel (TNF-αR) |
| Small proteins | Humalog (Inulin) |
| Vaccines | Prevanir, Flumist |
| Sugars | Calciparin (Heparin Mucopolysaccharide) |
| Nucleic acids | Macugen (anti-VEGF aptamer) |
| Cells | Islet cells from donor |

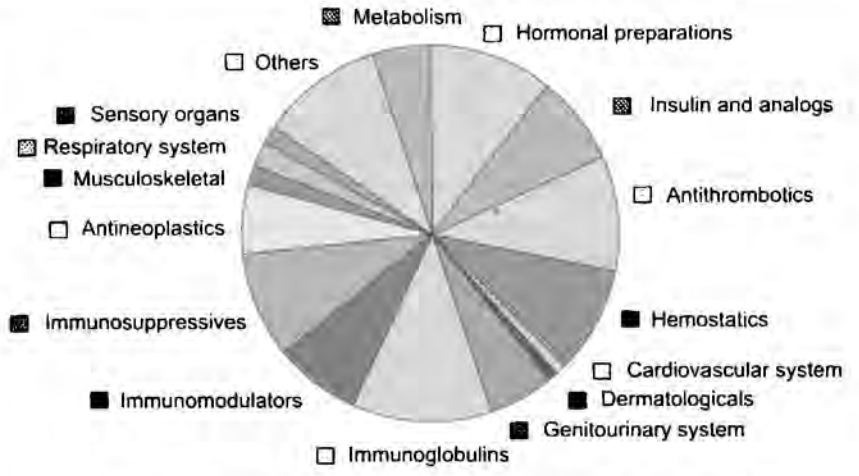


**Fig. 2.1:** Percentage of biologicals approved between January 1995 and June 2007 and classified by therapeutic class *(For color version, see Plate 4)*

that by the year 2025, 70% of the pharmaceutical market would be taken up by biotechnology-based products.

In the United States, the sales of biological products between 2001 and 2006 have shown an annual growth rate of 20% (Giezen et al, 2008). In 2006, the sale of top 12 biologics has been estimated at $63 billion and is expected to touch up to $100 billion by 2011. Considering the fact that the amount spent on the development of biologics is a mere 3% of the total spending, the returns are encouraging and there is scope for tremendous evolution.

The biological products are bringing golden reaps for the pharmaceutical industry and many mutually beneficial deals are being materialized. To cite the case of Sanofi Pasteur which announced that it had acquired the worldwide rights for KB-001, a monoclonal antibody (mAb) fragment of KaloBios Pharmaceuticals. The product is in Phase I/II development to treat and prevent *Pseudomonas aeruginosa* infections. The agreement involves an upfront payment of US$35 million and potential milestones of up to $255 million. In addition, KaloBios has retained the development and marketing rights for cystic fibrosis and bronchiectasis indications.

In another case, MassBiologics and Medarex published positive Phase II results showing that two mAbs targeting *Clostridium difficile* toxins A and B (called CDA1 and CDB1, respectively) significantly reduced the recurrence of *C. difficile* infection when administered together. Merck had licensed the development and commercialization rights for these mAbs in April 2009 for a $60 million upfront fee. MassBiologics and Medarex could also be eligible for additional cash payments of up to $165 million, if certain milestones are met (Lowry et al, 2010). Some of the biologicals that have been approved recently, are enlisted in Table 2.2.

**Table 2.2:** Biological license application approvals in 2010

| *Trade name/ Proper name* | *Indication for use* | *Manufacturer* | *Approval date* |
|---|---|---|---|
| **Hizentra** Immunoglobulin Subcutaneous (Human) | Treatment of primary immunodeficiency | CSL Behring AG | 3/4/2010 |
| **Menveo** Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria | For active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A,C, Yand W-135 when administered to individuals 11 through 55 years of age. | Novartis Vaccines and Diagnostics, Inc | 2/19/2010 |
| **Prevnar 13**[3] Pneumococcal 13-valent Conjugate Vaccine | For active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, for use in children 6 weeks through 5 years of age; For the preven tion of otitis media caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. | Wyeth Pharma ceuticals, Inc | 2/24/2010 |

## WHY A HALO AROUND BIOLOGICS?

Biologics are being heralded as the "gold standard" for the future. Extensive and sophisticated research is being carried out to identify the best molecule in terms of potency, affinity and half-life against a target. Such biologics are capable of delivering great value for the patients due to the following points:

### Unique Target Space

Broadly classifying from the pharmacology point of view, the intervention sites of most of the drugs can be identified as:

i. Ligand-receptor interactions
ii. Intracellular pathways
iii. Cell-cell talk
iv. Cell-matrix talk

Traditionally, the drugs in the form of small molecule have acted by affecting intervention sites (i) and (ii), while nominally targeting (iii) and (iv). However, with the advent of biologics, the target space available has expanded manifold. They are being successfully used to target any of the intervention sites. In fact, a novel approach is being developed wherein the two therapies will be used together. They will affect different intervention sites to expand the target space, thereby yielding better results.

### Good R and D Survival Rate

Drug discovery and development program requires that any novel molecule should be sequentially analyzed for various paradigms in preclinical and clinical stages. This helps to remove chaff and bring out successful molecule. However, it makes the process cumbersome, costly with high attrition rates. It has been recorded that traditional small molecules have had a low survival rate, with only 1 in 51 molecules making it to the market. In contrast, the overall R and D survival rate of novel biologics is as high as 1 in 21. The higher success rate of biologics can be attributed to their higher survival rate of almost 90% in preclinical studies.

## BIOMARKER-BASED STRATEGY IN THE DISCOVERY AND DEVELOPMENT OF BIOLOGICS

Recent advances in drug discovery have been in a core area namely, structure-based design. This involves developing the design of typically small molecules that bind to a biomolecular target and inhibit its function. In contrast, the strategy in developing biomarker protein as biologics target site involves in designing process features that build three-dimensional structures of complexes of the small molecules with the target. Structure-based design can be carried out with nothing more than the target structure, which most often comes from X-ray crystallography, and graphics tools for placing small molecules in the proposed binding site. Many such molecules are now in the clinical phase of development. The following are cases in point.

- Identification of molecular alterations in key proteins involved in breast cancer cell proliferation and survival resulted in the development of a new treatment strategy with target-based agents. The anti-ErbB-2 monoclonal antibody (mAb) Trastuzumab and the dual epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor Lapatinib are effective in patients with breast cancer that overexpresses ErbB-2. The antivascular endothelial growth factor-A mAb Bevacizumab is approved in combination with taxanes for treatment of unselected patients with metastatic breast cancer. In addition, preclinical data suggest that signaling inhibitors can prevent or overcome resistance to endocrine therapy in estrogen receptor positive (ER+) breast cancer (Normanno, 2009).
- Sepsis is currently the 10th leading cause of death overall and accounts for significant healthcare expenditures in the developed world. Incidence

of deaths attributable to sepsis are rising and unfortunately, to date, there are very few successful therapeutic agents available in the clinical setting. Several novel therapeutic adjuncts for the management of critically ill patients with sepsis are being developed which largely focus on therapies that directly target the host inflammatory response, specifically those that result in activation of the transcription factor, nuclear factor (NF)-κB. Activated protein C (Drotrecogin alfa, Xigris®, Eli Lilly and Co), and Afelimomab, a monoclonal antibody F(ab')2 fragment directed against tumor necrosis factor (TNF)-α are biomarker-basedbiologics that are currently being investigated in clinical trials (Wheeler et al, 2009).

- CD4 cell has been identified as the 'primary receptor' for the AIDS virus. Recently, role of additional molecules such as CXCR4 have been identified as the coreceptor for X4 HIV-1 isolates. In addition, it has been demonstrated that CCR5 is the coreceptor along with CD4 that allows entry of R5 HIV-1. The discovery of the HIV coreceptors provided a logical target in the management of HIV-1 infection. Recently, orally bioavailable CCR5 blocking agent, Maraviroc, is the first such therapeutic to be approved by the U.S. Food and Drug Administration. CXCR4-based blocking agents are less attractive due to the crucial role of CXCR4 in many other biological processes. However, agents that are aimed at downmodulating CXCR4 expression are also being explored as they might provide some benefits for HIV-positive patients (Alkhatib, 2009).
- Monoclonal antibodies are a promising new class of therapeutic agents that can be employed to target specific molecules of the immune system or any tissue. They are currently being tested in a number of clinical trials in autoimmune diseases such as multiple sclerosis (MS). One of these, the humanized monoclonal anti-CD25 antibody Daclizumab (Zenapax), is directed against the interleukin-2 (IL-2) receptor alpha chain (CD25) that is involved in clonal expansion of autoreactive T-cells by binding of its ligand IL- 2.
- Many orphan conditions are being successfully treated by biosimilars. The discovery that clinically unrelated conditions, such as rheumatoid arthritis and Crohn's disease, share similar immune dysregulation has led to a shift in the management of these conditions (Kuek et al, 2007). They have been collectively named as immune-mediated inflammatory diseases (IMIDs) and the management has shifted from one of organ-based to symptom relief to mechanism-based treatment. To cite an example, anticytokine therapy has been effective in treating IMID due to its widespread role in pathogenesis of multiple inflammatory conditions (Table 2.3).

AIHA, autoimmune haemolytic anaemia; CIDP, chronic inflammatory demyelinating polyneuropathy; GCA, giant cell arteritis; GN, glomerulonephritis; JIA, juvenile idiopathic arthritis; PMR, polymyalgia rheumatica; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis*; SLE, systemic lupus erythematosus. (Adapted from Kuek et al, 2007).

**Table 2.3:** IMIDs in which biologic therapy appears promising

| *Infliximab* | *Etanercept* | *Adalimumab* | *Rituximab* |
|---|---|---|---|
| Sjogren's | Sjogren's | Crohn's disease | Polymyositis/ dermatomyositis |
| Polymyositis/ dermatomyositis | Polymyositis/ dermatomyositis | UC | Wegener's granulomatosis |
| Wegener's vasculitis | Wegener's vasculitis | Psoriasis | GCA/PMR |
| Behcet's | Behcet's | JIA | Polyarteritis nodosa |
| GCA/PMR | GCA | Behcet's | JIA |
| Takayasu's arteritis | Takayasu's arteritis | Takayasu's arteritis | Graft-versus-host disease |
| Polyarteritis nodosa | Polyarteritis nodosa | Sarcoidosis | Cryoglobulinemic vasculitis |
| Sarcoidosis | Sarcoidosis | Adult onset Still's disease | ITP |
| Adult onset Still's disease | Adult onset Still's disease | Hydradenitis suppurative | TTP |
| JIA | Cryoglobulinemic vasculitis | Pyoderma gangrenosum | AIHA |
| Kawasaki disease | Relapsing polychondritis | Pemphigus | Antiphospholipid syndrome |
| Cryoglobulinemic vasculitis | Hydradenitis suppurative | | Idiopathic membranous GN |
| Relapsing polychondritis | Pyoderma gangrenosum | | Hep C associated GN |
| Hydradenitis suppurative | Graft-versus-host disease | | Multiple sclerosis |
| Celiac disease | Chronic hepatitis C | | Myasthenia gravis |
| Myelodysplastic syndrome | ITP | | Pemphigus |
| Pyoderma gangrenosum | Refractory asthma | | Graves' disease |
| Erythema nodosum | Amyloidosis | | CIDP |
| SAPHO syndrome | Multicentric reticulohistiocytosis | | |
| Graft-versus-host disease | Pemphigus | | |
| Chronic hepatitis B/C | Graves' disease | | |
| ITP | CIDP | | |

The use of biomarkers presents an opportunity in understanding target engagement and disease impact while accelerating drug development. For effective integration in drug development, it is essential for biomarkers to aid in the elucidation of mechanisms of action and disease progression. The recent years have witnessed significant progress in biomarker selection, validation, and qualification, while enabling surrogate and clinical endpoint

qualification and application. Biomarkers play a central role in target validation for novel mechanisms. They also play a central role in the learning/confirming paradigm, particularly when utilized in concert with pharmacokinetic/pharmacodynamic modeling. Clearly, these attributes make biomarker integration attractive for scientific and regulatory applications to new drug development (Krishna, 2008).

The rapidly increasing availability of genomic data for numerous biological entities presents exciting possibilities for understanding human health and disease. Biomarkers are playing a pivotal role in diagnosis of disease condition. Etiopathological studies have brought fore ideal biomarker, or panel of biomarkers associated with each disease condition that can be used in its early detection. This when coupled with biotechnology techniques such as microarray, can help to screen large number of samples in a cost-effective manner using minimum time and labor. In contrast to traditional serological/microbiological assay-based diagnosis, biomarker based system of diagnosis can accurately analyze low quantity of samples and delineate complicated cases of resistance or relapse, etc. in a single test. This mode of high-throughput diagnosis has revolutionized diagnostic sciences and is being widely used for many viral diseases (AIDS, HCV, influenza, etc.), cancer, tuberculosis (Pai et al, 2006; Besson and Kazanji, 2009).

## CHALLENGES IN THE DISCOVERY AND DEVELOPMENT OF BIOLOGICS

The discovery and development of biologics is fraught with numerous challenges, some of which are critically discussed below:

a. The production and purification process of biologics is complex, as it involves numerous steps. Minor alterations at any of the step in the production cascade can lead to drastic changes in the characteristics of the end product.
b. Small differences and changes in the production process can therefore have major implications on the safety profile of biologics. For example, pure red cell aplasia is an extremely rare complication recorded in patients treated with recombinant human epoetin. The incidence was observed to be unexplainably elevated in patients. The reason provided was that these patients were administered one particular formulation of recombinant human epoetin in which human serum albumin had been replaced with polysorbate 80 and glycine.
c. The risk of contamination with pathogens by the donor is another problem related to the production process (e.g. for products extracted from human blood or plasma).
d. As the knowledge of a new drug is incomplete at the time of approval, due to a variety of factors including constraints in the sample size and the design of randomized controlled trials. Therefore, a huge risk is attached with the use of biologicals especially with regards to their safety

profile. Identification of important safety problems, has led to the withdrawal of drugs from the market.

e. Biologicals are specifically prone to the induction of immunogenicity. In many cases, immunogenicity can lead to loss of efficacy of the drug or, even worse, lead to autoimmunity to endogenous molecules.

f. The predictability of preclinical data to humans is limited for biologicals due to the species-specific action and immunogenic properties in animals. To cite a recent example, healthy volunteers participating in a phase 1 clinical study of a CD28 agonist monoclonal antibody (TGN1412; TeGenero Inc.), recorded a serious adverse event. The observed cytokine storm following infusion had not been observed in the preclinical studies. Thus, in order to obtain valuable results from the preclinical studies, the battery of tests should not only be selected based on pharmacological and pharmacokinetic properties but its potential for immunogenicity should also be taken into account.

g. In some cases, the preclinical program has been complicated by a complex pharmacodynamic-pharmacokinetic relationship.

h. Limited information is available on the safety-related actions of biologics. It is difficult to extrapolate the actions, kinetics and adverse effects of drugs belonging to the same mechanistic classes. This complicates the associated regulatory actions.

i. From the patients' perspective, biologics pose a challenge because majority of them have to be administered from the parenteral route. This is inconvenient in long-term therapy and affects compliance. In addition, trained healthcare staff may be required to administer the drug, which translates into frequent hospital visits and additional cost burden on the patient.

j. How biosimilars might be developed is a burning question that is doing the rounds. It is quite evident that the skills that are required to develop biosimilars are quite different from typical generics. In case of biosimilars, the new drug has to go through the complete rigors of preclinical, manufacturing and clinical studies, as data from class biologic cannot be extrapolated. This means additional cost burden on the pharmaceutical industry and time lapses.

k. Most of the biologics are temperature and humidity-sensitive, susceptible to microbial contamination products with short shelf-lives. These products have to be stored under appropriate conditions, as use of improperly stored products can prove to be hazardous. Thus, they require cold chain storage during transportation. Therefore, their use may be limited amongst developing nations, which are often the biggest markets of pharmaceuticals.

l. A shortage situation occurs when the total supply of all licensed or approved product available at the market level will not meet the current demand and there is no adequate alternative therapy available that is judged by appropriate medical staff to be a suitable alternative. Many of

the launched products face shortages due to many reasons including manufacturing issues, corporate decisions to discontinue the product, distribution disruptions, regulatory actions, or natural disasters. Some of the useful products that are facing shortage have been enlisted in Table 2.4. The goal of Center for Biologics Evaluation and Research (CBER) is to help prevent or alleviate shortages of biological products, and to work with all parties involved to make certain medically necessary products available within the United States.

m. Many of the commercially successful therapeutic biologics will go off patent between 2013 and 2017. This will lead to drop in inventors' market share, unless a follow-on biologic is developed before the deadline. Consequently, there has been a surge in investments on follow-on biologics.

One such product is the drug filgrastim (Neupogen, Amgen Co.), approved for the treatment of neutropenia, whose patent is expected to expire in 2013. Insmed claims to have replicated the product already and is ready to launch it (Waltz, 2008). Other products whose patents are likely to expire include the monoclonal antibodies (mAbs) infliximab (Remicade) and adalimumab (Humira) (Lanthier et al, 2008).

To take care of the practical barriers in the development of the follow-on biologics and pave path for their successful use, Merck Co., announced the creation of Merck BioVentures. Similarly, leading generic manufacturer Teva Pharmaceuticals announced a strategic partnership with Lonza — a company that provides custom manufacturing of biopharmaceuticals in 2009—with the aim of becoming a global provider. Merck has further acquired Insmed, a US biotech company that aimed to be the first company to develop a comprehensive portfolio of follow-on biologics. Through the US$130 million acquisition, Merck will gain Insmed's pipeline of follow-on products, as well as its commercial manufacturing facilities.

**Table 2.4:** Biological products facing shortage

| *Products* | *Shortage status* |
|---|---|
| Immunoglobulin (Human) **GamaSTAN® S/D**Talecris Biotherapeutics, Inc. | Jan 2010-Ongoing |
| Antivenin (Latrodectus Mactans) **Antivenin (Black Widow Spider Antivenin)**Merck & Co., Inc. | Jan 2009-Ongoing |
| Hepatitis B Vaccine **Recombivax HB®** Merck & Co., Inc. | Jan 2009-Ongoing |
| Pediatric and Adult Hepatitis A Vaccine **VAQTA®** Merck & Co., Inc. | Feb 2008-Being monitored |
| *Haemophilus influenzae* Type b (Hib) Conjugate **PedvaxHIB®** and **Comvax®** Merck & Co., Inc. | Dec 2007- Ongoing |
| Rubella Virus Vaccine Live **Meruvax II®** Merck & Co., Inc. | 2008- Ongoing |
| Zoster Vaccine Live **Zostavax®** Merck & Co., Inc. | July 2008- Ongoing |
| Measles, Mumps, Rubella and Varicella Virus Vaccine Live **ProQuad®** Merck & Co., Inc. | June 2007- Being monitored |

n. Monoclonal antibodies (mAbs) and immune-based therapies prove to be useful as adjunctive and not mainline therapy. They may be given in addition to antibiotics, antivirals, anticancer and antiallergic drugs.
o. Most biologics are complex mixtures that are not easily identified, purified or characterized. Their manufacture requires elaborate biotechnology-based techniques that have to be carried out on aseptic principles.
p. There are diverse application areas of drugs that include diagnosis, prevention and cure. Their use may be intended for exploring or modifying both physiological and pathological states. Due to their inherent limitations, biologics cannot be used in all areas.

## BIOLOGICS VS SMALL MOLECULES: WHAT IS THE SCORECARD?

It has been estimated that all the known small molecules taken together, target around 14% of the druggable genes, 50% of disease modifying genes and over 1,500 potential targets. In contrast, the biologics mainly act on 31% of the known extracellular targets, 12% of disease modifying genes and approximately 900 potential targets. There are 375 unique targets for small molecules as compared to 225 targets available for biologics with an overlap of 75-80% targets between small molecules and biologics. Thus, from the scorecard it is evident that the two classes of drugs run head-to-head, as far as their feasible applications are concerned. In such a condition the real determinants are the efficacy and safety profiles.

To cite a case in the point, breast cancer is the most common female malignancy in many industrialized countries. Approximately one-fourth of all women diagnosed with early breast cancer present with tumors that are characterized by Erb-B2 amplification. While the associated Her-2/neu receptor overexpression results in a high risk of relapse and poor prognosis, these tumors also represent a target for a selective monoclonal antibody therapy with trastuzumab (Herceptin®). The combination of trastuzumab with chemotherapy has led to a considerable reduction of recurrences and to a significant reduction in breast cancer mortality both in the adjuvant and metastatic setting. Unfortunately, despite Her-2/neu overexpression, not all patients equally benefit from trastuzumab treatment, and almost all women with metastatic breast cancer eventually progress during antibody therapy. Moreover, trastuzumab is burdened with cardiotoxicity, thus increasing the risk of symptomatic congestive heart failure. In addition, the marginal costs for a 1 year therapy of trastuzumab-based therapy, which is currently considered to be the most effective treatment regimen in the adjuvant setting, may amount for up to US$ 40.000 (Fischer et al, 2003).

Thus, it becomes clear that even "star drugs" have their limitations and contentious issues in terms of efficacy and safety need to be resolved.

## SAFETY BIOLOGICS

Drug safety has always been a key aspect of drug development. Recently, the Vioxx case and several cases of serious adverse events being linked to

high-profile products have increased the importance of drug safety, especially in the eyes of drug development companies and global regulatory agencies. Safety biomarkers are increasingly being seen as helping to provide the clarity, predictability, and certainty needed to gain confidence in decision making: early-stage projects can be stopped quicker, late-stage projects become less risky. Public and private organizations are investing heavily in terms of time, money and manpower on safety biomarker development. An illustrative and "door opening" safety biomarker success story is the recent recognition of kidney safety biomarkers for pre-clinical and limited translational contexts by FDA and EMEA. This milestone achieved for kidney biomarkers and the "know how" acquired is being transferred to other organ toxicities, namely liver, heart, vascular system. New technologies and molecular-based approaches, i.e., molecular pathology as a complement to the classical toolbox, allow promising discoveries in the safety biomarker field.

## CONCLUDING REMARKS

When targeting new disease areas with the objective of drug discovery, 'target validation' is the first approach that is adopted, which is nothing but extensive biologic studies. The crux lies in knowing for certain that the target pathway plays an important role in the pathogenesis of the disease and developing appropriate modality that targets the same. Target engagement, and disease-related biomarkers have significantly accelerated drug development. The use of biomarkers as tools facilitated design of clinical efficacy trials while streamlining dose focus and optimization, the net impact of which reduced overall cycle time to filing as compared to the industry average (Krishna, 2008).

Biologics and small molecules complement each other. They are the two faces of the same coin and are complementary to each other as they are developed with the same objective of ameliorating the disease. Based on the validated target, suitable approach either in the form of small molecule or biologic, either singly or in combination has to be pursued.

Very high stakes have been placed on the drug discovery program, world over. A portfolio based complementary approach in tapping small molecule and biologics will yield better results. It will help in making the program efficient, and will help to evenly spread the overall risk in the discovery and development phases.

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CHAPTER

# 3 Clinical Development of New Drugs

## HISTORY

Clinical trials were first introduced in Avicenna's The Canon of Medicine in 1025 AD, in which he laid down rules for the experimental use and testing of drugs and wrote a precise guide for practical experimentation in the process of discovering and proving the effectiveness of medical drugs and substances. The principles and rules for testing of new drugs are still the basis of modern clinical trials.

- The drug must be free from any extraneous accidental quality
- It must be used on a simple, not a composite, disease
- The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones
- The quality of the drug must correspond to the strength of the disease
- The time of action must be observed, so that essence and accident are not confused.

One of the most famous clinical trials was James Lind's demonstration in 1747 that citrus fruits cure scurvy. He compared the effects of various different acidic substances, ranging from vinegar to cider, on groups of afflicted sailors, and found that the group who were given oranges and lemons had largely recovered from scurvy after 6 days.

## INTRODUCTION

Drug development is a precarious pharmaceutical business with risks outweighing benefits. Though risky, many major pharmaceutical companies are involved in drug development process, as it is essential for the survival of pharmaceutical companies and for the betterment of people with newer therapy for treating diseases that afflict millions of people worldwide. There are two phases in the genesis of any new drug, namely drug discovery and drug development. The growth of an idea into a product may take over a decade of dedicated research by team of researchers including organic chemists, pharmacists, pharmacologists, toxicologists and clinicians. This is a target oriented multi-stage ongoing process of critical importance as each new discovery means relief to millions. The first stage of drug discovery involves the identification of the target, drug designing and synthesis followed

by its preliminary *in vitro* screening. With the advent of high throughput screening technology, the number of new chemical entities (NCE) that are being generated has increased in leaps and bounds. NCE undergoes drug development that involves determination of its safety, efficacy, kinetics and developing formulation. There are two overlapping phases of drug development that can be differentiated, namely preclinical and clinical. Preclinical evaluation involves rigorous testing of efficacy and safety of the new molecule by various *in vivo* assays using animals. The necessary data for evaluation in humans is generated here and the test drug is now ready for its last and most crucial stage of evaluation, i.e. clinical evaluation. The clinicians in co-ordination with the pharmacists evaluate the efficacy and safety of the sample over four stages starting from healthy volunteers and moving on to small group of patients and then larger number of patients and special groups. phase one or clinical pharmacology forms the basis for clinical trial for any new drug and provides the link between pre-clinical and clinical research. Finally, the application for FDA review and approval may be applied and the approval sought. The successful development of a drug from laboratory to market may take well over 10 to 15 years and require investment of millions of dollars (Figs 3.1 and 3.2). Most new drug candidates are identified through one or more of the following approaches:

- Chemical modification of an already known molecule
- Screening for biologic activity for large numbers of natural products, data mining of previously discovered chemical entities or large libraries of peptides, nucleic acid or other large organic molecules
- Rational drug design based on an understanding of biologic mechanisms and chemical structure
- Biotechnology and cloning using genes to produce larger peptides and proteins. Moreover, automation has generated the process known as "high throughput screening" which permits millions of assays per month.

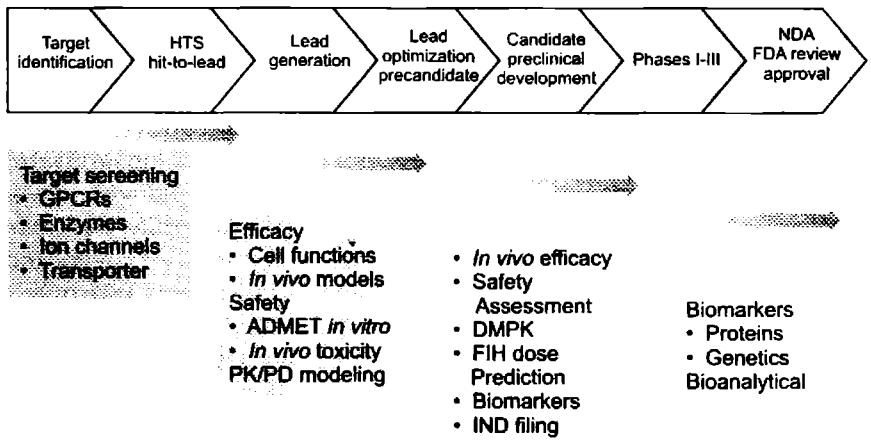



**Fig. 3.1:** Phases of drug discovery

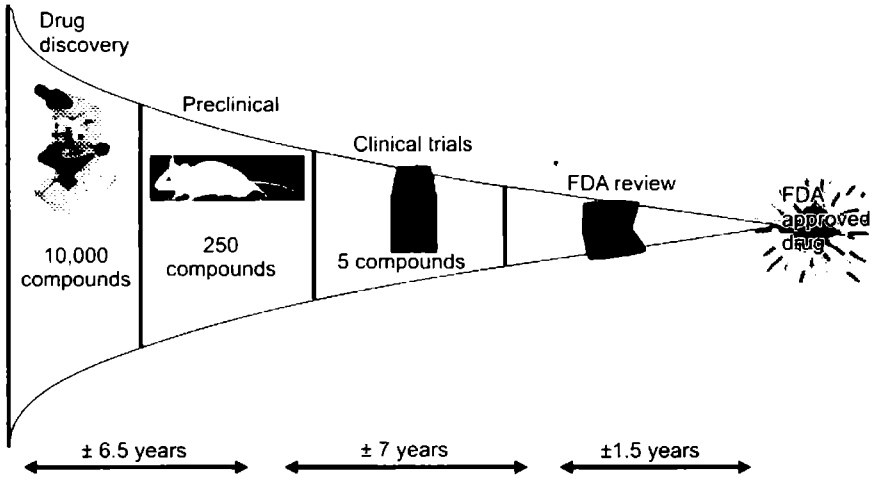



**Fig. 3.2:** The process leading to a drug discovery is lengthy and costly *(Source USFDA)*

## DRUG DEVELOPMENT PROCESS

There are following steps of research activities, which begins the process and results in the development of new drugs:

### Target Identification

Drugs usually act on either cellular receptor or genetic chemicals in the body, known as targets, which are believed to be associated with disease. Various methods are used by the scientists to identify and isolate a target, and learn more about its functions and how these can affect disease. Compounds are then identified that have various interactions with the drug targets, which are helpful in treatment of a specific disease.

### Target Validation

In order to select the most useful target among the identified targets, scientists analyze and compare each drug target to others based on their association with a specific disease and their ability to regulate biological and chemical process/molecules in the body. Various studies are conducted to confirm that interactions with the drug target have demonstrated a desired change in the behavior of diseased cells. The data from these studies help the research scientists to identify compounds that have an effect on the target selected.

### Lead Identification

A molecule that is believed to have potential to treat disease is a lead molecule. The scientists in the laboratory compare standard drug in that specific disease with new molecules to determine their likelihood of success. Leads are sometimes developed as collections, or libraries, of individual molecules that

possess properties, which are required in a new drug. Thereafter evaluation is done on each of these molecules to confirm its effect on the drug target.

### Lead Optimization

While working on the lead optimization, properties of various lead compounds are assessed which help to select the compound or compounds with the greatest potential to be developed into safe and effective medicines.

## SUCCESS RATE OF DEVELOPING A NEW DRUG

Not every compound that is tested in lab is marketed. Before a drug is marketed, it has to undergo several stages of development. A company has to screen through many thousand compounds that show promising result before it could take on the task of development of a promising compound. This eventually increases the cost of development of drug as many compounds that are tested are discarded in the preliminary stages of development. For every 1,000 compounds that are identified by a company, only about 30 show promising results. Moreover, for every 30 compounds that show promise, three get past the first round of clinical trials and finally, only one hit the market. Sometimes compounds are to be dropped off during regulatory approval process. Thus, to introduce one new drug, a company needs to start with many thousands of compounds.

## TIME REQUIRED TO DEVELOP A NEW DRUG

It is well known that drug development is a very sluggish process which is scrutinized at every stage of development by the USFDA in the US and respective regulatory agencies in various countries. It may take anywhere between 12 to 15 years to develop a new drug according to PhRMA (Pharmaceutical Research and Manufacturers of America—pharma industry trade group of America). This slowness of drug development is attributed to numerous steps a drug has to go through before it is ultimately launched in the market. Drug development includes about six-and-a-half years of discovery, preclinical testing, and toxicity studies; one-and-a-half years in phase I trials to assess safety in healthy volunteers; then two years in phase II trials with a few hundred patients to evaluate the drug's effectiveness and side effects. The development process continues with three-and-a-half years in phase III trials involving thousands of patients and scores of research centers to confirm effectiveness and evaluate long-term effects, then one-and-a-half years of Food and Drug Administration review, where all the clinical trial data are presented. Even after the drug is approved, it may undergo further phase IV testing so more safety and efficacy data can be collected. The drug development stages explained above can be shown in Figure 3.3.

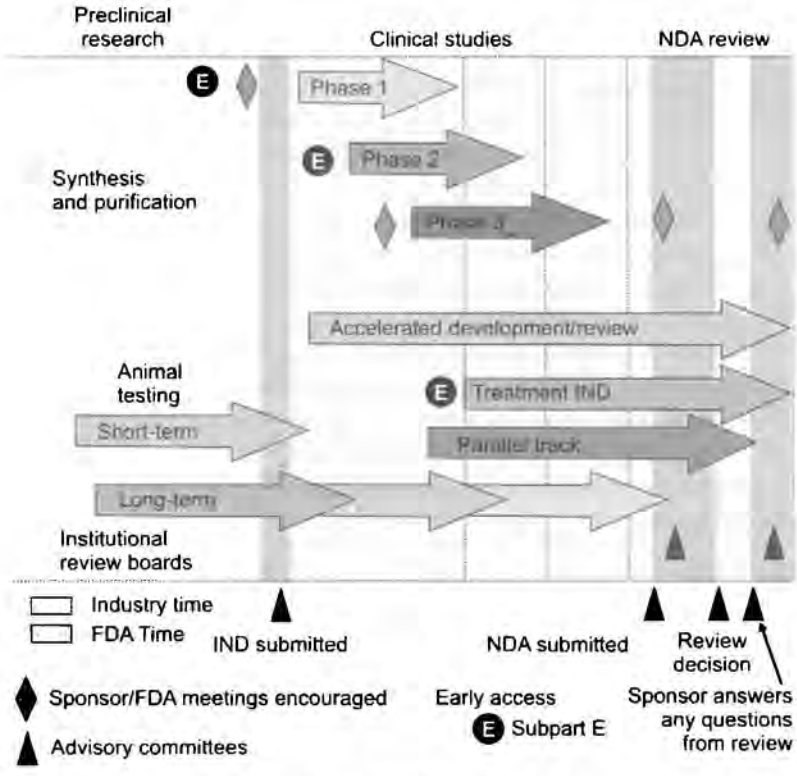



**Fig. 3.3:** The new drug development process: Steps from test tube to new drug application review (*Source:* USFDA)

Drug development in addition to taking longer time for marketing approval (12 to 15 years as discussed above) requires mammoth investment from pharmaceutical companies. It is estimated, according to various sources that cost of developing a single new drug including commercialization varies from US $ 800 million to US $ 1.7 billion. Thus, in addition to increasing approval time for a single drug, cost of development is also escalating. This is partly attributed to scrutiny by regulatory agencies and lengthening time for review of applications. It is quite possible that during the stage of development, a drug under review may not make to next stage due to reasons like quality, safety, toxicity or efficacy and thereby increasing the cost of development. The money invested by the company for such unsuccessful molecules is sunk cost and cannot be recovered.

## STAGES OF DEVELOPMENT OF A NEW DRUG

### Preclinical Stage

This stage comprises of study on animals to find out various parameters for a drug under development. During preclinical drug development, the drug's

toxic and pharmacological effects are evaluated *in vitro and in vivo* laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. At the preclinical stage, the FDA may require:

1. a pharmacological profile of the drug;
2. data of the acute toxicity of the drug in at least two species of animals, and
3. data of short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

During the pre-clinical development of a drug, laboratory tests register the effect of the investigational drug in living organisms (animal testing) and in cells in the test tube. The preclinical testing results are used to find out how best to formulate the drug for its proposed clinical use. Regulatory agencies require testing that documents the characteristics—chemical composition, purity, quality and potency of the active ingredient and of the formulated drug.

### Phase 0 (Microdosing)

As the saying among pharmacologists goes, the rat is not a good human—which is to say, there is just no real surrogate for early-stage human data, no matter how many laboratory animals you sacrifice in whatever ways. In the heroic times of medicine, drug developers used to test their invention on themselves before applying it to patients. This would be mostly meaningless today because, given the current regulatory framework, it would not yield data that would be accepted in support of initiating regular trials. However, another option has now been formally adopted and endorsed by the world's major regular bodies: human microdosing. The concept of microdosing calls for the administration of an investigational compound to healthy human volunteers in doses at least two orders of magnitude lower than those that, based on animal studies, would have a pharmacological effect in humans. Table 3.1 explains upsides and downsides of microdosing vs. conventional pathway to first-in-human milestone.

## HUMAN CLINICAL TRIAL PHASES

Clinical trials are conducted to collect data regarding the safety and efficacy of new drug and device development. There are several steps and stages of approval in the clinical trials process before a drug or device can be sold in the consumer market, if ever. Drug and device testing begins with extensive laboratory research which can involve years of experiments in animals and human cells. If the initial laboratory research is successful, researches send the data to the Food and Drug Administration (FDA) for approval to continue research and testing in humans. Once approved, human testing of experimental drugs and devices can begin and is typically conducted in four phases. Each phase is considered a separate trial and, after completion of a phase, investigators are required to submit their data for approval from the

**Table 3.1:** Microdosing vs conventional pathway to first-in-human milestone (Phase 0)

| | *Conventional approach* | *Microdosing approach* |
|---|---|---|
| Time and cost from selection of preclinical candidate to finalized first-time-in-man study | 12 to 18 months<br>$1.5 to $3.0 million | 5 to 8 months<br>$0.3 to 0.5 million |
| Minimum amount of compound required and qualification | Approx. 100 grams (GMP qualified for phase I) | Less than 100 milligrams in GLP quality only |
| Predictive power for pharmacokinetic parameters at pharmacologically effective doses | Definite | Generally good if mass effects and/or protein binding make no significant contributions |
| Need for 14C labeled compound for first-time-in-man study | No | Yes (if AMS is used)<br>No (if LC/MS/MS is used) |
| Available options for outsourcing | Huge number of certified preclinical and clinical stage CROs and analytical laboratories in all major pharmaceutical markets | Use of AMS requires certification of clinical CRO for 14C work; analytics restricted to a handful of highly specialized providers |
| Standardization and degree of establishment of regulatory path | Firmly established and internationally harmonized through ICH guidelines; few if any variations possible | Very new - authorities and developers are on a learning curve; US and European regulations not identical in some points |

*Source:* Cambridge Healthtech Associates

FDA before continuing to the next phase. Comparison of preclinical and different phases of clinical trials and their outcomes are shown in Table 3.2. Flow chart 3.1 shows clinical trials in nutshell.

### *Phase I*

Studies assess the safety of a drug or device. This initial phase of testing, which can take several months to complete, usually includes a small number of healthy volunteers (20 to 100), who are generally paid for participating in the study. The study is designed to determine the effects of the drug or device on humans including how it is absorbed, metabolized, and excreted. This phase also investigates the side effects that occur as dosage levels are increased. About 70 percent of experimental drugs pass this phase of testing.

### *Phase II*

Studies test the efficacy of a drug or device. This second phase of testing can last from several months to two years, and involves up to several hundred patients. Most phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded"

**Table 3.2:** Various stages of preclinical and clinical testing with purpose and success rate at each stage

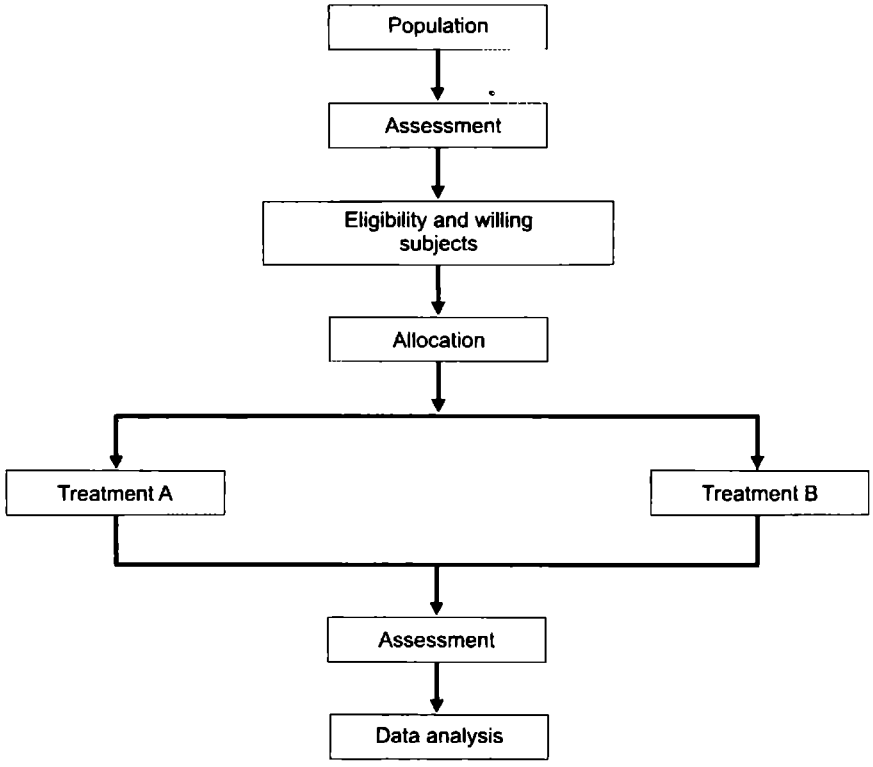
| | *Preclinical testing* | *Phase I* | *Phase II* | *Phase III* | *Phase IV* |
|---|---|---|---|---|---|
| **Objective** | Assess safety and biological activity | Determine the metabolic and pharmacological actions and the maximally tolerated dose | Evaluate effectiveness, determine the short-term side effects and identify common risks for a specific population and disease | Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risk-benefit ratio in a demographically diverse sample | Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the FDA |
| **Factors to be identified** | The drug's toxic and Pharmacological effects are evaluated *in vitro and in vivo* laboratory animal testing | – Bioavailability<br>– Bioequivalence<br>– Dose proportionality<br>– Metabolism<br>– Pharmacodynamics<br>– Pharmacokinetics | – Bioavailability<br>– Drug-disease interactions<br>– Drug-drug interactions<br>– Efficacy at various doses<br>– Pharmacodynamics<br>– Pharmacokinetics<br>– Patient safety | – Drug-disease interactions<br>– Drug-drug interactions<br>– Dosage intervals<br>– Risk-benefit information<br>– Efficacy and safety for subgroups | – Epidemiological data<br>– Efficacy and safety within large, diverse populations<br>– Pharmacoeconomics |
| **Data focus** | Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's | Vital signs<br>– Plasma and serum levels<br>– Adverse events | – Dose response and tolerance<br>– Adverse events<br>– Efficacy | – Laboratory data<br>– Efficacy<br>– Adverse events | – Efficacy<br>– Pharmacoeconomics<br>– Epidemiology<br>– Adverse events |

*Contd...*

*Contd...*

| | *Preclinical testing* | *Phase I* | *Phase II* | *Phase III* | *Phase IV* |
|---|---|---|---|---|---|
| | metabolites, and the speed with which the drug and its metabolites are excreted from the body | | | | |
| **Design features** | Pharmacokinetic pharmacodynamic studies | – Single, ascending dose tiers<br>– Unblinded<br>– Uncontrolled | – Placebo controlled comparisons<br>– Active controlled comparisons<br>– Well-defined entry criteria | – Randomized<br>– Controlled<br>– 2 to 3 treatment arms<br>– Broader eligibility criteria | – Uncontrolled<br>– Observational |
| **Duration** | 3.5 years | Up to 1 month | Several months | Several years | Ongoing (following FDA approval) |
| **Population** | Animals | Healthy volunteers or individuals with the target disease (such as cancer or HIV) | Individuals with target disease | Individuals with target disease | Individuals with target disease, as well as new age groups, genders, etc. |
| **Sample size** | Experimental design | 20 to 80 | 200 to 300 | Hundreds to thousands | Thousands |
| **Example** | Determine the acute toxicity of the drug in at least two species of animals | Study of a single dose of Drug X in normal subjects | Double-blind study evaluating safety and efficacy of Drug X vs placebo in patients with hypertension | Study of Drug X vs. standard treatment in hypertension study | Study of economic benefit of newly-approved Drug X vs. standard treatment for hypertension |
| **Success rate** | 50000 compounds evaluated | 5 enter clinical trials | | | 1 approved |

**Flow chart 3.1:** Parallel designs




which means that neither the patients nor the researchers know who has received the experimental drug. This allows investigators to provide the pharmaceutical company and the FDA with comparative information about the relative safety and effectiveness of the new drug. About one-third of experimental drugs successfully complete both phase I and phase II studies.

### *Phase III*

Studies involve randomized and blind testing in several hundred to several thousand patients. This large-scale testing, which can last several years, provides the pharmaceutical company and the FDA with a more thorough understanding of the effectiveness of the drug or device, the benefits and the range of possible adverse reactions. Seventy to ninety per cent of drugs that enter phase III studies successfully complete this phase of testing. Once phase III is complete, a pharmaceutical company can request FDA approval for marketing the drug.

### *Phase IV*

Phase IV studies, often called postmarketing surveillance trials, are conducted after a drug or device has been approved for consumer sale. Pharmaceutical companies have several objectives at this stage: (i) to compare a drug with other drugs already in the market; (ii) to monitor a drug's long-term effectiveness

and impact on a patient's quality of life; and (iii) to determine the cost-effectiveness of a drug therapy relative to other traditional and new therapies. phase IV studies can result in a drug or device being taken off the market or restrictions of use could be placed on the product depending on the findings in the study. Table 3.2 shows details of various stages of preclinical and clinical testing with purpose and success rate at each stage.

## CLINICAL TRIAL DESIGN

The major objective of a comparative trial is to provide a precise and valid treatment comparison.

The trial design can contribute to this objective by:

- preventing bias
- ensuring an efficient comparison
- possessing sufficient simplicity so as to encourage participation and minimize errors.

Three components of clinical trials

I. Experiment:
   1. Statement of problem
   2. Objective of the study
   3. Choice of response variable
   4. Selection of factors to be varied
   5. Choice of levels of these factors (fixed, random, quantitative or qualitative)

II. Design:
   1. Sample Size
   2. Method of randomization
   3. Mathematical Model
   4. Hypothesis
   5. Blind Procedure

III. Analysis:
   1. Data collection and processing
   2. Computation of test statistics
   3. Preparation of graphics and tables
   4. Interpretation of results for the primary investigator

### Parallel Group Design

The most common clinical trial design for confirmatory trials is the parallel group design in which subjects are randomized to one of two or more arms, each arm being allocated a different treatment. These treatments will include the investigational product at one or more doses, and one or more control treatments, such as placebo and/or an active comparator. The assumptions underlying this design are less complex than for most other designs.

### Group Sequential Design

In-group sequential design, a number of subjects are entered and studied. During the study an interim analysis of the data is conducted, and if the results are significant or if the treatment groups that is non-significant (statistically) or if the treatment groups are totally alike, then the clinical trial is stopped. If there is a difference between the two groups that is statistically non-significant, then a second group of subjects is enrolled, and the same type of randomization is used as was employed for the original group.

### Factorial Design

In this design two or more treatments are evaluated simultaneously through the use of varying combinations of the treatments. The simplest example of 2 × 2 factorial design in which subjects are randomly allocated to one of the four possible combinations of two treatments, A and B are A alone; B alone; both A and B; neither A nor B. In many cases this design is used for the specific purpose of examining the interaction of A and B.

Another important use of the factorial design is to establish the dose-response characteristics of the simultaneous use of treatments C and D, especially when the efficacy of each monotherapy has been established at some dose in prior studies.

### 2 × 2 Crossover Design

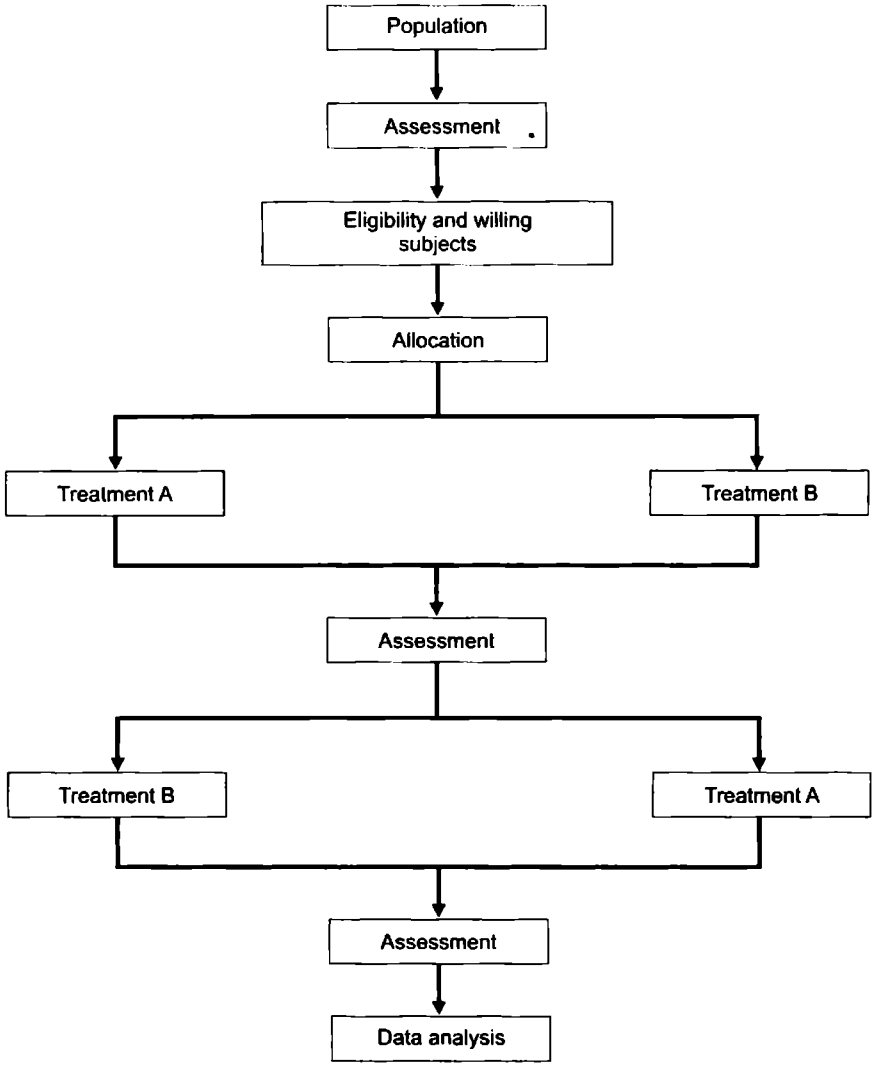
Crossover designs are very commonly used for bioequivalence studies. In chronic conditions disease also this design is used.

The most commonly used statistical design for comparing average bioavailability between two formulations of a drug probably is a two-sequence, two-period, crossover design (2 × 2 crossover design) (Flow chart 3.2). For a standard 2 × 2 crossover design, each subject is randomly assigned to either sequence RT (Reference test) or sequence TR (Test reference) at two dosing periods. In other words, subjects within RT receive formulation R at the first dosing period and formulation T at the second dosing period. The dosing periods are separated by a washout period of sufficient length for the drug received in the first period to be completely metabolized or excreted from the body.

### Multicenter Trials

Multicenter trials are carried out for two main reasons. Firstly, a multicenter trial is an accepted way of evaluating a new medication more efficiently; under some circumstances, it may present the only practical means of accruing sufficient subjects to satisfy the trial objective within a reasonable time-frame. Multicenter trials of this nature may, in principle, be carried out at any stage of clinical development. They may have several centers with a large number of subjects per center or, in the case of a rare disease; they may have a large number of centers with very few subjects per center.

**Flow chart 3.2:** Two period crossover design




## Types of Trials

One way of classifying clinical trials is by the way the researchers behave. In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the experiment. This is also called a natural experiment. An example is the Nurses' Health Study. In an interventional study, the investigators give the research subjects a particular medicine or other intervention. Usually, they compare the treated subjects to subjects who receive no treatment or standard treatment. Then the researchers measure how the subjects' health changes.

**Table 3.3:** Types of trials

| | |
|---|---|
| *Treatment trials* | Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiology/radiation therapy |
| *Prevention trials* | Look for better ways to prevent disease in people who have never had them or prevent them from returning |
| *Diagnostic trials* | Conducted to find better tests or procedures for diagnosing a particular disease or condition |
| *Screening trials* | Test the best way to detect certain diseases or health conditions |
| *Quality of life* | Explore ways to improve comfort and the quality of life for individuals with chronicillness |

Another way of classifying trials is by their purpose. The US National Institute of Health (NIH) organizes trials into five different types (Table 3.3).

### Trial Objectives

The trials, when are designed to compare an Investigational new drug with an active comparator may have one of the following objectives

#### *The Superiority of the IND*

Efficacy of investigational new drug is most convincingly demonstrated by showing superiority to placebo, active comparator or in dose response relationship studies.

### Noninferiority of the IND

There are many active control trials, which are designed with the objective to show that the efficacy of investigational new drug is not inferior (no worse) to that of active comparator.

In phase III drug development, noninferiority trials are more common than equivalence trials. In these trials it is shown that a new treatment is no less effective than an existing treatment – it may be more effective or it may have a similar effect. Again a confidence interval approach is the most straightforward way of performing the analysis but here we are only interested in a possible difference in one direction.

#### *The Equivalence of the Two (Equivalence Trial)*

Equivalence trials are those when investigational new drug is compared to reference treatment with the objective to demonstrate that both the treatments are equivalent.

In case of bioequivalence studies a coverage probability of 90 percent for the confidence interval has become the accepted standard when evaluating whether the average values of the pharmacokinetic parameters of two formulations are sufficiently close.

## CLINICAL OPERATIONS

Understanding and implementation of good clinical practices (GCP) is very essential in the conduct of a clinical trial.

GCP is defined as, "A standard for the design, conduct, performance, monitoring, auditing, recording, analyzes, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected." This definition accurately captures the whole of GCP, both data integrity and subject protection, and specifies areas of trial implementation that directly affect GCP.

- **Protocol:** Protocol is a document, which states the background, objectives, rationale, design, methodology (including the methods for dealing with AEs, withdrawals etc.) and statistical considerations of the study. It also states the conditions under which the study shall be performed and managed. The content and format of the protocol should take into consideration the adopted SOPs, the regulatory requirements and the guiding principles of GCP
- **Case record form (CRF):** CRF is in line with protocol, to record data on each study subject. A CRF may be in printed or electronic format. Instructions to fill the CRF are part of the CRF
- **Facility Audit (Sponsor's Prestudy Site Visit):** Before commencement of any clinical study the sponsor should visit and verify the site and facilities that should comply with standards laid down by regulatory guidelines
- **Site initiation visit:** Before the patient enrollment starts, it is important to have a meeting with patient site(s) personnel with the purpose to acquaint them with the relevant aspects of the study. This involves the review/ discussion of the protocol, case report form completion, missed visits, IRB/IEC reporting requirements, adverse event reporting, etc.

### Techniques to Avoid BIAS

The most important design techniques for avoiding bias in clinical trials are blinding and randomization, and these should be normal features of most controlled clinical trials intended to be included in a marketing application. Most such trials follow a double-blind approach in which treatments are prepacked in accordance with a suitable randomization schedule, and supplied to the trial center(s) labelled only with the subject number and the treatment period so that no one involved in the conduct of the trial is aware of the specific treatment allocated to any particular subject, not even as a code letter.

Bias can also be reduced at the design stage by specifying procedures in the protocol aimed at minimizing any anticipated irregularities in trial conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems, and also to handle the problems that do occur in the analysis of data (Annexure IV).

### Blinding

Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed.

A double-blind trial is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. This includes anyone determining subject eligibility, evaluating end-points, or assessing compliance with the protocol. This level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded. If any of the sponsor staff who are not involved in the treatment or clinical evaluation of the subjects are required to be unblinded to the treatment code (e.g. bioanalytical scientists, auditors, those involved in serious adverse event reporting), the sponsor should have adequate standard operating procedures to guard against inappropriate dissemination of treatment codes. In a single-blind trial the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa. In an open-label trial the identity of treatment is known to all. The double-blind trial is the optimal approach. This requires that the treatments to be applied during the trial cannot be distinguished (appearance, taste, etc.) either before or during administration, and that the blind is maintained appropriately during the whole trial.

### Randomization

Randomization introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomization helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments (Annexure IV).

## CLINICAL DATA MANAGEMENT

A clinical data management system or CDMS is used in clinical research to manage the data of a clinical trial. The clinical trial data gathered at the investigator site in the case report form are stored in the CDMS.

CDM is an integral part of the clinical trials process, which ensures the validity, quality and integrity of data collected from trial subject to a database

system. CDM delivers a clean and high-quality database for statistical analysis and consequently enables clinical scientists to draw conclusions regarding the effectiveness safety and clinical benefit/risk of the drug product under investigations. An invalid and/or poor quality database may result in wrong and/or misleading conclusions regarding the drug product under investigation. Thus the objective of the CDM process in clinical trials is not only to capture the information that the intended clinical trials are designed to capture, but also to ensure the validity, quality and integrity of the collected data. In general the CDM process includes:

- Case report from (CRF) development
- Database development and validation
- Data entry, query, and correction
- Data quality assurance and
- Data lock, archive, and transfer
- The implementation of good data management practice (GDMP) is necessary. GDMP is a set of standards/procedures for assurance of the validity, quality and integrity of clinical data collected from trial subjects to a database system.

## CONTRACT RESEARCH ORGANIZATION (CRO)

Contract Research Organization, (CRO) is a service organization that provides support to the pharmaceutical and biotechnology industries. CROs offer clients a wide range of "outsourced" pharmaceutical research services to aid in the drug discovery and clinical development. In the Code of Federal Regulations (CFR), the US Food and Drug Administration regulations state that a CRO is "a person (i.e. a legal person, which may be a corporation) that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g. design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration". [21 CFR 312.3(b)].
Services offered by CROs include:

- Product development
- Formulation and manufacturing
- Clinical trial management (preclinical through phase I to IV)
- Clinical, medical and safety monitoring
- Preclinical, toxicology
- Clinical laboratory services for processing trial samples
- Data management
- Biostatistics and medical writing services for preparation of an FDA new drug application (NDA)
- Abbreviated new drug application (ANDA), or biologic license application (BLA)
- Regulatory affairs support.

### Human Subject Protection Guidelines

- Belmont Report
  Ethical Principals in Human Subjects Review
  Respect, Beneficence, Justice
- International Conference of Harmonization (ICH)
  Brings together the regulatory authorities of Europe, Japan, and the US to discuss scientific aspects of human research
- Good Clinical Practices (GCP)
  Defines the roles and responsibilities of clinical trial sponsors, investigators and monitors
- Declaration of Helsinki
  Developed by the World Medical Association (WMA), as a set of ethical principles for the medical community regarding human experimentation
- Nuremberg Code
  A set of principles for human experimentation set as a result of the Nuremberg Trials at the end of the second World War. Specifically, they were in response to the inhumane Nazi human experimentation carried out during the war by individuals such as Dr. Josef Mengele.
  (source:www.wikipedia.org)

## CLINICAL TRIAL REGULATIONS

(Adopted from CDER, USFDA)

### Investigational New Drug (IND)

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population
- Emergency Use IND2 allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.233 or Sec. 312.34.4. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist
- Treatment IND5 is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies—Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experiences with the drug in humans (often foreign use)
- Manufacturing Information—Information pertaining to the composition, manufacturer, stability and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug
- Clinical Protocols and Investigator Information—Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators—professionals (generally physicians) who oversee the administration of the experimental compound—to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations (Table 3.4).

### New Drug Application (NDA)

The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the US. The data gathered during the animal studies and human clinical trials of an investigational new drug (IND) become part of the NDA.

**Table 3.4:** Regulations apply to the IND application process

| | |
|---|---|
| 21CFR Part 312 | Investigational new drug application |
| 21CFR Part 314 | INDA and NDA applications for FDA approval to market a new drug (New drug approval) |
| 21CFR Part 316 | Orphan drugs |
| 21CFR Part 58 | Good lab practice for nonclinical laboratory [animal] studies |
| 21CFR Part 50 | Protection of human subjects |
| 21CFR Part 56 | Institutional review boards |
| 21CFR Part 201 | Drug labeling |
| 21CFR Part 54 | Financial disclosure by clinical investigators |

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality and purity.

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged. The following resources provide summaries on NDA content, format and classification, plus the NDA review process.

- Therapeutic biologic applications (BLA)
- The therapeutic biological products now under CDER's review include: Monoclonal antibodies for *in vivo* use cytokines, growth factors, enzymes, immunomodulators; and thrombolytics. Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other nonvaccine therapeutic immunotherapies.
  (Source CDER: USFDA)

### Abbreviated New Drug Application (ANDA): Generics

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic are listed in Orange Book.

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e. performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.
*(Source CDER:* USFDA)

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# CHAPTER 4 Phase 0 Trials in Cancer Drug Development

## ADVANCES IN CLINICAL DRUG EVALUATION

Developing new molecularly targeted drugs for patients with cancer has presented unique challenges for clinical drug development research. Increasing complexities of drug discovery and development, lack of validated preclinical disease models for predicting human efficacy, prolonged timelines for clinical evaluation, and high failure rates have highlighted the inadequacies of the current clinical development paradigm (Table 4.1). Traditionally, first-in-human clinical development of new chemotherapeutic agents begins with phase I clinical trials to establish the dose and dosing schedule for any subsequent phase II trials. Only after phase II and III trials have demonstrated that a drug is safe and has activity, measured by tumor regression, stabilization, or statistically significant improvements in patient survival, is it likely to be considered for approval by the US Food and Drug Administration (FDA).

At present, approximately 75 to 95 percent of agents entering phase I clinical trials for oncology indications fail to achieve FDA approval; the

**Table 4.1:** Summary of clinical trial phases and their objectives

| *Trial(s)* | *Objective(s)* |
|---|---|
| Phase I | Evaluate the safety, toxicities, and pharmacokinetics as well define the maximum tolerated dose and recommended Phase II dose of a drug or regimen through step-wise dose escalations |
| Phase II | Determine whether a new therapeutic agent or regimen has some minimally acceptable level of activity and to provide a rough estimate of this activity level |
| Phase III | Determine the drug effectiveness and the relative role and merits of the treatment through direct comparison to current standard of care |
| Phase IV | Postmarketing studies conducted in special population (e.g. children, elderly, patients with renal or hepatic dysfunction, etc.) or to confirm clinical benefit |

Adapted from Kummar S, M. Gutierrez, JH Doroshow, and AJ Murgo (2006) Drug development in oncology: Classical cytotoxics and molecularly targeted agents. Br J Clin Pharmacol 62:15-26, with permission from Jon Wiley & Sons

majority of these failures occur late in clinical development, adding to the cost and time to develop effective new therapies for cancer (Kola and Landis, 2004; DiMasi and Grabowski, 2007). Estimates for the cost to develop a drug in the United States are approximately $900 million, with the most money being spent later in the development phase (Kola and Landis, 2004). A further consideration is that the current clinical trial process, with traditional endpoints, could result in hundreds of patients being treated with ineffective therapies (e.g. matrix metalloproteinase inhibitors) (Hidalgo and Eckhardt 2001; Moore et al. 2003). Approximately 30 percent of agents fail due to lack of efficacy, and this often occurs late in development (Kola and Landis 2004).

In 2003, these considerations prompted the FDA to hold meetings with the National Cancer Institute and major pharmaceutical companies to review its investigational drug evaluation process. One of the main outcomes of this review was the exploratory investigational New drug (IND) Guidance, which changed the emphasis of first-in-human clinical trial design from assessing safety and tolerability to mechanism-of-action studies and assessment of target drug concentrations (US Food and Drug Administration, 2006a; Collins, 2008).

Phase 0 trials occur early in the drug development process and allow a variety of informative trial designs in which a limited number of patients are administered subtherapeutic or subpharmacologic doses of the study drug. For example, a phase 0 trial with pharmacodynamic (PD) endpoints has the primary objective of measuring drug effects on a molecular target; such an objective is normally not explored until late in phase II or phase III trials. As first-in-human trials, phase 0 trials provide an initial opportunity to assess PD and pharmacokinetic (PK) relationships, which can then form the basis for decisions regarding further clinical development. The conduct of phase 0 trials can identify therapeutic failures, such as agents that do not modulate their intended molecular target, early in the drug development process, allowing for reallocation of resources to more promising drug candidates (Kummar et al, 2007). Table 4.2 outlines the key differences between phase 0 and phase I clinical trials.

## TYPES OF PHASE 0 TRIALS

The FDA's Exploratory IND Guidance provides general examples of three different phase 0 trial designs, which include imaging studies or measurement of agent PK, comparison of analogs to select a lead agent for further evaluation, and assessment for modulation of a molecular target in a tumor (US Food and Drug Administration, 2006a). Two important distinctions between these different types of phase 0 trials are the objectives of each trial and the dosing criteria, including use of either sub-pharmacological microdosing or administration of pharmacologically active, but subtherapeutic doses (Table 4.3). The pharmacologically active dose is defined by the PK and PD relationships established in the preclinical models,

**Table 4.2:** Summary of key differences between Phase 0 and phase I clinical trials

| *Variables* | *Phase I trials* | *Phase 0 trials* |
|---|---|---|
| Primary endpoint | Establish the maximum tolerated dose | Target modulation, achieving target plasma concentrations, or ability to image the target of interest |
| Dose escalation | Determine safety and toxicities; starting dose is low but then escalated to therapeutic and potentially toxic doses | Subtherapeutic, nontoxic doses; dose escalation performed to achieve desired systemic exposure or target modulation, enabling dose selection for future studies |
| Preclinical biomarker studies | Not consistently performed before the trial | Required to have plasma drug (PK) and preclinical PD assay development and qualification before the initiation of the clinical trial |
| Correlative studies for PD effect | Not performed consistently, most Phase I trials do not emphasize PD markers | PD assays and/or imaging studies are integrated to establish the mechanism of action |
| Number of patients | Usually >20 | 10–15 |
| Dosing | Multiple | Limited |
| Therapeutic benefit | May occur; tumor response is evaluated to enable continued dosing in case evidence of clinical benefit is found | None; no assessment of response |
| Tumor biopsies | Optional | Serial tumor biopsies required to evaluate the effect of the drug on its target(s) in PD-driven Phase 0 studies |
| PK/ PD analysis | Samples are usually batched and analyzed at a later time | Real time |

PK: pharmacokinetics; PD: pharmacodynamics

Adapted from Kummar S, Kinders RJ, Rubinstein L, et al. 2007; Compressing drug development timelines in oncology using phase '0' trials. Nat Rev Cancer 7:131-139, with permission from Nature Publishing Group

and the highest dose that can be administered as part of a phase 0 trial is defined by the results obtained from IND-directed toxicology studies conducted in two species. Microdosing is used in imaging studies or in studies with PK as their primary endpoint. However, the use of microdosing

**Table 4.3:** Examples of phase 0 studies supported by the FDA's exploratory IND guidance

| *Type of study* | *Objectives* | *Doses* |
|---|---|---|
| Pharmacokinetics or imaging | Evaluate biodistribution and target binding | Microdosing, less than 1/100th of the pharmacologically active dose (up to a maximum of 100 μg or 30 nmol for protein products) |
| Pharmacologic endpoint | Compare pharmacokinetics and/or pharmacodynamics (bioavailability) of analogs to select lead agent | 1/50th of the NOAEL determined in 2 week rodent toxicology studies |
| Pharmacodynamic endpoint | Measure modulation of target | Less than 1/4 the rat NOAEL, or dose at which the total exposure measured in human blood samples is 1/2 of that determined in the most sensitive species, whichever is lower |

NOAEL: no observed adverse effect level

to study PK raises considerations such as accurate measurements of extremely low plasma drug levels, nonlinearity of PK measurements between doses, and the ability to predict the PK of eventual therapeutic doses based on data obtained from microdosing (Boyd and Lalonde, 2007; Lappin and Garner, 2008).

Even though evaluation of drug-target effects in early-phase trials is an attractive option, the incorporation of such endpoints requires extensive preclinical validation of the PD assay and the putative drug effect. Also requiring careful consideration is the appropriate statistical method for the study design as the ability to interpret a significant PD response in a small patient population is a direct consequence of assay precision and the expected level of PD effect for the dose administered (Rubinstein et al, 2010 (In press)). Questions such as the baseline expression of the target, tumor heterogeneity, the ability to reliably detect changes in expression or activity of the target in a small number of patient samples, and the effect of sampling techniques and sample handling and processing on the target need to be addressed prior to the initiation of such trials. Establishing and following clinical research—specific standard operating procedures (SOPs) for sample collection, handling, and processing, as well as for biomarker analysis, ensures consistency and accountability during all stages of assay performance; this level of detail is necessary for phase 0 trials. Validated SOPs are tested using clinically relevant sampling procedures on preclinical models and clinical samples to ensure sample handing and sample-to-sample

variability is accounted for in the final assessment of PD effect. For example, an SOP may define that core biopsies be immediately flash frozen (instead of stored on ice) to prevent nontreatment-related accumulation of a DNA damage marker that is being used to measure drug effect.

Close collaboration between bench scientists, clinicians, the interventional radiology staff, and statisticians during SOP creation and institution is vital. Training of clinical staff on the SOPs for sample collection and handling is essential, and clear documentation of all steps in the process helps ensure that reliable conclusions can be drawn from assay results. For example, during a phase 0 trial, several samples may need to be collected within a short time period to clearly define the PD/PK parameters of a particular drug; with a limited number of patients, all samples need to be collected according to the SOP and at the predefined time points to be of use. Finally, the assay itself must be sufficiently sensitive, accurate, and precise such that any drug effect on the target is not obscured by the imprecision of the assay (Kinders et al, 2008). The conduct of phase 0 trials requires that these considerations be addressed and the PD assay validated using clinical procedures prior to entering the first subject on trial.

## DECISION REGARDING FIRST-IN-HUMAN TRIALS: PHASE 0 OR PHASE I

There are several factors to consider in deciding whether to conduct a first-in-human trial as a phase 0 or phase I study. PD-driven phase 0 trials can inform development of molecularly targeted agents, whereas PK-driven phase 0 trials are particularly useful when the clinical development of an agent is based on whether target plasma concentrations can be achieved (e.g. determining oral bioavailability). phase 0 trials are not a replacement for phase I trials that establish a maximum tolerated dose and toxicity profile, but they can lead to accelerated phase I, combination phase I, or phase I/II trials (Kummar et al, 2008). Even though information on PK and/or PD of the agent attainable through a phase 0 trial may be highly desirable, agent characteristics must be appropriate for useful information to be obtained in this setting. The agent must have a wide therapeutic index to allow evaluation at sub toxic but pharmacologically active doses of drug. A drug that modulates the target but only at doses associated with preclinical toxicity is more appropriate for phase I evaluation.

As mentioned previously, validated assays are needed for phase 0 evaluation. In a phase 0 trial comparing several analogs, a validated PK assay would be needed for each analog. PD assay validation for phase 0 trials has been described in detail and involves preclinical modeling to ensure meaningful results can be obtained (Doroshow and Parchment, 2008; Kinders et al, 2008; Kummar et al, 2008). Consideration of the target and analyte to be measured is also important—a link between the PD biomarker and antitumor effect should have been established preclinically so that drug development

decisions from a phase 0 trial can be made with confidence. Consultation with a statistician is advisable to determine the level of change in the PD endpoint required to achieve statistical significance given the small sample size and imprecision of the PD assay. This involves defining what constitutes a PD response for each patient and the dose level for the agent to be considered biologically effective (Rubinstein et al, 2010 (In press)). If, based on preclinical studies, the decision is made not to move forward with a phase 0 trial, assays that have undergone rigorous validation may still provide useful information when employed in traditional clinical studies with correlative end-points.

## EXPLORATORY IND REQUIREMENTS

The exploratory IND affords some flexibility in terms of toxicology studies and drug manufacturing requirements. As summarized in the FDA's Exploratory IND Guidance, "because exploratory IND studies present fewer potential risks than do traditional phase I studies that look for dose-limiting toxicities, such limited exploratory IND investigations in humans can be initiated with less, or different, preclinical support than is required for traditional IND studies" (US Food and Drug Administration, 2006a). The ability to safely conduct trials remains the objective of all preclinical toxicology studies. The schedule and doses evaluated in toxicology studies in two species is dependent on the clinical trial design and doses proposed. Therefore, more limited toxicology studies are required to support phase 0 trials because a single or a limited number of low doses are given to subjects participating in a phase 0 trial as opposed to the repeated dosing and dose escalation to toxicity performed in phase I trials.

Also, given the limited amount of drug required to conduct the phase 0 trials, it could be possible to make a single batch of clinical-grade drug to conduct the IND-enabling studies and the clinical trial, thereby eliminating the need to demonstrate comparability of various batches of study drug. An FDA guidance document released with the exploratory IND guidance on complying with current good manufacturing practice (cGMP) regulations (US Food and Drug Administration, 2006b) describes an incremental (i.e. "laboratory" scale) approach to the manufacture of investigational drugs for early-phase clinical trials. This approach would still include appropriate quality control procedures for manufacturing, labeling, and documentation, as required in a traditional IND application.

These limited preclinical requirements allow for more expeditious evaluation of new investigational agents, saving time and resources (Fig. 4.1). These savings may offset some of the costs of PK and PD assay development required earlier in the drug development process for phase 0 trials. Complete pharmacology and toxicology studies would be conducted only after results from a phase 0 study indicate that the drug is worth pursuing, at which time the exploratory IND would be closed and a traditional IND in support of phase I studies prepared.

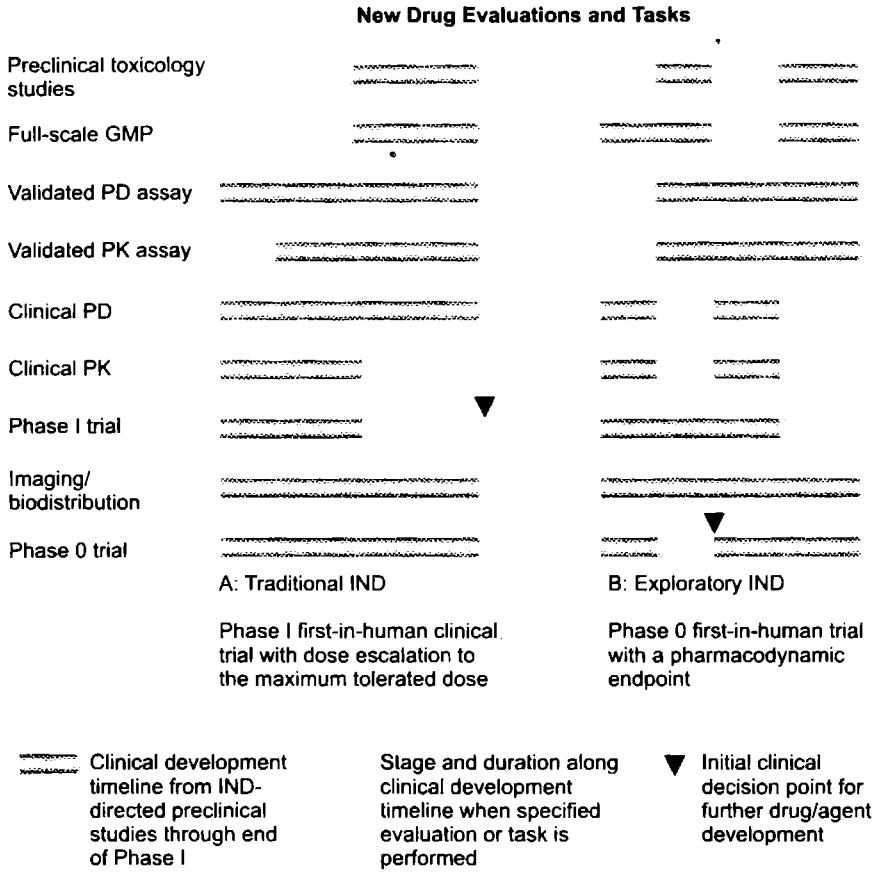


**Fig. 4.1:** Shortening clinical development timelines with an exploratory IND. The preclinical support required for clinical trials conducted under an exploratory IND differs from that required for a traditional IND because limited dosing is anticipated to present a lower risk to study participants. Key differences include that the exploratory IND requires less extensive preclinical toxicology studies and "laboratory scale" cGMP drug production; complete preclinical toxicology studies and full-scale cGMP are needed before phase I evaluation. The decision for whether or not to continue clinical development of an agent under a traditional IND can be made once the phase 0 study proof-of-principle is met. Unlike phase I trials, phase 0 trials with a PD endpoint must have a validated PD assay prior to clinical trial accrual.
(Adapted from Kummar S, Rubinstein L, Kinders R, et al. Phase 0 clinical trials: Conceptions and misconceptions. Cancer J 2008;14(3):133-137, with permission from Lippincott, Williams and Wilkins)

## IMAGING STUDIES

Another option for the evaluation of molecularly targeted agents in phase 0 studies is noninvasive whole-body imaging to assess tissue distribution and target-binding affinity (Kelloff et al, 2005; Collins, 2008). For such studies, the exploratory IND guidance supports administration of microdoses of drug, as described in Table 4.3 (US Food and Drug Administration, 2006a).

Radiolabeled agents can be followed over time to collect invaluable information on dosimetry, biodistribution, and metabolism with repeated noninvasive imaging techniques. Such information would be virtually impossible to obtain with tissue sampling in light of the need for multiple sampling procedures with their associated risks and ethical considerations. In the United States, a fast-track option is to conduct imaging studies with drugs that have previously undergone clinical investigation. These drugs can be labeled and administered at subpharmacologic doses in phase 0 trials after Radioactive Drug Research Committee approval; this process is not available for agents being evaluated in first-in-human trials.

## ETHICAL CONSIDERATIONS

There has been considerable discussion about the ethics of enrolling patients on phase 0 clinical trials, because, unlike a first-in-human phase I trial, there is no possibility of therapeutic benefit to justify the risks of taking an investigational agent. This risk is mitigated by the fact that doses given are a fraction of those that caused toxicity in preclinical safety studies. The administration of a single or limited number of doses provides additional safety information for drugs that will eventually be developed for chronic dosing, including many oral targeted anticancer agents. It should be noted that, as with all clinical studies, all participants of phase 0 trials are carefully monitored for any evidence of toxicity.

It is essential that patients have a clear understanding of the nontherapeutic nature of the trial and the associated risks. Therefore, the process of obtaining informed consent must allow patients the opportunity to review and discuss the consent form; it may then be advisable to ask patients (prior to their signing of the consent form) to verbalize their understanding that their participation in the trial will not confer any possibility of therapeutic benefit (Gutierrez and Collyar 2008). Patients who require immediate palliative care are not eligible to participate. While considering the potential clinical options for the patient, physicians must evaluate whether participation in the phase 0 trial will unduly delay or affect the eligibility of the patient for subsequent trials that may offer potential therapeutic benefit. Again, this is something that should be explained to potential patients during the consent process. So as not to affect future treatment options for phase 0 participants, cooperation can be sought from other investigators to reduce the wash-out period after administration of an experimental agent in a phase 0 trial from, for example, 4 to 2 weeks because toxicities are not expected during this period. Clinicians should also consider revising the eligibility criteria for later-stage trials to ensure that patients who received an agent as part of a phase 0 trial are not excluded from participation in further studies with that agent or class of agents (Kummar et al, 2009a).

The ethics debate for phase 0 trials also brings into question the collection of biopsies for research purposes when there is no possibility of therapeutic

benefit. Patients who agree to participate in a PD-driven phase 0 trial should be willing to consider donating biopsy samples because these are necessary to achieve the primary objectives of the trial; of course, to proceed with the biopsy, it must be considered medically safe by the study team. Obtaining tumor biopsies is an invasive procedure with the possibility of complications, and therefore confers more than minimal risk to patients (Dowlati et al, 2001). However, it should be emphasized that in any clinical trial, tumor biopsies are done for research and do not provide benefit to the patient. Our experience and published reports indicate that patients are generally amenable to donating biopsies for research purposes (Agulnik et al, 2006; Gutierrez and Collyar, 2008). The proper handling and analysis of all patient samples, as discussed previously, may also be considered an ethical obligation to ensure that donated samples can result in useful PD and PK data; these data represent the value of a phase 0 trial and must not be compromised by sample mishandling (Helft and Daugherty, 2006).

## PHASE 0 EXPERIENCE

The NCI conducted its first phase 0 trial in oncology with the agent ABT-888, an inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP). The agent was selected for the PD-driven phase 0 trial because it had good oral bioavailability as well as activity in tumor xenograft models in combination with DNA-damaging chemotherapeutic agents (Donawho et al, 2007). Additionally, demonstration of effective PARP inhibition by ABT-888 in humans was considered crucial to its successful development, and information on the dose range that inhibited PARP would be useful for future combination clinical trials. In the phase 0 trial, a single dose of ABT-888 was given to patients with refractory solid tumors, followed by multiple blood collections for PK and PD analysis; paired tumor biopsies were also collected before and after administration of ABT-888 (Kummar et al, 2009b). Cohorts of patients received increasing doses of study drug to determine the dose range that inhibited PARP activity in tumor biopsy samples and peripheral blood mononuclear cells. Real-time PK and PD results from the trial, available within 48 hours of sampling, were used to determine sampling in individual patients and dosing for successive patients. These data were discussed between the laboratory scientists and clinicians prior to administering drug to a given patient, an example of the team-science approach that is critical to the conduct of phase 0 studies (Kummar et al, 2009b). The immunoassay used to measure poly(ADP-ribose) (PAR), a product of PARP, was sufficiently reproducible and precise to measure a 50 percent reduction in PAR levels, a primary objective of the trial, where a greater than 50 percent reduction in PAR levels in post-dose patient samples of tumor or the surrogate tissue, peripheral blood mononuclear cells, would provide statistically significant evidence of targeted PARP inhibitor activity (Kummar et al, 2009b).

Accrual began in the summer of 2006, and the study closed in the summer of 2007. Fourteen patients participated, none of whom experienced toxicity related to the study agent. Participants indicated reasons for participating were altruism and/or waiting for another study (Gutierrez and Collyar, 2008). The PD and PK data obtained from this trial supported further clinical evaluation of ABT-888. The first of several phase I trials with ABT-888 in combination with chemotherapeutic agents opened approximately one month after the phase 0 study closed.

The NCI has started accrual to its first phase 0 imaging trial and is currently designing a study with both imaging and PD endpoints to evaluate a nucleoside analog as a potential radiosensitizer by measuring uptake of the analog into the DNA of tumors.

## CONCLUSION

Changes in the anticancer drug development paradigm were much needed, as demonstrated by the low FDA approval rates for new oncology drugs despite what is often millions of dollars spent and years of effort exhausted per investigational agent. phase 0 trials provide an opportunity to obtain, at the earliest stage, human data on whether the investigational agent achieves the desired concentrations and/or modulates its target. This allows rational decision making regarding allocation of development resources and potentially shortens the clinical development timeline of the most promising new anticancer drugs.

Awareness of the exploratory IND requirements and assessment of the suitability of agents for phase 0 trials are important in making an informed decision regarding whether to undertake a phase 0 trial, because such trials are not useful or appropriate in all cases. Additionally, to be successfully carried out and to obtain meaningful data, these trials require extensive preclinical investment and teamwork among scientists, clinicians, laboratory personnel, and statisticians both before trial initiation and throughout the conduct of the trial.

Our limited experience with a PD-driven phase 0 trial at the National Cancer Institute indicates that phase 0 trials are feasible and can provide useful information. An increasing number of trials are being conducted under the FDA's Exploratory IND Guidance, especially by the pharmaceutical sector, which is using phase 0 trials to compare the PK profiles of various analogs in a single study (Robinson, 2008). As molecularly targeted therapies are brought to the forefront of the fight against cancer, phase 0 trials offer a way to evaluate agents with specialized targets prior to a large-scale investment in development. Whether phase 0 trials eventually achieve their goals of compressing the drug development timeline, deprioritizing therapeutic failures early in development, and increasing the success rates of promising compounds will need to be continually assessed as phase 0 trials are more widely conducted.

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# CHAPTER 5

# Bioethics in Clinical Research

## INTRODUCTION

### Definition and Scope

Is it ethical to have genetic screening and allow for the abortion of selected fetuses? What are the ethical issues in legalizing euthanasia or human cloning? How to protect the rights of human volunteers involved in clinical research? Several such questions are raised by ordinary citizens and professionals from various fields. Bioethics examines such moral questions, makes intellectual enquiry and tries to put forth guidelines for professional biological and clinical practice. It is an interdisciplinary approach involving experts and practitioners from a variety of fields such as medicine, nursing, public health, law, religion, philosophy, social sciences and medical humanities. Over the past 20 years, the field of bioethics has shown explosive growth and institutionalization intertwined with the rapid advancement of biomedical technology. Today the principles of bioethics apply not only in clinical practice for the selection of treatment modalities/technologies, timing of the institution of treatment, diagnostic and preventive strategies but also in clinical research for validity of research question, subject selection, protocol designing, data analysis and sharing the research outcomes. The scope of bioethics has expanded beyond the narrow confines of medical institutions to include the concern for the environment and global health.

The widening horizons of the bioethics permit the experts in the field to work at various levels. As academicians, bioethicists explore and discuss the possible solutions to various ethical questions with a multifaceted approach. This effort is to facilitate the application of scientific principles keeping in view the requirement of law, principles of philosophy and social, religious and ethnic practices. Theoretical discussions into the various ethical questions may not lead to final solution; however it definitely influences the bioethical practice in clinical care and research as well as the policy decisions with regards to the bioethical practice. The bioethicist may directly be involved in the process of clinical care when ethical issues are raised by patients and healthcare providers. In such situations the bioethicist has to reach a decision within the available time frame. Further, the bioethicists also work as policy analysts and help in formulating the policy frameworks that will ultimately influence a large population. The difficulties faced by bioethicists while

involved in clinical care or policy formulation become challenges for academicians, who then try to explore various disciplines and stimulate discussions involving experts from related fields.

### Ethics in Practice and Research

Clinical practice and clinical research although not mutually exclusive, differ from each other in their purpose and goal. The clinical practice primarily deals with diagnosis, prevention and treatment of various disease ailments. It aims to enhance the well-being of individual patients and the population at large and has a reasonable expectation of success. Clinical research on the other hand aims to find a solution to unanswered questions arising in clinical practice and in doing so involves participation of human being as the experimental tool. Although, during participation in clinical research an individual participant may receive excellent medical care but this is not the goal of clinical research and therefore clinical research does not meet the health needs of an individual and may not benefit the individual participant. In spite of differences in the primary goal of clinical research and clinical practice, researchers are not immune from the ethical obligations of clinical care. However, the degree to which they can deviate from the ethics of clinical care is governed by their approved protocols.

### Research Ethics

Clinical researchers often find their research interest at conflict with their obligations to health care needs of individual patients. As a consequence complex ethical, social and legal issues are raised. The field of research ethics examines such questions and does scientific and systematic analysis to ensure that the study participants are adequately protected and at the same time the research is conducted in most ethical and professional manner for the benefit of individual patient and society at large. Researcher has the obligation to design the study in such a way that it can answer the research questions efficiently. The study should be implemented in such a way that the results obtained are valid, reliable and reproducible. In the process researcher needs to enroll sufficient number of subjects for a reasonable time period and enrolled subjects must comply with the treatment allocated to them. Various policies and legal requirement have been formulated to ensure that the research is conducted in accordance with nationally and internationally accepted ethical guideline.

The conduct of clinical research with highest scientific and ethical standards depends on three basic principles: respect for persons, beneficence and justice.

Respect for persons requires the respect for decisions made by autonomous individuals and to provide adequate protection to individuals who are incapable of making decisions. It is reflected in adequately performing the duty to obtain the informed consent and maintain the confidentiality on

their behalf. The principle of beneficence requires the assessment of potential risks and benefits to the individual by participating in the research. Justice demands that the researcher should make sure that vulnerable people are not exploited. It also demands that the subjects, who are expected to be benefited by participation in the research, should not be excluded unless there are valid reasons to do so.

## HISTORICAL PERSPECTIVE

Research involving human subjects differs from other areas of research where humans are not involved as subjects. The reason is that humans have a decision-making power and must be respected. Several decades before experiments were conducted on humans illegally in the US and elsewhere. The human subjects were exposed to biological/chemical weapons, radiations, radioactive/toxic substances, deadly diseases, physical and mental torture and many more. The tests were mostly performed on children, mentally disabled individuals, poor racial minorities and prisoners. Sick and disabled people were selected for such kind of deleterious experimentations on the pretext that they were being treated for the disease they were suffering from. No consent was taken from them neither they were informed about the experiments. The information about such studies reached the common people several years after the studies were performed. The public disapproval and furor upon finding about these human experimentations by the government resulted into numerous congressional investigations and hearings some of which are Church Committee, Rockefeller Commission and Advisory Committee on Human Radiation Experiments. Nobody has been prosecuted for human experimentation till now and many victims have not yet received compensation for it (http://en.wikipedia.org/wiki/Human_experimentation, accessed on 31st May 2010).

Currently, a number of codes, oaths, prayers and guidelines have been formulated to guide physicians treating the human being and researchers studying the human subjects. The earliest oath is that for the medical students from *Charaka Samhita* which calls upon the students to follow the path of personal sacrifice and commitment to duty. Hippocratic Oath had a great influence in western medicine. In the mid twentieth century, efforts were made to protect the human subjects through national agencies, institutional review boards and informed consent. In 1947, six points were submitted by Dr Leo Alexander to define legitimate medical research to the Counsel for War Crimes. The verdict adopted these points along with four other additional points. Together these ten points constituted Nuremberg Code in 1947, this code came into existence in response to atrocities during World War II. The Nuremberg Code was designed to protect the integrity of subjects, the conditions required to conduct research on human beings were defined and voluntary consent from the subjects was emphasized. Accordingly, it was considered important to allow for the human experimentation because such

experiments yielded results for the good of society and were not obtainable by other means. However, certain basic principles must be observed to satisfy moral, ethical and legal concepts. In 1948, newly established World Medical Association adopted the Declaration of Geneva, which was updated on Nuremberg Code to make it suitable for the current practices. World Medical Association International Code of Medical Ethics (1949) was an attempt to develop international standards of medical ethics. In 1964, World Medical Association developed Declaration of Helsinki which has undergone repeated amendments since then. US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research presented ethical framework for human experimentation in Belmont Report in 1974. This report presented three guiding ethical principles, i.e. respect for persons, beneficence, and justice as discussed in previous section. Besides the three basic principles outlined above additional ethical requirements have been proposed from time to time such as: (i) research question must be of sufficient value so as to justify the risk exposure of human subjects, (ii) the study design must be scientifically valid so that research question can be answered, (iii) research protocol must be strictly adhered to, (iv) the results/outcomes must be accurately reported. Indian Council of Medical Research (ICMR) has also adopted the ethical framework to guide the physicians and researchers. The guidelines stress that physicians and researchers must apply the ethical principles so as to safeguard the health, rights, privacy and dignity of human participants (Annexure I).

## RESEARCH INVOLVING HUMAN SUBJECTS

In principle, all ethical guidelines proposed by a number of national and international organizations agree on three basic ethical principles:

i. *Respect for persons:* This includes:
   a. *Respect of autonomy:* Persons capable of thinking and deciding about their personal choices should be given respect for their freewill.
   b. *Protection of persons with diminished or impaired autonomy:* Security against any harm or abuse should be provided to the vulnerable or dependent persons.

ii. *Beneficence:* It is the ethical requirement to maximize expected benefits and to reduce the risks involved. The research should be conducted in such a way by the trained person so as to get the maximum output side by side safeguarding the interest of the subjects.

iii. *Justice:* The benefits and burden of research should be equally distributed among the participants. The participant should be treated with righteousness and given whatever is due to him or her. The inequality in distribution among persons is acceptable only in case of vulnerability where the participant is not able to protect his own interest, for example, he is incapable of giving informed consent, obtaining medical aid or other necessities or he is junior member of a hierarchical group.

In different circumstances these three basic principles may vary in their moral weight and application, leading to different decisions and course of action.

International Ethical Guidelines for Biomedical Research Involving Human Subjects as prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), 2002, define some of the general terms within the ethical framework as follows:

### Research

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge 45 CFR 46.102(d).

Research involving human subjects includes:

- Studies of a physiological, biochemical or pathological process or of the response to a specific intervention—whether physical, chemical or psychological—in healthy subjects or patients
- Controlled trials of diagnostic, preventive or therapeutic measures in larger groups of persons, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation
- Studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures
- Studies concerning human health-related behavior in a variety of circumstances and environments.

### Human Subject

A living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information [45 CFR 46.102(f)].

### Intervention

Physical procedures and manipulations of the subject's environment performed for research purposes.

### Interaction

Interaction includes communication or interpersonal contact between investigator and subject.

### Private Information

Private Information is information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, as well as information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.

### Definition of Human Research

The research involves human volunteers such that the data is derived from:

- Living individuals
- Biological material from living individuals
- Interaction or intervention with a living individual
- Use of a non-FDA approved, drug, device or biological tool.

According to CIOMS (2002) guidelines, research with human subjects should be carried out only by, or strictly supervised by, suitably qualified and experienced investigators and in accordance with a protocol that clearly states: the aim of the research; the reasons for proposing that it involves human subjects; the nature and degree of any known risks to the subjects; the sources from which it is proposed to recruit subjects; and, the means proposed for ensuring that subjects' consent will be adequately informed and voluntary. The protocol should be scientifically and ethically appraised by one or more suitably constituted review bodies, independent of the investigators along with the informed consent form, patient information sheet, case report form and all other appendices.

### Informed Consent

As per WHO guidelines informed consent is, "A subject's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof". The consent is only required when all appropriate information about the clinical trial is given or explained to the subject including the objective, possible benefits, risks, problems, alternate treatment if any and his rights and responsibilities in accordance with the current revision of the Declaration of Helsinki. It is the responsibility of the investigator/sponsor to get the approval from the ethics committee for the clinical trial protocol along with the appendices, and materials to be used in obtaining and documenting the informed consent of the subjects.

Principles of informed consent should be followed in each clinical trial as per Declaration of Helsinki (Annexure II), the International Ethical Guidelines for Biomedical Research Involving Human Subjects and International Conference on Harmonization Guidelines (Annexure III). Both oral and written information should be provided to the subject in a simple and understandable language. It should be made clear to the subjects that the trial is a research procedure and their participation is voluntary. If at any stage they want to withdraw from the trial or they do not wish to participate, their treatment or the care will not be affected. Subject should not be forced or obliged to participate in the clinical trial. Sufficient time should be given to the subject, his/her relatives, guardians or, if necessary, legal representatives to enquire about details of the trial and to decide whether they wish to participate or not. Subjects should be informed that their participation and information should be strictly confidential and will not be publicly available but it may be scrutinized during monitoring, auditing by authorized persons,

sponsors or relevant authority. This may be modified by national laws and regulations. The subject should have knowledge about insurance, and other procedures for compensation and treatment if he/she becomes injured or disabled during participating in the trial.

Professionals whose roles combine investigation and treatment have a special obligation to protect the rights and welfare of the patient-subjects. An investigator who agrees to act as physician-investigator undertakes some or all of the legal and ethical responsibilities of the subject's primary-care physician. In such a case, if the subject withdraws from the research owing to complications related to the research or in the exercise of the right to withdraw without loss of benefit, the physician has an obligation to continue to provide medical care, or to see that the subject receives the necessary care in the healthcare system, or to offer assistance in finding another physician (CIOMS, 2002).

Medicinal drugs, new vaccines, therapeutic measures such as stem cell therapy, gene therapy or the diagnostic and therapeutic use of medical devices must be tested on human subjects in clinical trials before being approved for general use. Such trials constitute a substantial part of all research involving human subjects. These research areas are highly specialized and each one of them faces specific ethical issues. Not only these areas of research but also some of the specialized therapeutic procedures such as organ transplant have evoked enormous ethical debate. Subsequent section of this chapter will discuss the ethical issues in some key areas of research and practice.

## ETHICS OF RESEARCH INVOLVING VULNERABLE SUBJECTS

### What is Vulnerability?

A person registering in a clinical trial should participate on his or her own free will. He should be in his right senses to take the decision whether the study is beneficial to him/her, what are the objectives of the study, how the study will be conducted, what treatment options are available to him, whether he can leave the study in between or he had to continue till the study terminates. Situations to coerce him against his will to participate in the trial should not be created. However, keeping the interests of certain populations in view, the related progress requires inclusion of vulnerable population or special population in research. This gives rise to additional issues as they have diminished capacity to safeguard their interests.

Vulnerable population is prone to physical or emotional injury. As per International Ethical Guidelines for Biomedical Research Involving Human Subjects of Council for International Organizations of Medical Sciences (CIOMS), "Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other

needed attributes to protect their own interests". The vulnerability can be intrinsic or circumstantial. These individuals can be compelled to join the trials in ethically inappropriate ways. Therefore, these subjects require special provisions for protection of their rights and welfare in addition to the protection given to normal subjects.

### Causes of Vulnerability

The vulnerability can be mainly due to:

i. *Serious Health Conditions:* The subject is not in a condition to understand the procedure or give consent due to unconsciousness or trauma.
ii. *Inability to Make Decision:* Subjects are not able to make decision on their own either due to cognitive inability or due to certain situations. The decision making incapacity may also be due to lack of communicative ability.
iii. *Economic:* Participants who do not have resources for getting proper medical care or other costly materials. Undue inducements are provided so that they get lured for participating in the study.

### Vulnerable Groups and their Protection

Specific guidelines have been framed for the protection of interests and rights of such persons who are vulnerable or in other words are relatively or completely not capable of protecting their own interests. They may have inadequate intelligence, education, power, resources, etc. Guideline 13 of CIOMS, 2002 describes the considerations of involving vulnerable persons in research. It states, "Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied." Similarly, WHO, National Health and Medical Research Council (NHMRC), ICMR, and other international organizations have also laid down guidelines for the protection of these vulnerable populations that includes children, pregnant women (fetus as well), geriatric persons, persons having dementia, mentally impaired, persons junior in hierarchy like students, employees, minorities, poor people, etc. The protection of right and welfare of the vulnerable groups in clinical research trials can be done by the following:

- *Investigator:* The investigator is responsible for evaluating the degree of vulnerability of the subject and justification of his participation in the study. He is also responsible for obtaining the appropriate informed consent. He should include any additional protective measure required for safeguarding the interest of such subjects in the study design.
- *Institutional Review Boards (IRB) or Research Ethics Committees (REC):* The institutional review boards or ethics committees should check that there are additional protective measures for the vulnerable subjects in the study group. The limitations may be set for the risk level and a check may be imposed on the lucrative compensation to the vulnerable groups. The risk

can be minimized by employing the more experienced persons as investigators; the invasive procedures can be replaced by the less invasive/noninvasive ones.

- ***Informed consent*** as an additional safeguard should be complemented by independent ethical review of research protocols. The surrogate informed consent should be obtained from the legal guardian. The additional protection should be provided to the vulnerable individuals incapable of giving adequate informed consent such as young children, adults with severe mental or behavioral disorders, and persons unfamiliar with medical concepts and technology.

### *Mentally Disabled*

Adults with mental retardation have histories of cognitive and adaptive deficits posing unique ethical challenges for research consent assessment (Fischer et al 2006). People with a cognitive impairment, an intellectual disability, or a mental illness are entitled to participate in research. While research involving these people need not be limited to their particular impairment, disability or illness, their distinctive vulnerabilities as research participants should be taken into account (NHMRC, 2007).

The investigator must ensure prior to conducting the research involving persons with mental or behavioral disorders that such persons will not be subjects of a research that might equally be carried out on persons that are capable of giving informed consent. He should get the approval of ethics committee prior to the initiation of the study. He should also ensure that the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioral disorders. The consent of each subject should be obtained to the extent of that person's capabilities. The subject's refusal to participate in research should always be respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection. In cases where the subject is incapable of deciding, then permission should be obtained from a responsible family member or a legally authorized representative in accordance with applicable law. It should be recognized that these proxies do not have their own interest in the research (CIOMS , 2002).

As per General Assembly resolution 46/119 of 17 December 1991, a mentally disabled person should not be treated unless his or her informed consent is obtained except if the patient at that time is incapable of giving consent, a personal representative is empowered by law to consent to treatment for the patient, or a qualified mental health practitioner authorized by law determines that it is urgently necessary in order to prevent immediate or imminent harm to the patient or to other persons. It also states "clinical trials and experimental treatment shall never be carried out on any patient without informed consent, except that a patient who is unable to give informed consent may be admitted to a clinical trial or given experimental treatment, but only

with the approval of a competent, independent review body specifically constituted for this purpose". If the treatment is authorized without the informed consent of the patient all efforts should be made to explain the nature of the treatment and any other possible alternative and involve the patient in the treatment plan as much as possible. All treatment details must be incorporated straight away in the patient's record form indicating whether it was involuntary or voluntary. Patient should not be subjected to physical restraint or involuntary seclusion except in accordance with the officially approved procedures of the mental health facility and only in case to prevent harm to the patient or others. The period of restraint or seclusion should not exceed the period strictly necessary for this purpose. Records should be maintained of all instances of physical restraint and seclusion with their nature, extent and the reason for using them. He should be kept under humane conditions under the close supervision of qualified staff and the personal representative should be promptly informed about the restraint or involuntary seclusion. Psychosurgery and other intrusive and irreversible treatments for mental illness can only be done when the patient has given informed consent and an independent external body has satisfied itself that there is genuine informed consent and that the treatment best serves the health needs of the patient. The patient or his or her personal representative, or any interested person, shall have the right to appeal to a judicial or other independent authority concerning any treatment given to him or her.

According to NHMRC guidelines, the clinical research design should consider the factors that may affect the capacity to receive information, to consent or to participate in the research. It should be carefully determined whether participants' cognitive impairment, intellectual disability or mental illness increases their susceptibility to some forms of discomfort or distress. The procedure for minimizing effects of this susceptibility should be described in the research proposal. People with a cognitive impairment, an intellectual disability, or a mental illness are entitled to participate in research and because of their vulnerability it should be justified that the risk and burden involved are justified by the potential benefits of the research.

Consent to participation in research by such persons should be sought either from him/her if they have the capacity to consent, or from the person's guardian or any person or organization authorized by law. And, if the disability is temporary, then the consent should be sought when the condition is not interfering with the person's capacity to give consent. This should be witnessed by a person who is independent of the research team and knows the participant and is familiar with his condition.

When the consent is given by a legally authorized person, even then the information regarding the trial should be explained to the subject and in case at some point of time the subject recovers the capacity to consent, the researcher should give him the opportunity to choose to continue with the research study or to withdraw from it.

Ethics committees should be informed by the researchers how they would determine the capacity of a person with such disabilities to give consent. They should explain the following:

a. How the decision about the person's capacity will be made?
b. Who will make that decision?
c. The criteria that will be used in making the decision.
d. The process for reviewing, during the research, the participant's capacity to consent and to participate in the research.

And above all, the refusal or reluctance to participate in a research project by a person with a cognitive impairment, an intellectual disability, or a mental illness should be respected.

### *Children*

Children differ from adults in number of physiological processes. Therefore, they may respond differently to the drugs and may have different side effects as compared to adults. Development of efficacious and safe medicines for children requires clinical trials in children. In order to conduct clinical trial in children, one has to face practical and ethical challenges. Recruitment of children for clinical trial is practically difficult, besides the number of specialty centers in pediatric research is less in comparison to the facilities available for the adults. Children are not able to take their decision regarding the participation in the study. Hence, the informed consent of the parent or the legal guardian is required and if the child is able to understand the procedure and is still a minor, then the assent of the child to agree to participate is also required. Ethical concerns are more when the children are under care having lost both the parents. Without the parents they may be more vulnerable and require extra protection (GSK, 2009).

The document on "Ethical considerations for clinical trials on medicinal products conducted with the pediatric population" has been finalized in 2008 for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use by European Commission. This document provides recommendations on various ethical aspects of the performance of interventional clinical trials falling under the provisions of Directive 2001/20/EC and its implementing texts. The document states that children deserve special protection and should not be the subject of clinical trials when the research can be done in adults who are capable of giving informed consent. If research with children is very essential then the least vulnerable among them, i.e. older children should be included. The recommendations provided in this document are also relevant to clinical trials conducted in non-EU countries, especially developing countries. (http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf)

In the United States, the Department of Health and Human Services provided an amendment to the traditional requirements of informed consent

for research involving pediatric subjects, codified as 45 Code of Federal Regulations 46, Subpart D, which was also recently endorsed in US Food and Drug Administration regulations. In this substitute for individual informed consent, parents or legally authorized representatives (also known as proxies) give permission (agreement for the participation of their child or ward), and children give assent (affirmative agreement to participate in research) (Erb et al 2002, ICMR 2008).

The definitions in CFR 45 section 46.402 are given below:

- *Children* are persons who have not attained the legal age for consent to treatments under the applicable law of the jurisdiction in which the research will be conducted.
- *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research.
- *Parent* means a child's biological or adoptive parent.
- *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

### *Process of Assent*

Children or adolescent were earlier not considered mature enough to take their own decisions and give consent for participating in the trial. Children below 18 years are not adults legally, therefore, the consent was usually given by their parents or guardians. This consent is known as "proxy consent". For the past few decades ethical concerns on involving children in clinical trials have become more. Many believe that the child or the adolescent should be involved in making the decision of participation in the trial.

According to the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research, age 7 is a reasonable minimum age for involving children in some kind of assent process. Most of the children of this age are believed to understand the information customized for their knowledge and developmental level. Health providers also want to know the queries of young participants and value their inputs. Since they cannot give consent which means complete understanding, therefore, they are nowadays routinely asked whether they agree (assent) or not (dissent). The parents are also not asked to give "proxy consent" instead they give "informed permission".

Participation of parents in informed consent process is a must as per Federal regulations. They should be involved in a similar way as if they were going to participate in a trial and permit legally the participation of their child following the guidelines for the requirements of informed consent. The IRBs also should look into the assent process and how it is documented.

Assent should include at least the following elements according to the American academy of pediatrics (1995):

1. Helping the patient achieve a developmentally appropriate awareness of the nature of his or her condition.
2. Telling the patient what he or she can expect with tests and treatment(s).
3. Making a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she is responding (including whether there is inappropriate pressure to accept testing or therapy).
4. Soliciting an expression of the patient's willingness to accept the proposed care.

Similarly, the child participating in a research trial should be informed, in a simple understandable language appropriate for his age, about the details of the study, discomforts and inconvenience he/she is going to experience if he/she agrees to participate. Parents should also give the child a true picture of the trial explaining all the benefits as well as the pain or discomfort he would be going to suffer.

Assent process usually occurs in absence of parents or key researchers to avoid undue pressure on the child but sometimes in case of adolescent it could become a discussion between the young participant, parent and the researcher. Videotapes, pictures, drawings, etc. may also sometimes be used to explain the study to the child.

The patient's dissent or refusal to participate in the study, where he is not gaining any direct benefit, should also be treated with respect. He should not be coerced until he agrees.

An assent is not required if one or the other of the following situations exists. However, the consent of the parent or guardian is still needed:

1. The child is found incapable of participating, or
2. The clinical trial offers a treatment or procedure that "holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research." In other words, researchers are not required to ask for children's assent to participation if the study offers a treatment that is thought to be a better option than those currently available, or if it offers the only alternative.

In India as per Indian Council of Medical Research guidelines, 2008, children should not be enrolled in clinical trials which could be conducted appropriately with adults. It should be ensured that the purpose of the research is to gain knowledge relevant to the health needs of children. It is recommended to clinically evaluate a new drug in children only after the Phase III clinical trials in adults, if the drug has a therapeutic value in a primary disease of the children then it can be studied earlier. Proxy consent should be obtained from the parent or legal guardian. The assent of child should be obtained in the case of mature minors from the age of seven years up to the age of 18 years. This also mentions that benefits of research must be justified in relation to the risks involved in the study and the child's refusal to participate in the study must always be respected unless there is no other alternative medical therapy, provided the consent of parents or guardian has been obtained.

### Pregnant Women

Pregnant women should be given additional protection as they are vulnerable to unethical clinical research. As per 45 CFR 46 Subpart B the research involving pregnant women and neonates may only be approved by the IRBs when: (i) Preclinical studies including pregnant animals and clinical studies on nonpregnant women have been carried out and provide data for evaluating possible risks to pregnant women and fetuses (ii) The risk is caused only by interventions/procedures that offer the prospect of direct benefit to the women/fetus and if they do not get the direct benefit and the purpose of the research is to develop biomedical knowledge that cannot be availed through any other means then the risk to them should be minimal (iii) If the benefit is for the pregnant women, both to pregnant women and fetus or there is no prospect of benefit to the fetus/pregnant women, risk to fetus is minimal and the purpose of research is to gain development in the existing knowledge, then the consent of the women should be obtained according to the guidelines (iv) If there are prospects of direct benefit to the fetus only, then the consent of the pregnant woman and the father is obtained according to the guidelines. Father's consent is not needed in case of his unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest (v) No coercion to terminate the pregnancy should be done in from of monetary inducement or otherwise (vi) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy, and (vii) Individuals engaged in the research will have no part in determining the viability of a neonate.

Indian Council of Medical Research Ethical Guidelines on Biomedical Research on human participants states that pregnant/nursing women in any circumstances should not be the participant of any research unless the research causes only a minimal risk to the fetus or nursing infant and the purpose of research is to gain knowledge about the fetus, pregnancy and lactation. Exceptionally they can participate in such trials which are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants and for which the nonpregnant women would not be suitable. These pregnant/nursing women should not be denied arbitrarily the opportunity to benefit from investigations, drugs, vaccines or other agents with promising benefits. Pregnant women desiring to undergo Medical Termination of Pregnancy (MTP) could participate in research trials related to termination of pregnancy as per The Medical Termination of Pregnancy Act, 1971. In pregnant women, research related to prenatal diagnostic techniques should be limited to detect the fetal abnormalities or genetic disorders as per the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994 and not for determining the sex of the fetus (ICMR, 2008).

*Others*

Apart from mentally disabled, children, pregnant and nursing women, there are individuals and communities that are vulnerable such as socially or economically disadvantaged, some ethnic and racial minority groups, persons with reduced autonomy like students, prisoners, employees, etc. These require careful consideration as their willingness to participate can be unduly influenced and could result in inequitable distribution of burdens and benefits. Elderly persons are commonly regarded as vulnerable. With advancing age, people are increasingly likely to acquire attributes that define them as vulnerable. They may be institutionalized or develop varying degrees of dementia. On acquiring such vulnerability-defining attributes, it is appropriate to consider them vulnerable and to treat them accordingly (CIOMS, 2002).

According to ICMR guidelines, 2008, the persons selected as subjects for research should get the burdens and benefits of the research equally. The guidelines states that genetic research should not cause racial inequalities, economically or socially disadvantaged should not be used to benefit those who are better off than them, and adequate justification is needed for the participation of prisoners, students, subordinates, employees, service personnel, etc. with reduced autonomy as the consent obtained may be under some or the other compelling reasons.

## ETHICS IN KEY AREAS OF RESEARCH AND PRACTICE

### Ethics in Vaccine Research

Vaccines are truly one of the miracle discoveries in modern medicine that have benefited the global health tremendously. Vaccines are considered as generally safe and effective means of providing protection against several formidable diseases. They are cost-effective and have been successfully used to improve public health worldwide. In spite of their successful use in the past, their public health use and social acceptability has always remained controversial. The concerns about public health use that have been raised from time to time by scientists as well as the members of community are primarily related to their safety, adverse effects and interference with the normal immune functions. Concerns about the social acceptability of useful vaccines arise as the people need to be compelled to get vaccinated for the good of public health although they may not get huge benefits individually. Safe and effective vaccines reduce the disease burden among individual members of community and indirectly protect the unvaccinated individuals in the community by 'herd immunity'.

The process of vaccine development is expensive and requires considerable time. It involves basic as well as clinical research. The subjects enrolled in vaccine-related clinical research are expected to participate with

the knowledge that they will be exposed to risk for the benefit of public health at large and individual benefit is only 'provisional'. This means that the individual benefits may only be experienced if they are sufficiently exposed to infectious agent in future, have received the vaccine under investigation and this vaccine has sufficient efficacy (Christine, 2004). Keeping in view the basic principles of clinical research, i.e. respect for persons, beneficence and justice, vaccine development faces a number of ethical challenges.

The respect to study participants in vaccine trials needs to be ensured by maintaining the confidentiality of private information and continuously monitoring their well-being. The right of subjects to withdraw from the trial at any time point must be respected and they should be assured of the accessibility of new information and beneficial outcomes of the ongoing research. In trials that have cross-over design, the control subjects are also benefited by receiving the vaccine, if it was found protective. The need for providing appropriate treatment and compensation to participants who get infected during the trials, is widely realized. However, the guidelines to do so have not been formulated (Berkley, 2003). National Vaccine Injury Compensation Program in United States provides compensation for injuries due to licensed vaccines but no such provision is there for investigational vaccines.

The principle of beneficence requires the vaccine trials to provide such value and benefits that can justify the exposure of individuals to risk and inconvenience. The studies must be designed in a way that can maximize the benefits and minimize the risks. The study design in vaccine trials must choose the most appropriate methodology and implement it in a manner that is most suitable to answer the research question. The data collected must be generalizable to target population. The endpoints that are often the clinical endpoints must be carefully defined.

The assessment of the "value" of a research question may be context driven. For example, rotavirus vaccine was withdrawn from US market due to higher incidence of intussusception in vaccinated children (risk 1 in 10,000). In developed countries even the most serious forms of diarrhea can be successfully treated and, therefore, even a minimal risk of life-threatening complication was unacceptable (Weijer, 2000). However, the large trials for the same vaccine were considered appropriate in developing countries where the incidence of childhood deaths due to rotavirus infection was high (Lisa, 2005). Thus, the risk-benefit ratio may differ from one population to other, affecting the "value" of research. Ethical questions often arise when placebo receiving individuals develop infections and a partially effective vaccine is available. Intervention with existing means will alter the clinical endpoint and will interfere with the assessment of efficacy of investigational vaccine. The benefit obtained by such intervention needs to be weighed against the risk imposed by not providing the available intervention (Snider, 2000).

In challenge studies, study participants are deliberately infected with a microbe before studying the efficacy of the investigational vaccine. Although such studies are very useful in providing scientific information about etiology, pathogenesis, pathology, immune responses, etc. they cause considerable amount of discomfort to participants (Levine, 1998). Therefore, for such studies microbes should be selected carefully so that the symptoms are mild, self-limiting or treatable and risk is low.

In vaccine trials, the risks are borne by the individuals but the benefits apply to the community at large. Individuals may receive benefits in future and indirectly. The vaccine trials allow risk of harm to few for the benefit of many. For example, in the clinical trial for transmission-blocking malaria vaccine, individuals who receive this vaccine are not protected from malaria but they protect others by interrupting the transmission cycle (Hoffman & Richie, 2003). The vaccine trials, therefore, require individuals to accept some risk for the benefit of society and no expected benefit for themselves. At times, study participants receiving the investigational vaccine may assume that they are adequately protected and may expose themselves to the risk of acquiring infection. Therefore, the study participants who consent must be counseled and educated to minimize the risks.

Maximizing the benefits of research involves adequate assessment of its value to individuals, society and science. Research is valuable when it contributes to health and advances useful knowledge. Vaccine trials differ from other therapeutic trials in their goal of finding a useful tool to promote public health rather than to determine the best therapeutic option for a group of individuals. The benefits of the discovery of a safe and effective vaccine depend upon its usefulness in the context in which it will be used in future, the population in which it will be used and its acceptability among those who will use it. The assessment of such benefits requires knowledge about the public health needs such as prevalence and burden of disease in the community and existing methods for its prevention and control. Other factors that need to be considered while evaluating benefit-risk profile of a new vaccine include its safety compared to existing methods, cost, facilities for its distribution, political support, means of counseling and educating target population and acceptability. The benefits of a new discovery can further be maximized by disseminating knowledge, product development, research collaborations and development of efficient healthcare systems.

Justice for the study subjects requires fair subject selection and need to protect vulnerable population. Vaccine trials in early days were done in vulnerable subjects that were either prisoners or institutionalized mentally ill patients. Presently, inclusion of such population is restricted by specific laws and regulations. The appropriate subject selection in a research study requires selection from a population that has sufficient and predictable incidence of the disease under investigation so as to show the efficacy of vaccine. The sample size needs to be large enough to show the result with

reasonable amount of confidence. The World Medical Association Declaration of Helsinki states that "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research" (Ethical principles for medical research involving human subjects; http://www.wma.net/e/policy/b3.htm). Therefore, the appropriate subjects for vaccine trials are usually healthy children. Besides, the sample size is usually large as it is calculated based on expected incidence, demographics of target population and characteristics of expected participants. In order to make sure that vulnerable population is not exploited, it was argued that vaccines intended to be used against infections prevalent in developing countries should be investigated in the sponsor's country during early stages (Macklin & Greenwood, 2003). However, the need to shift such trials to developing countries is now widely realized because it is important that the results of the trial are applicable to target population and should benefit the people who need it the most.

The children that are expected to participate in vaccine trials cannot protect their interest by giving informed consent instead parents are required to give informed consent and permit their children to participate in the trial. Although the value of informed consent has widely been accepted, its implementation is often far from satisfactory, especially so in case of vaccine trials. As the public education programs widely promote the use of vaccines as safe and effective means of protection against infections, people often fail to differentiate between *'the vaccine in use'* and *'the vaccine in trial'*. The understanding of the process of randomization and use of placebo is often poor and individuals fail to understand that some of the participants are at definite risk of getting infection, while others may be protected by the experimental vaccine (Leach, 1999). It is the duty of researcher to make sure that the parents are adequately informed before they make a decision to allow the child to participate in the trial. In some studies, when an entire community is randomized to participate in vaccine trial, a method of getting stepwise consent was adopted. First, the leaders of community are informed and consulted to seek permission. Next, the information is spread to community members through public meetings and media. Finally, the interested individuals are given detailed information and sufficient time to allow them to consult with the family or their health care providers. Individual consent is necessary even when the community permission is indicated (UNAIDS, 2000). The entire process helps the future participants to give informed consent for themselves or their children in most appropriate manner. The participation of local community is crucial not only to establish the recruitment procedures but also to decide for the adequate compensation to study participants. The right of the individuals to refuse to participate in the trial should be protected at all time. Institutional review boards should play an active role to ensure that parents and guardians have been given adequate information to enable them to make decisions compatible with the

interest of their child. Moreover, the vulnerable population must also be protected by negotiating the availability of benefits, from research, to them in most appropriate and cost-effective manner.

## Ethics in Organ Transplant

Organ transplant is a process whereby a failing or damaged organ in the human body is replaced by another organ. The term 'organ transplant' refers to the transplant of solid organs such as kidney, liver, heart, lung, pancreas and intestines. It also includes corneal, skin and bone marrow transplant. There are two main sources of organ donors: (i) cadaveric organs from recently deceased people and (ii) organs from living donors that may or may not be the close relatives. Other sources of organs include animal organs, artificial organs and stem cells.

### *Ethical Issues Concerning Organ Recipients*

The ethical dilemmas concerning organ transplant primarily arise due to severe shortage of donor organs. The requirement of organs for transplant is consistently rising but the availability of donor organs is not increasing at the same pace. United Network of Organ Sharing (UNOS) maintains a comprehensive website giving information about people waiting for organ transplant in United States (updated daily at www.unos.org). UNOS website reports that during the period of January-May 2009, a total of 11,905 transplants were done and during the same period 6,004 organs were recovered from living and deceased donors. More than 102,000 people were waiting for transplant as on July, 2009. The number of people requiring organ transplant is consistently rising whereas the number of organ donors has remained static or is declining (CNN Ethics Matters). The reasons for rapidly increasing number of people requiring organ transplant can be attributed to advancements in medical technologies, improved health care facilities and aging population. Some investigators have suggested that decrease in the number of car accident fatalities has reduced the availability of cadaveric organs because the victims of car accidents are important source of transplantable organs (Hauptman & O'Connor, 1997; Childress, 2001).

Clearly, there are not enough organs available for everyone who needs it. Therefore, with limited resources, ethical principles need to be formulated in such a way as to justify the preference for allocation of an organ to one person over others. In this regard, the concept of distributive justice provides some guidance. The principles of distributive justice are normative principles designed to guide the equal allocation of the benefits and burdens. According to these principles, there is no single criterion that can decide the "right" way to distribute organs but there are multiple ways to justify organ donation to one person over others (The Stanford Encyclopedia of Philosophy webpage). The distributive criteria discussed in the following section are from the website of University of Washington School of Medicine.

*Criteria of equal access:* This criteria allows all individuals to have access to all available donor organs based upon:

a. The time period that they have been waiting for the organ. The patient registered first will receive the transplant first.
b. *The age:* Younger patients are given priority over older ones.

This process allows distribution of transplantable organs free of biases based on gender, race, religion, income, etc. (Douglas, 2003). The argument in favor of criteria of equal access is that all individuals who are in need of organ transplant have equal right to access the organ because everyone could potentially benefit from the procedure (Benjamin, 1988).

Some people, who believe in the criteria of equal access, do not wish to allow the biases due to individual's 'worthiness' to affect the organ distribution, while others consider it an important factor to be taken in to account. In general, individual's worthiness in this context is often defined in terms of "medical worthiness" and "social worthiness". If a person develops organ damage due to lifestyle choices such as smoking or alcohol consumption, he is likely to develop similar damage after organ transplant. His medical worthiness will be considered less as compared to another person without such lifestyle choices in spite of being younger or ahead in waiting list. "Social worthiness" also allows bias and refers to patient's place in society based on significant contributions made by him before developing the organ failure.

*Criteria of individual's worthiness:* The reasons for not allowing bias in organ distribution due to individual's worthiness are based on the fact that the worth of the individual cannot define his medical needs. Secondly, what should be the exact criteria to determine individual's worth and who should decide it? People who wish to consider individual's worthiness in organ distribution argue that if not considered, distribution is biased against worthy individuals (Saint-Arnaud, 1997). The argument says that the criterion of equal access without considering people's lifestyle choices is not fair. One of the article by Kluge (1994) states that people who engage in poor lifestyle choices are behaving irresponsibly and could have prevented their illness and are, in essence, increasing the need for organs and depriving people who, "have no control over their need", of necessary treatment.

*Criteria of maximum benefit:* Since, the organ transplant is a highly valuable procedure and availability of organs is scarce, the aim should be to maximize the benefits of available organs. Therefore, another school of thoughts believes that organs should be distributed in such a way that the wastage can be minimized and distribution criteria should take in to account the severity of illness and the possibilities of a successful transplant. Accordingly, a person more in need due to severity of his illness should be given priority over the other with less severe illness. Secondly, if a person is more likely to have a successful implant than the other, he should get the priority (Williams, 1997; Ubel et al, 1993). The success of transplant is measured in terms of 'life years'

gained, i.e. the number of years that a person will live with a successful organ transplant that they would not have lived otherwise. This maximum benefit distribution criterion is therefore based on the prediction of medical success which is often difficult as the clinical outcome may vary. Secondly, the question that the success of transplant should be based on the number of years that the patient lives post-transplant or the number years the organ keeps functioning post-transplant needs to be answered. Moreover, the measurement of success of transplant should take in to account not only the 'life years' but also the quality of those 'life years' gained (Childress, 2001). According to some ethicists, the organ distribution based on maximum benefit criteria devalues the remaining life of older patients who are likely to loose it due to non-availability of organ (Small, 2002). Whatever may be the length of the rest of the life it is valuable to everyone. Moreover as the criteria of maximum benefit are highly subjective, there is enough room for unfair practices (Childress, 2001).

In developing countries like India, since the health care resources are poor and organ transplant is expensive, care must be taken to fairly distribute the available organ. Currently, UNOS encourages transplant centers to consider the following criteria for distributing organs: (i) medical need; (ii) probability of success; and, (iii) time on the waiting list (www.unos.org). Policies need to be formulated to aim for increase in the number of organ donations and facilitate the allocation of organs in the fairest possible way.

### *Ethical Issues Concerning Organ Donors*

The problem of scarcity of available organs may be dealt with by adopting policies that can maximize the availability of transplantable organs from all sources keeping in view the ethical boundaries. However, these ethical boundaries are not clearly defined and several controversies are raised concerning the three sources of transplantable organs donation.

*Organs from cadaveric source:* Cadavers are the major source of transplantable organs. In 1968, a committee of Harvard Medical School made a historic proposal and recommended the criteria of death based on the cessation of brain activity. In 1976, the Royal College of UK published a code of determination of "brain death". Now most countries, including India in 1994, redefined death as cessation of brainstem activity and organs can legally be removed after brain death.

The manner in which the consent is obtained from the donor varies from country to country. A person can express his/her desire to donate organs during his/her lifetime. If the wishes of the deceased person are not known, various other procedures are adopted. UK and some of the European countries follow an "opting-in" system. According to this system, the person in lawful possession of the body can authorize the removal of organ. Another "opt-out" or "presumed consent" system is followed in Singapore, Austria and Belgium. According to this system, it is presumed that the deceased person

has already given his/her permission to donate the organs unless specified otherwise. United States follows the system of "required request" in which doctors must make a routine enquiry of the next-of-kin of the potential donor.

One cadaveric donor can provide organs for several recipients. Therefore, increase in the number of cadaveric donors can tremendously increase the availability of transplantable organs. Several strategies have been proposed to increase the availability of cadaveric donors. The first strategy is to educate individuals and families about the need to opt for organ donation. Various organizations are working to promote the concept of "gift of life" and social responsibilities. Secondly, to devise a strategy to facilitate the early and informed consent from potential donors such as "presumed consent" or "mandated choice". With "presumed consent", organs are removed at the time of death unless specified otherwise. Accordingly, it is believed that citizens have a duty to donate their organs when they do not need them for other who are in need. But the system requires adequate training of general public and secondly for people deciding not to donate, the procedure may put extra burden (Hill et al, 1999; Siminoff and Mercer, 2001). The method of "mandated choice" requires citizens to specify their wishes in documents like income tax or driving license, and at the time of death the wishes are followed without any consideration to the choices of family. The method although enforces individual autonomy, but when forced to choose, it is expected that large number of people will choose not to donate unless they have been given adequate knowledge about the related issues. Thirdly, to provide incentives for organ donation which can be in various forms such as expenses for funeral, recognition in the form of donation in the name of deceased to charity or in the form of a memorial or financial incentive (Arnold et al, 2002). The ethicists in favor of giving incentives believe, it is always better to bye rather than to let die. Besides, since the person is not living, the benefit will not be received by him and this will amount to coercive action (Delmonico et al. 2002). Opponents of giving incentives to organ donors believe that giving incentives might make people to decide for organ donation and it is coercive and unfair (Veatch, 2000). Instead, the society needs to culture its thinking so that individuals willingly opt for organ donation (Etzioni, 2003). Fourthly, some ethicist justify the organ retrieval from executed prisoners with "presumed consent" in place, others consider it an immoral act unless the prisoner willfully opts to donate the organs.

*Organs from living donors:* A patient in need of a transplantable organ may receive it from a living donor and this helps him/her to bypass the waiting pool for cadaveric organs. If the patient has to receive the organ from a living donor, arrangements, such as initiation of anti-rejection drugs, can be made well in advance to ensure higher success rate. Besides, if the donor is genetically related, tissue matching will be better and there will be psychological benefits for both the recipient and donor (www.transplantliving.org/livingDonation). However, when the organs are

obtained from living individuals, he/she has to go through the pain, discomfort and even sometimes the complications of the procedure. The family members of a sick person who requires an organ may be under pressure to donate and may suffer from psychological stress. Often the medical, nursing and psychological support that is available for recipients is not available for donors and that may increase the health-related risk for the donor.

Some ethicists believe that living organ donation is inappropriate under any circumstances and should not only be discouraged but should be abandoned completely (Spital, 2002). The procedure exposes donors to health risks and the cost and complications invested in the procedure are not likely to promote the overall community health (Kuczewski, 2002). In spite of these arguments against living organ donation, it is a potential source of transplantable organs and is a way to reduce the shortage of organs. Various policies have been adopted in different parts of world to increase living organ donation. Educational campaigns, to help people perform their civic duties and come forward willingly to donate organs, have been organized by various organizations. Nonfinancial incentives in the form of providing medical leave, travel cost, special insurance, etc. can encourage people to donate their organs. Financial incentives to encourage organ donation has largely been criticized worldwide, and most experts believe that buying and selling of human organs is an immoral and disrespectful practice. On one hand wealthy people have unfair access to organs and on the other hand poor people are unfairly pressurized to donate organs in desperation for money without realizing the consequences of the procedure. In one of the studies by Goyal et al (2002), assessment of economic and health consequences of selling a kidney in India, shows that 96% of people sold their kidneys to pay off debt; 74% of people who sold their kidneys still had debt 6 years later; 86% of people reported a deterioration in their health status after donation and 79% would not recommend to others that they sell their kidneys. Keeping in view the critical shortage of organs some of the ethicists have started advocating the financial incentives for organ donation only when appropriate safety guidelines have been followed.

*Organs from alternative sources:* The animal organs can be utilized as a potential source of transplantable organs. Experiments have been done in the past using baboon heart and pig liver. The procedure carries high risk of rejection and risk of transmitting animal pathogens to human. Artificial organs have also been experimented, however, the cost involved is very high and effectiveness is questionable. Fetuses aborted late in pregnancy are considered another source of transplantable organs. But there are fears that such a practice might encourage people to conceive with the intention of aborting it near term and the practice of organ farming would be encouraged. Possibilities of using stem cells to grow an organ or a group of specialized cells are now giving researchers great hope for future. Currently, stem cell research is facing an enormous ethical debate which will be considered in next section.

*Organ Transplant: Legislation in India*

The "Transplantation of Human Organ, (THO) Act", 1994, allows multi-organ transplant activities from brain dead donors. This legislation is on the lines of UK Transplant Act. The aim of the Transplantation of Human Organs Act is "to provide for the regulation of removal, storage and transplantation of human organs for therapeutic purposes and for the prevention of commercial dealings in human organs". The Act now accepts "brainstem death" as death and this has helped removal of organs from "beating-heart donors". The Act prohibits commercial dealing in human organs and does not allow the exchange of money between donor and recipient. The Act also defines the first relatives (father, mother, brother, sister, son, daughter and wife) who can donate organ without permission from government. If a person wishes to donate his/her organ to an unrelated person "out of affection", he must file an affidavit in the court of a magistrate stating that the organ is being donated out of affection. The donor then has to undergo a number of tests to prove his/her fitness for organ donation. Subsequently, an authorization committee will examine the documents and will make sure that no exchange of money takes place between the donor and the recipient. The penalty incurred under the THO Act is very high. In spite of the Act being enforced for 15 years now, unregulated practices are common and there are numerous problems in implementation of the Act.

The Union Ministry of Health, Government of India, has proposed amendments to existing Act to facilitate organ donation. Proposed amendments to the Transplantation of Human Organs Act 1994, seek to facilitate the organ transplantation by simplifying cadaver transplant procedures, increase the availability of transplantable organs by widening the definition of 'near relative' and allowing organ swaps among needy families. The proposed amendments are as follows:

1. The age limit of 60 years to be removed for cadaveric donors.
2. If the family members of a patient are not able to fulfill his/her requirement due to mismatch, swap or exchange with the member of other family, who are also facing the same situation, to be allowed.
3. Direct as well as the indirect losses to the donor should be compensated.
4. Higher penalties to be imposed on those breaching the law.

The ban of donating organs to foreigners by Indian donors has also been proposed. The definition of "near relative" is proposed to include grand-parents and grandchildren, thereby significantly widening the pool of organ donors. The concept of "required request" is proposed to be introduced. The new law will make it mandatory for hospital ICUs to declare all brain deaths and register them with an online central organ registry. Besides, the Health Ministry is working to make it possible for prospective donors to be able to mention their willingness to donate organs on their driving license. New law proposes prohibition of removal of an organ or tissue from a living minor, except in the case of regenerative cell donations within families, in

the absence of a compatible adult donor, and kidney transplantation between identical twins. There exists a huge pool of brain-dead patients in India, which, if utilized with effective implementation of the proposed new law, will definitely help to meet the demand for transplantable organs in the country.

## Ethics in Stem Cell Research

Human embryonic stem cell (HESC) research aims to alleviate human suffering due to a wide range of diseases and trauma. Embryonic stem cells have the capacity to regenerate and can differentiate into all types of cells in the body. The stem cell research focuses on identifying the factors governing the differentiation of parent stem cell into a specific mature cell that can be used in specific disease or injury. HESCs are derived *in vitro* typically from a 5-day old embryo which consists of about 200 to 250 cells. Out of all 200 to 250 cells, about 30 to 35 cells form the inner core which is the actual source of HESCs. To harvest the HESCs for culture inner core needs to be disaggregated from the outer trophoblast and this eliminates the possibility of further development of embryo. The ethical issues in stem cell research are mainly linked to the unjust killing of human embryo to harvest the stem cells. Other areas of ethical concerns in stem cell research involve the issue of moral distinction between creating embryos for reproductive end or research, and the moral issues in case the researcher is involved in research but not in harvesting the HESCs.

### *Unjust Killing of Human Embryos*

*Time when human being begins to exist*: It is morally impermissible to kill a human being. The same moral principle also applies to human embryo because human embryo is also a human being. But the question "when does the human being begins to exist?" remains unanswered. According to one view the existence of human being starts with formation of one-cell zygote, immediately after fertilization as the zygote is capable of growing into an adult with its own identity. The opposite views state that zygote may not be considered as the beginning of existence of human beings as monozygotic twinning is possible up to about 14 to 15 days post-fertilization (Smith & Brogaard, 2003). A monozygotic twin is not numerically identical with the zygote as both the twins are derived from the same zygote. Based on the same ground it cannot be ascertained that all individuals begin to exist at the zygotic stage. In spite of this argument it cannot be said that zygote is not a human being as it is capable of growing into an individual and in case it divides then also its own existence cannot be denied.

Another view that rejects the acceptance of human embryo as human being is based on the grounds that early human embryo is a collection of homogeneous cells that although alive are not capable of performing essential biological functions in a coordinated manner to sustain an individual life

(Smith & Brogaard, 2003; McMahan, 2002). The required amount of cell differentiation to perform coordinated functions takes place at about 16 weeks postfertilization and, therefore, disaggregation of 5-day-old embryo will not amount to killing a human being. The dispute against this view is based on the observation that only a few embryonic cells differentiate into inner core while others become the trophoblast. This kind of differentiation is possible only when there is some level of intercellular coordination, otherwise cells may be directed to differentiate into only one or the other cell type (Damschen et al, 2006). However, it cannot be said with certainty that this amount of coordination is sufficient to render a 5-day old embryo a human being (McMahan, 2007).

*Moral status of embryo for "right to life":* The argument against HESC research states that human beings have moral status that confers them the right not to be killed at all stages of life. However, it remains to be ascertained that whether a 5-day old embryo has the moral status that can confer the same right of not to be killed. It is suggested that some level of mental capacities such as reasoning and self-awareness are required to determine the moral status necessary for right to life (Kuhse & Singer, 1992; Tooley, 1983). However, there is no consensus about what should exactly determine the moral status requisite to right to life as the human infants also lack these mental capacities. It is argued that the difference in the mental capacities of embryo, infant, child and adult are only quantitative which means that although the embryo has the basic natural capacities but is unable to exercise them immediately whereas a human can actualize the natural capacities due to their ability of reasoning. Therefore, based only on the quantitative differences in mental capacities, moral respect cannot be denied to one person while giving it to others (George and Gomez-Lobo, 2002).

Based on the theory of quantitative differences in the mental capacities at different stages in life, it can be concluded that the embryo has the potential to grow into a human being with full capacity of reasoning (Sagan & Singer, 2007). But the ability to grow into an entity with full reasoning does not confer it the same moral status as an entity which already has exercised its mental capabilities. Moreover, if only the potential to grow in to a human being with sufficient mental capacity, confers great moral weight on embryo's right to life, then the same must be considered for the somatic cells as well. A single somatic cell has the potential to grow into a human being if its nucleus is transferred to an enucleated egg, which is then electrically stimulated and placed in a woman's uterus to allow it to grow to term. One of the argument that tries to differentiate between the moral status of human embryo from the somatic cells, states that embryo has the "intrinsic ability" to grow into an individual whereas the somatic cells require technological intervention before they can realize the same potential (Lee and George, 2006). But the "intrinsic ability" of the embryo to grow also depends upon the availability of external factors that can support its growth. In the context of HESC research, technological intervention is needed

to implant the embryo into the uterus of a willing woman. Therefore, it is difficult to differentiate between the moral status of an embryo and somatic cell for the right to life (Devolder & Harris; 2007).

*Right of embryo for protection and respect:* Although, the embryo lacks some properties to support its moral status for right to life, it has been argued that it represents a form of human life and human life in all forms must be protected and respected. But the extent of respect the embryo deserves remains to be determined. The opponents of the HESC research believe that the benefits of such research are too speculative and may not meet the expectations and, therefore, sacrificing embryos for research is not justified. Those who support, believe that the value of human embryos is much less than the therapeutic benefits that are expected from HESC research (Holm, 2003).

*Fate of spare embryos:* During the fertility treatment of infertile couple, spare embryos often exist and the couple has the right to decide the future of these spare embryos. They can store them for future use, donate them to other infertile couples, donate for research or can decide to discard them. If they first decide to discard the spare embryos and then subsequently decision is taken to donate them for research, it can be considered that the embryos were already destined to die before the researcher receives them. Morally it is permissible to kill an individual who is about to be killed by another person if killing aims for the benefit of others (Curzer, 2004). In this process researcher only changes the manner of killing. The arguments against these views advocate that the couples may choose to discard the embryo first only because it is a prerequisite for donation for research and if this option of donation for research was not available to them, they might decide to donate the embryo to other infertile couples. Therefore it cannot be presumed that embryos were destined to die only because the decision to discard them was taken before the decision to donate them for research. Moreover, the researcher once obtains the embryo may protect them by storing and donating them to other couples. Although it will unlawful to do so, it cannot be claimed that embryos were doomed to death once a decision to discard them has been taken.

### *Using Embryos without Being Complicit in Killing*

HESC research is permissible if the researcher is not complicit in the killing of embryo just like a transplant surgeon using organs from a victim of murder or drunken driving is not responsible for the death of the said person. Most of the investigators involved in HESC research obtain stem cells from existing pool of cell lines and are not involved in deriving the cells themselves from the embryo. Researcher, therefore, cannot be assigned the moral responsibility for killing the embryo. However, in situations when the derivation of stem cells from embryo is done as per demand for research, the researchers involved will be considered complicit in the killing of embryos. Therefore, if the derivation of stem cells is done in the absence of demand for research,

researchers should not be considered complicit in the crime of killing innocent embryos (Siegel, 2004). Although the researcher in such circumstances would be considered not complicit in the destruction of embryos, it may give rise to a feeling of guilt of being associated with a wrongful act. The researchers need to overcome such guilt keeping in view the requirement of undertaking HESC research for the sake of noble service to mankind.

Another area of concern arises from future outcomes of HESC research. It is argued that if HESC research yields positive results, demand for stem cells will increase and their availability will be facilitated by private investment. Such an outcome indirectly makes the researchers complicit in the killing of embryos. This speculation about future demand seems inappropriate for various reasons. One, the parallel research in other areas is facilitating the understanding about HESCs and is also responsible for increasing demand for stem cells. Secondly, advanced research using HESCs may actually contribute in reducing the demand for stem cells by increasing the knowledge of using alternate sources of stem cells.

### *Creating Embryos for Research and Therapy*

As stated above, the spare embryos from fertility clinics are the potential source of HESCs and are especially helpful in studying the factors controlling cell differentiation. But there are scientific limitations when their use is applied for basic research and therapeutics. Basic research such as in genetic diseases prefers to utilize the cell line that has been cloned by using genetically modified cells. Similarly, cloned cells from an individual when implanted for therapeutic purpose will provide an exact genetic match for that individual which is not possible if cell lines from spare embryos are used.

Creating embryos for research either by *in vitro* fertilization or by cloning, faces ethical challenges. The opponents of HESC research believe that all embryos created for reproductive end have equal chance of growing into human beings and if are destroyed, destruction of some although may be foreseeable in certain circumstances is always unintended. On the other hand, the embryos created for research are viewed as research tools from the very beginning and their destruction in intended. In response to these arguments, people who favor HESC research provide a solution in the form of including them all in a pool for lottery. From this pool some can be donated for reproductive purpose while others are used for research. In this case, all embryos stand a chance to grow into a human being and destruction of some of them although foreseen, will not be intended for them. Therefore, there are doubts that moral distinctions exists between creating embryos for procreation and for research purpose.

## Ethics of Human Cloning

*(This section is based on the Chapter 6: Human Cloning and Human Dignity: An Ethical Inquiry, The President's Council on Bioethics, Washington DC, July, 2002 www.bioethics.gov)*

The ethical issues related to human cloning in biomedical research are serious and difficult. On one hand, such research seems promising as it can lead to improved knowledge that can be utilized in treating diseases due to genetic abnormalities, production of transplantable organs to treat various injuries and illnesses like Parkinson's disease and Alzheimer's disease (NRC/IOM report, 2001; NAS report, 2002). On the other hand there are moral and ethical issues due to possibilities of utilizing cloned human embryos to produce cloned children. There are fears that this research might raise false hopes in patients and physicians and in the process the morally important issues related to the methods used in this research might get ignored.

*Recombinant DNA technology* that involves cloning of a DNA segment of interest has been utilized not only as a scientific tool in research, but it has also impacted the diagnosis and treatment of many diseases. The technique involves isolation of the DNA segment of interest, its insertion into a vector such as a bacterial plasmid, introduction of this recombinant vector into a suitable host cell and then reproduction along with the host cell DNA. Insulin, growth hormone, FSH and many other are now available in recombinant form. The technique has helped in identification of mutant gene related to malignancies and other diseases and also in gene therapy in certain diseases. Wide ranging therapeutic utility of this technique does not raise many ethical questions, and those related to gene therapy are discussed in next section. When the cloning involves "embryo cloning" or "reproductive cloning" serious ethical issues need to be considered.

*Embryo cloning* is the production of cloned human embryos for stem cell research. The technique involves production, use and ultimate destruction of embryos. In case of research involving embryos by *in vitro* fertilization, embryo are produced for the purpose of reproduction and only the leftover embryos are used for research as they are destined to die in any case. But cloned embryos are produced solely for research and will necessarily require to be destroyed and this becomes a morally significant issue for those opposing creation of cloned embryos. According to others, reproduction involving *in vitro* fertilization produces embryos with prior knowledge that some of them will be destroyed and there should be no moral difference from the cloned embryos produced solely for research. Views opposing the use of embryos for research argue that all the embryos produced in *in vitro* fertilization have an equal chance to grow into a child and it is not known that which embryo will be implanted whereas all embryos are destined to die when cloned for research. Considering the enormous benefits that the research on human cloning can provide to society, it becomes important to encourage biomedical research in this area and the embryos used for the purpose must not be treated only as a resource alone. All other ethical issues discussed in the previous section in relation to ethics of stem cell research also apply to embryo cloning for stem cell research.

*Reproductive cloning* refers to production of an animal that has same nuclear DNA as another existing or dead animal. "Dolly" the much-celebrated sheep was created by Scottish scientists at Roslin Institute by reproductive cloning using somatic cell nuclear transfer (SCNT). SCNT involves transfer of the genetic material of an adult cell to the egg from which its own nucleus has been removed. The reconstructed egg is then stimulated to divide using electrical or chemical stimuli. Once this cloned embryo reaches a certain stage of division, it is implanted in the uterus for further growth. Animal produced by this technique is an identical clone of the donor animal. The technique, if used to produce cloned human children, will allow the existence of asexually produced human life meaning that it has a single genetic parent and has a genetic constitution that was known and selected in advance. It allows deliberate genetic manipulation of human life whether produced for research or reproduction. Such a genetic control of cloned embryos is appealing to researchers but is highly unethical if genetically selected cloned embryos are allowed to grow. The cloning techniques might achieve more and more perfection in future leading to intentional production of cloned children. At the moment advocates of human cloning recommend use of early embryos (blastocyst stage) for research but in future the demand may extend to fetal organs requiring growth of cloned embryo beyond blastocyst stage. Society has the responsibility to identify the limits and take measures to allow for the useful research within the appropriate moral and ethical boundaries and protect human dignity.

The best way to ensure that cloned embryos are not allowed to grow beyond blastocyst stage is to prohibit the creation of cloned embryos. But such an approach will also restrict the biomedical research in this area. Another option is to prohibit the implantation of cloned embryo in any uterus, i.e. human, animal or artificial. This will ensure that no cloned embryo will be allowed to grow beyond 14 days period. All individuals engaged in research involving human cloning must register with the regulatory authority, all research proposals requiring human cloning must be reviewed thoroughly to look for expected scientific and medical benefits and all embryos produced during research must be accounted for so as to ensure that they have not been removed from the laboratory to allow for their further growth. Specific laws will be required to regulate the research involving human cloning. As is possible with all other regulations, regulations of human cloning are also likely to have some errors. However, the overall benefits of biomedical research in this area overweigh some additional risk of producing cloned children. The regulations prohibiting implantation of the cloned embryos would require their destruction and this brings into consideration the moral status of embryo. Keeping in view the human good achieved through biomedical research involving cloned human embryos, human cost in the form of nascent human life may be justified. However, it is important that embryos used for research are given due respect and are not treated just as research tools.

The capability to produce asexually produced embryos shows the advancement of science and technology and scope of human power to change human life, but this power needs to be utilized only for the purpose of curing disease and relieving sufferings and should not undermine the human values.

### Ethics of Gene Therapy

Gene therapy is a technique developed in the wake of recombinant DNA (rDNA) technology. It primarily aims to introduce a normal gene in place of an abnormal gene which is responsible for a genetic disease. Genes, which are carried on chromosomes, consist of specific sequence of bases encoding specific proteins. The proteins not only are the structural components of cells but also perform vital cellular functions. Any alteration in the genes, such as due to mutation, causes production of altered proteins that are unable to perform their normal functions leading to genetic diseases. Today, when entire human genome has been mapped, use of gene therapy to cure diseases and human sufferings seems extremely promising.

The technical details of gene therapy are highly complex, however, the basic concept is easy to understand. The defective gene needs to be identified first before it can be corrected. For the identification of defective gene rDNA techniques are being utilized. This technique uses restriction enzymes which are capable of excising the DNA at specific points. The excised fragments of DNA are inserted into bacterial plasmids. The study of the end products of these gene inserts helps to determine the dysfunction of certain genes. For gene therapy, the cells from the tissue of affected individual are removed and a normal copy of the defective gene in inserted by means of a vector. The vectors used for gene therapy, can be viruses such as disarmed retrovirus or adenovirus or non-viruses such as ligand-DNA conjugates, lipofection or direct injection of DNA. Among all, retroviruses are very promising as they are capable of transducing almost 100% of the target cells. Retroviruses are not capable of transferring their own genetic material and transfer only the modified new genetic material. Once the cells acquire the corrected gene they are reintroduced into the individual.

If the target cells for the gene therapy are the human germ cells, the therapy will affect not only the treated individual but also the future generations. This type of gene therapy has not been experimented in human so far. Somatic gene therapy, in which the target cells are the somatic cells, has been experimented in human. The therapy affects only the treated individual and the future generations are not affected. For the first time somatic gene therapy was used in the treatment of adenosine deaminase deficiency (ADA) in children. It is a rare immune system disorder which makes the child incapable of fighting simple infections such as common cold. The affected child was successfully injected with the cells containing corrected gene (Gorman, 1995).

Numerous ethical issues have been raised concerning gene therapy. Most of the people believe that gene therapy is a noble technique for providing cure of diseases that otherwise cannot be corrected. However, concerns have been raised about its use for human enhancement or eugenics which can go beyond treating the serious diseases. Other ethical issues are largely related to the safety of gene therapy. The famous Asilomar conference held in 1975 addressed most of the ethical issues. Some of the important ethical issues considered were the unpredictability of the relatively new techniques, possibility of the risk to the health researchers and public at large and consequences of the long-term presence of genetically engineered viruses in environment. Possibilities of an engineering mistake leading to disastrous consequences were considered seriously. Continued research following the conference has shown that genetic engineering techniques are safe and pose no risk to public health.

The opponents of genetic engineering believe that altering the God-given body is wrong and sinful and whatever is created by Mother Nature must be accepted and respected. For the same reasons, most people believe that germ cell gene therapy must not be experimented. Single gene disorders that have no other treatment option are generally considered suitable for gene therapy. Using gene therapy for the relief of human pain and suffering from diseases like Parkinson's disease, development of cancer vaccines or protection of human cells from HIV is considered completely ethical (Henderson 1997a, Henderson 1997b). However, to define the "human pain and suffering" is difficult. The diseases like Parkinson's fit in the definition but issues have been raised about the "pain" caused by a particular physical trait such as below average height. Clearly, the pain in two conditions cannot be considered equivalent. Ethical guidelines are, therefore, needed to differentiate therapeutic gene therapy from non-therapeutic genetic modification of our native endowments and to prevent the industry and individuals from taking undue advantages.

### Ethics in Medical Device Research

A medical device is an object that is used for diagnostic or therapeutic purpose and achieves its purpose without chemically interacting with the body. Such devices include intraocular lenses, imaging equipments, diagnostic kits, pacemakers, arterial grafts, orthopedic implants and pins and other similar objects. Investigational medical devices are considered "low-risk devices" if they are not invasive and do not present significant risk to the health and welfare of participating individuals. The examples include tongue depressors, cotton swabs, etc. Others that are invasive and expose the participants to significant health risk are considered "high-risk devices". FDA classifies medical devices into 3 categories depending upon the degree of control needed to ensure the safety and efficacy of the device.

Class I devices are those that are not intended for use in support of human life, least invasive and do not present significant risk to human health such as gloves, bandages, tongue depressors. Such devices are subject to only general control procedures to address the issues such as adulterations, misbranding, etc.

Class II devices are also subject to general control measures as in case of class I devices, however, it is considered that the safety and efficacy of these devices must be ensured and they must comply with the performance standards for each device. Examples include infusion pumps, wheel chairs, etc.

Class III devices are the ones that are intended to use in support of human life and can impose significant health risk such as pacemakers, ventilators. Premarketing approval is required and manufacturers need to ensure the safety and efficacy of such devices before obtaining approval for marketing.

The regulatory requirements for approval of medical devices significantly differ from those required for approval of drugs.

1. The evidence for safety and efficacy can come from sources other than well-controlled clinical trials such as partially controlled studies, studies without matched controls, case reports by experts or reports of significant human experience. Anecdotal reports and opinions are not acceptable in this regard (FDA, 2004).
2. For ensuring safety and efficacy of devices, regulations require "reasonable assurance" whereas for approval of drugs "substantial evidence" to prove efficacy and safety is required (US Congress 1938, Hutt et al 1992).
3. For approval of medical devices, evidence from single pivotal clinical trial is considered sufficient whereas in case of approval for drugs, replication of clinical findings is required in more than one clinical trial. This is because the performance of devices can be evaluated *in vitro* as it primarily depends upon the product design (FDA, 1993).

Rapid advancement of technology and its ever-increasing application in health care has presented ethical challenges for physicians, manufacturers as well as regulators. In case of life-saving devices, not only is the process of ensuring safety of efficacy of device important but also important is its correct use in intended population according to recommended guidelines.

The patients, eligible for the use of life-saving devices, risk death with or without the use of such a device. The patient's right to decide about the use of device must always be respected. To help such a patient to make a decision of whether to use the device or not, physicians need to explain to the patients the risks associated with the use of device. Physicians need to assess the risk of dying due to failure of device against the risk of dying without the use of device and communicate it to the patients. Some of the cardiac devices may prolong and complicate the natural dying process. In case of such a possibility, patients should be informed and be allowed to make a decision about whether or not to inactivate the device to lessen the pain as they die.

The patients using medical devices at the time of emergency may not be able to provide vital information about the use of device to the medical personnel either because of their illness or because they are unconscious. To help such patients, subcutaneous implantation of Radiofrequency Identifications (RFID) tags is advised. RFID tags are of the size of a rice grain and carry a password or code which can be read by electronic scanner and provides information about the patient's medical condition. However, at times people using RFID tags may not have control over who is accessing their medical information without their consent. This possibility threatens the individual's privacy and at times the vital information may reach the hands of health insurance companies or employers.

If the use of implant is intended to restore the lost body function, usually there are no serious issues. However, if the use of implant is intended to enhance some of the body functions or structures, it becomes controversial. As for example breast implantation when done for cosmetic purposes, is opposed by many due to associated risks. Breast implantation is known to be associated with complications like infection, hematoma, painful hardening of breast, loss of nipple sensation, inability to breastfeed and interference with diagnosis of breast cancer. According to other experts, women have right to decide for this cosmetic surgery and at times this may help in treating the psychological damage resulting from stigma of having small breasts.

Enhancement of normal body functions by using implants may be taken to the extreme and experts now visualize the possibilities of such brain-machine interfaces that can enhance memory and other mental faculties and enable new capabilities such as virtual perception. Such extreme neural implants if intended for disabled patients will not raise serious issues. But if used for normal persons, serious ethical issues will be involved as it can potentially affect our sense of "self" and the way in which we perceive and interact with the world around.

With explosive growth and evolution of medical device industry, issues related to safety and efficacy are becoming increasingly important. Accordingly, regulatory bodies around the world are taking steps to securitize the devices for safe and effective use before they appear in market and also after marketing. Delay caused by the scrutinizing procedures raises ethical issues concerning missed opportunities and time lost for the people who are in immediate need.

The close cooperation among physicians, regulators and manufacturers is essential for development of therapeutic and diagnostic technologies requires, but faces ethical dilemmas. Manufacturers may try to get their products in the market as class 1 or 2 product, to avoid time-consuming procedures required to scrutinize class 3 products. Physicians may sometimes promote one or the other product for incentives. In addition, inappropriate advertisements further lead to errors in decision making by the patients. Regulatory authorities are working to formulate guideline in a way that

safety and efficacy of existing devices in the market can be ensured, new devices could be made available to people at the earliest and adequate information is available to physicians and patients about the safe use of medical devices.

## ETHICAL CHALLENGES IN INDIA AND OTHER DEVELOPING COUNTRIES

India is viewed as the favored destination for international clinical trials due to its large pool of diverse and treatment-naïve population with a wide range of acute, cbhronic and lifestyle diseases, easy availability of trained, english-speaking manpower and government support to accommodate the needs of international clinical trials. Clinical trials in India are regulated by Schedule Y of the Drugs and Cosmetics Rules. Regulations are enforced by Drug Controller General of India (DCGI). DCGI is also responsible for monitoring the clinical trials for which it has given approval. For the development of new drugs, trials should be conducted from phase 1 onwards in India but for market approval of drugs that have been approved in other countries only phase 3 trials need to be conducted in India at 3 or more centers. Application for a new indication of already approved drug is treated like an application for new drug approval. New formulations of approved drugs require bioequivalence studies. For the conduct of clinical trials in India, approval is required from local ethics review committee (ERC) and according to revised ICMR guidelines (2006), ethics review committee is also responsible for monitoring the clinical trials approved by them.

Undertaking research involving human subjects in developing countries like India faces numerous ethical challenges. These challenging ethical issues are of concern for the regulatory bodies, the researchers as well as the subjects.

The highest regulatory authority in India, the DCGI is not adequately equipped for monitoring the ongoing clinical trials in the country and currently the clinical trial data is audited by contract research organizations (CROs) and sponsors. The role of local ERCs in maintaining good ethical standards during the conduct of clinical trials is extremely important. The ERCs aim to ensure that the research protocol is designed in such a way that it tries to answer a research question of sufficient value that can justify the risk posed to the participants, the study design is scientifically valid, researchers adhere to protocol during the conduct of trial and at the end of it the results are accurately and promptly reported. The expertise required to satisfactorily perform the functions of ERCs is often lacking and not all ERCs are established as per legal provisions. According to one of the surveys conducted by ICMR in 2005, only 40 of 179 institutional ethical committees follow the prescribed legal provisions and function as per various ethical guidelines (Mudur, 2005). Once the protocol is approved, the conduct of clinical trial as per ethical guidelines is the responsibility of the investigator. Clearly, it is vital that investigators undergo rigorous training and

understand the principles of bioethics before undertaking any clinical trial. ICMR as well as various private organizations are actively participating in investigator training program all over the country, however, a lot more is still desirable.

Informed consent forms the basis of all three principles of bioethics, i.e. respect for persons, beneficence and justice. Therefore, investigators are required to ensure that the subjects are fully informed about the purpose of study, study procedure that they have to comply with and the possible risks that they are likely to be exposed during the trial. Subjects must be given chance to ask questions and must be informed that the consent is purely voluntary and they are free to withdraw from participation without giving any reasons and still will be entitled to receive all benefits from the trial. Obtaining a meaningful consent as stated above often faces several difficulties. The pressure to meet the required recruitment sample size may not allow the researcher to fully comply with the ethical guidelines to obtain the informed consent. Using deceit or coercion to manipulate person's will to enroll him in a clinical trial is a direct violation of ethical principles. However, in certain circumstances especially in developing countries, requirements for a valid informed consent are violated without directly manipulating the will of the person. Cultural, economic and linguistic barriers often lead to ineffective communication between researcher and subject. If the investigator obtains consent from the subject without overcoming these barriers, the ethical principles are violated. The subjects in countries like India may often volunteer to participate in the clinical trial as it gives them access to otherwise unaffordable health care facilities. Subjects under these circumstances may volunteer to participate in spite of knowing the possible risks or the fact that the sponsor may not make the post-trial benefits available to their community. The tragic circumstances, therefore, can force individuals to participate rather than their incapability to decide otherwise. Issue of exploitation arises in such circumstance as it is morally wrong for the researchers to take advantage of poverty for their own gain.

The population of developing countries is also subject to exploitation when the research areas such as face transplantation, gene therapy, cessation of life-support primarily address the problems of world's affluent countries. Such issues appear "trivial" in developing and poor countries. Therefore, experimentation on the population of poor countries to address the "problems of affluence" amounts to exploitation of human subjects and violation of ethical principles. The "problems of affluence", however, may be of importance in some areas of developing countries or are likely to become important in future as the health care status of the country improves. In an effort to provide protection to participants involved in international clinical research in poor countries, development of new universal ethical guidelines that can be applicable in all cultural contexts is a renewed challenge. An initiative in this direction came in the form of Nuffield Council on Bioethics'

report *The Ethics of Research Related to Healthcare in Developing Countries* (2001), the Wellcome Trust's initiative to fund bioethics research in developing countries (started in 2002). The International Research Ethics Education and Curriculum Development Awards are offered by the Fogarty International Center at the National Institutes of Health (launched in 2000). The institute also provides training to health professionals in bioethics and research ethics relevant to developing world contexts at 18 institutions worldwide. The European and Developing Countries Clinical Trials Partnership (EDCTP) has offered funds for establishing ethics review committees and bioethics educational programs in sub-Saharan Africa. A peer reviewed journal "Developing World Bioethics" launched in 2001, publishes bioethical issues in resource-poor countries. Several national bioethics organizations both governmental and non-governmental are working to ensure protection of human subjects and adherence to ethical principles of bioethics.

## NATIONAL BIOETHICS ORGANIZATIONS

Some of the bioethics organizations in India, as listed on International Bioethics Organizations Database, are as follows:

- Indian Council of Medical Research Central Ethics Committee on Human Research, New Delhi
- Ministry of Science and Technology, Department of Biotechnology, National Bioethics Committee, New Delhi
- Society for Scientific Values, IIT, Kharagpur [Choprak]; School of Biotechnology, GGS Indraprastha University, New Delhi
- National Human Rights Commission, Faridkot House, Copernicus Marg, New Delhi
- Biomedical Ethics Indian Council of Medical Research, New Delhi
- Centre for Enquiry into Health and Allied Themes, Mumbai
- Centre for Studies in Ethics and Rights, Anusandhan Trust, Mumbai
- Forum for Medical Ethics Society, Mumbai
- FIAMC Biomedical Ethics Centre, International Federation of Catholic Medical Associations, Mumbai
- All India Association of Bioethics, Chennai
- Society for the Right to Die with Dignity, Mumbai.

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# CHAPTER 6 Medical Devices—Regulations and Research

## INTRODUCTION

Medical devices are an integral part of the entire healthcare delivery system. They assist in the diagnosis, prevention and treatment of a wide range of diseases and malfunctions in the human body. They range from a simple thermometer to the most complicated, computer assisted, programmable and implantable pumps and drug delivery systems.

In spite of the exponential growth of the clinical research industry, research on medical devices remains a very small part of the research that goes into the development. Research sites seem to focus on the more lucrative drug research and basic research. Nevertheless, clinical research of medical devices is critical. A lot of resources go into the conduct of a clinical trial and the clinical trial process cannot be left to chance. Because of the strict requirements of some government or other regulatory policies, poorly designed studies that may inadvertently put the patient at risk may meet regulatory enforcement action. In this chapter, we shall discuss about some of the regulations governing medical devices and also focus on the basics of clinical research of medical devices.

Since 2005, there has been a global harmonization of the regulations governing medical devices. This has been made successful by the Global Harmonization Task Force (GHTF). GHTF is a voluntary international group of representatives from medical device regulatory authorities and trade associations from Europe, the United States of America (USA), Canada, Japan and Australia.

As GHTF is a voluntary task force, the regulations are not binding across the globe. Each country has its own medical devices regulation which cater to the local needs and governs the manufacture, research, labelling, sale and disposal of these devices.

In India, the medical devices' market is not so well regulated – some of the devices are regulated under the drugs regulations while others are not regulated at all. The latest set of guidelines in India for the medical devices are still in the draft stage and await the nod from the government. This is entitled **Schedule M-III** – requirements for the manufacture, import and sale of medical devices.

## DEFINITION OF A MEDICAL DEVICE

Any instrument, machine or implant that is used in medical care is called a medical device. Some such as a sphygmomanometer or a PET-scan machine are used for diagnosis. Others such as a band-aid or a coronary stent are used for prevention and treatment of diseases.

The definition of a medical device varies from one country to the other. Some of the definitions from the key countries are enumerated below:

In the USA, a medical device is defined as per the Federal Food Drug and Cosmetic Act and is regulated by the Food and Drug Administration (FDA). A device is *"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article, including a component part, or accessory which is:*

- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

In the EU a directive issued by the European Parliament in 1993 and later amended in 2007 defines a medical device as *"any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings."*

The directive says *"Devices are to be used for the purpose of:*

- diagnosis, prevention, monitoring, treatment or alleviation of disease
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
- investigation, replacement or modification of the anatomy or of a physiological process
- control of conception."

As per the Pharmaceutical Affairs Law of Japan, a medical device is defined *as "equipments, instruments, etc. specified by the government ordinance which are intended for use in the diagnosis, treatment or prevention of disease in humans or animals, or intended to affect the structure and functions of the human or animal body".*

As per the GHTF definition, a medical device is *"any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article which:*

a. Is intended by the manufacturer to be used alone or in combination for human beings for one or more specific purpose(s) of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury
- Investigation, replacement, modification or support of the anatomy or of a physiological process
- Supporting or sustaining life
- Control of conception
- Disinfection of medical devices
- Providing information for medical or diagnostic purposes by means of *in vitro* examination of specimens derived from the human body; and

b. Does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means."

In India, the definition of medical device as per the proposed Schedule M-III is similar to the GHTF definition.

## PHASES IN THE LIFESPAN OF A MEDICAL DEVICE

The different phases in the life cycle of a medical device span from the concept ideation to the disposal of the device. Figure 6.1 shows the seven phases in the lifespan of a medical device. Each of the phases may affect the safety and performance of the device. So the scope of regulatory control includes each of these phases.

### Concept and Development

This phase includes the conception of the scientific principles based on which the device performs. It is fundamental to the safety and performance of the medical device. During this phase, scientific experts prepare the concept, design, construct and test the device to ensure that the design parameters and the performance characteristics are adequate in order to avoid any unwarranted safety hazards.

### Manufacture

An adequately managed manufacturing process ensures production of good, functional medical devices. A default in the manufacturing process can produce an inconsistent quality of products, even if the original prototype was well designed in the conception and development phase.

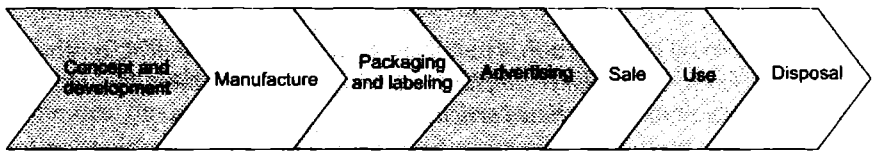


**Fig. 6.1:** Different phases in the lifespan of a medical device

### Packaging and Labeling

Proper packaging is important in order to ensure delivery of clean, sterile and protected medical devices to the point of use. A lapse in the packaging system can lead to serious consequences such as contamination of an implantable coronary stent. In other cases, unless the packaging system is designed to withstand various stresses, subtle damage may be caused even during transportation and handling.

Labeling is also a crucial part of device risk management. Appropriate hazard warnings or cautions and clear instructions help in identifying the medical device and specify instructions for proper use.

### Advertising

Advertising creates expectations and influences the belief in the capabilities of a medical device. Hence, it should be truthful and not misleading. A truthful advertising should allow consumers to make a proper informed choice about their health and prevent potential misconceptions about the treatment procedure. Done in the correct way, medical device advertising could provide important information about a new device, any new indications for an existing device, as well as treatable symptoms of the disease.

### Sale

According to the Food and Drugs Act, selling a medical device means to "offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration". This is a critical phase. Without a regulatory control on this phase, there would be a higher risk of low quality or ineffective devices being sold for use.

### Use (Including Installation and Maintenance/Calibration)

If the user is unfamiliar with the technology or the operating procedure, there may be device failure even in the absence of any defect in the inherent design or in the manufacturing process. This can also occur if the product is used for an indication beyond the ones mentioned in the labelling. Reuse of disposable devices against the manufacturer's instructions can be dangerous. Many devices require proper installation and testing prior to usage. Proper maintenance/calibration is crucial to ensure the devices continue to function properly.

### Disposal

Proper disposal of the medical devices after their use is essential. Certain safety criteria may need to be followed to avoid contamination and toxic hazards to the environment.

### Classification of Medical Devices

The phase of clinical development of a device depends on the classification of the device, which in turn is based on the risk of the device to the patient. The classifications and the regulations related to them differ from country to country:

**USA:** They are classified into 3 classes:

| Class | Risk | Approval/Regulatory |
|---|---|---|
| I | Low | Approval not required |
| II | Moderate | Approval required |
| III | Moderate to High | Approval required |

**EU:**

| Class | Risk | Approval/Regulatory |
|---|---|---|
| I | Low | Approval not required |
| II A | Medium | Approval required |
| II B | Medium | Approval required |
| III | High | Approval required |

**Japan**

| Class | Risk | Approval/Regulatory |
|---|---|---|
| I | Extremely Low | Approval not required |
| II | Low | Approval required |
| III | Middle | Approval required |
| IV | High | Approval required |

**India (Proposed)**

| Class | Risk | Approval/Regulatory |
|---|---|---|
| A | Low | Approval not required |
| B | Low-Moderate | Approval required |
| C | Moderate-High | Approval required |
| D | High | Approval required |

## CONDUCTING CLINICAL TRIALS ON MEDICAL DEVICES

The safety and effectiveness of an investigational device is to be demonstrated before the actual marketing. In most international markets such as the US, clinical studies are a regulatory requirement for implants and other significant risk (SR) medical devices prior to registration of a medical device. A clinical study helps to confirm, validate, or supplement the data from laboratory and/or animal testing. Commonly, clinical studies are done to support new designs, new technologies, and/or new indications for use. Most non-significant risk (NSR) products reach the market after only *in vitro* tests and animal tests. Yet, a carefully planned clinical research can play a significant role in enhancing product development and marketing of such devices.

Postmarketing studies are needed to confirm long-term safety and performance. It also provides information about uncommon adverse effects. Postmarketing studies help enhance product designs and extend labelling

claims. Comparative data from postmarketing studies also help to provide an economic analysis. For the manufacturers, it means they can extend their cost-benefit claims. For the users, it means they can get the best devices that the market has to offer at their specific budgets.

In comparison to the clinical trial of drugs, there are significant differences in the logistics of conducting clinical trials of medical devices. Blinding may not be possible in most device trials. Choosing appropriate controls may also be a problem. For example, in a drug trial, the subject can take a pill or get an injection and neither the investigator nor the subject may know whether it is a test agent or a placebo. The control in a device trial may be an older version of the device, different devices that have already been approved, devices looking similar to the test device but not delivering the therapy, a non-device therapy or no therapy at all. These are very easily recognized by the investigator. So, investigator blind trials may not be usually possible in device studies. Device trials are usually randomized parallel group trials where patients are randomized to receive either the accepted device or another treatment. Some trials have to compare results against historical data as a placebo group cannot be introduced. Some trials are crossover studies where the patient sequentially receives treatment with more than one device or drug treatment regimen. Thus, they effectively serve as their own controls.

Some unique features of medical device clinical trials are listed below:

- They tend to involve fewer subjects as compared to drug trials. Each subject may, however, require a longer follow-up.
- The use of the device may not be the sole diagnostic or therapeutic intervention. It may be part of a complex therapeutic procedure.
- The success of the procedure may not depend solely on the device. Factors such as the surgical procedure and the surgeon's skills may also be important.
- There are different requirements by the FDA for SR devices and NSR devices. The classification of medical device clinical studies is shown in Table 6.1.

**Table 6.1:** Classification of medical device clinical studies

| |
|---|
| Pilot or feasibility studies of safety, performance, and/or design in the premarketing stage |
| Pivotal studies of safety and effectiveness in the premarketing stage |
| Postmarketing studies |
| • For supporting expanded labelling claims |
| • For support of comparative performance claims |
| • Pharmacoeconomic studies |
| • Observational or analytical studies of specific issues regarding safety and performance |
| • Explant retrieval and failure analysis investigations |

*Source*: Becker KM and Whyte JJ. Clinical evaluation of medical devices: principles and case studies. 2nd Edition. Humana Press. New Jersey.

Typically, device trials have a short safety and biocompatibility study that is comparable to the phase I trial of drugs. A pilot or feasibility study compares to phase II in drug trials. This is followed by a larger pivotal clinical study that is comparable to a phase III drug trial. Then comes the post-marketing clinical studies.

### Pilot Studies

Pilot studies are feasibility studies. They are usually single center studies done on limited number of subjects. These are usually not hypothesis testing studies. They are done to generate data in support of the hypothesis testing studies. Pilot studies evaluate the role of the user in the device performance under actual clinical situation. They help gather information on design features that may need to be modified to ensure better performance. It is like a field test of the device.

### Pivotal Studies

Pivotal studies are usually multicenter studies. These are larger prospective, analytical studies that provide clinical evidence of effectiveness of the device based on single or multiple clinical outcomes of significance. In combination with laboratory testing and animal studies, a single, well-designed pivotal study is sufficient to 'reasonably' confirm the safety and effectiveness of the device. When directly compared to alternative treatment options, a device is expected to perform 'not worse than' other available treatments once the pivotal study has provided enough evidence of its safety and effectiveness.

### Postmarketing Studies

Postmarketing studies may be of two different kinds: mandated post-approval studies and postmarket surveillance studies.

FDA makes it mandatory for conducting a *postapproval study* for most Class III devices. This is a mandatory requirement put forward by the FDA during a premarket approval application. It adds to the information generated through pivotal studies in support of product approval. They are aimed to provide:

- Longer-term follow-up
- Additional data on the incidence and time course of adverse events
- Additional data in support of broader label claims.

Such studies may be an extension of the pivotal study or may be standalone studies.

### Postmarketing Surveillance Studies

Postmarketing surveillance studies are different from post-approval studies. These studies may be conducted as a regulatory requirement or at the

discretion of the FDA or it may be initiated by the sponsor itself. Post-market surveillance studies are required by FDA for Class II and Class III devices if the failure of the device is likely to cause serious health problems, if it is to be implanted in the human body for over a year or if it is a life-supporting device used outside a device user facility.

Postmarketing surveillance studies may be comparative studies with other drugs or devices. They may provide evidence for comparative effectiveness claims, pharmacoeconomic comparisons, or expanded label claims. For implanted devices, follow-up beyond 2 years may not always be feasible. In such cases, a carefully designed explant analysis and failure investigations are considered effective and efficient means of collecting data regarding long-term performance of medical devices. Many vigilant sponsors also evaluate the adverse event reports, returned goods, and complaints and help contribute to the collection of data on clinical experience with the device.

## MEDICAL DEVICE REGULATIONS ACROSS THE WORLD

Some developed countries like the US and EU have a well recognized system of medical device regulations. There is a dire need for similar regulations to be framed and implemented across the globe to ensure the launch of safe and reliable devices which will ensure the safety and well-being of the patients. Table 6.2 provides an alphabetically ordered list of countries and their respective medical device regulatory bodies.

### US Regulations

In the US, all device manufacturers have to register their organizations with the FDA. They can then market the device only after receiving the Premarket Approval (PMA) called a 510 (k) notification. This notification is basically a letter of substantial equivalence. The clinical study of the devices with significant risk has to be first approved by both, the FDA and the Ethics Committee. The studies with devices of nonsignificant risk can be initiated following the approval by the Ethics Committee only.

The devices undergoing clinical studies are granted an Investigational Device Exemption (IDE). These studies are conducted to gather data on both safety and effectiveness of the device and this data is essential for supporting the Premarket Approval (PMA) application or a PMA submission to the US FDA.

### EU Regulations

In the EU, the medical devices are regulated by 3 different EC Directives. They include:

- Medical devices directive (MDD) - governs most of the devices
- Active implantable medical devices directive (AIMDD)
- *In vitro* diagnostic medical devices (IVDD).

**Table 6.2:** Medical device regulatory authorities across the globe

| *Country* | *Regulatory authority* |
|---|---|
| Argentina | National Administration of Drugs, Foodstuffs & Medical Technology (ANMAT) |
| Australia | Therapeutic Goods Administration |
| Austria | Federal Ministry of Health Department |
| Belgium | Belgian Federal Public Service |
| Brazil | National Health Surveillance Agency (ANVISA) |
| Canada | Health Canada |
| China | State Food & Drug Administration |
| Czech Republic | State Institute of Drug Control |
| Denmark | Danish Medicines Agency |
| Egypt | Ministry of Health |
| Finland | National Agency of Medicines |
| Germany | Federal Institute of Drugs and Medical Devices (BfArM) |
| Greece | National Organization of Medicine |
| Hong Kong | Medical Device Control Office |
| Hungary | Authority of Medical Devices |
| India | Central Drug Standard Control Organization (CDSCO) |
| Israel | Ministry of Health |
| Japan | Ministry of Health, Labor and Welfare (MHLW) |
| Mexico | Secretariat of Health (Secretaria de Salud) |
| Singapore | Health Science Authority |
| South Korea | Ministry of Health and Welfare (MHW) |
| Taiwan | Bureau of Pharmaceutical Affairs (BOPA) |
| UK | Medicines and Healthcare Products Regulatory Agency (MHRA) |
| USA | Food and Drug Administration (FDA) |

All medical devices must have a CE Marking before they can be marketed in the EU countries. This mark is not a quality approval but it indicates that the manufacturer is in full compliance to any of the Directives.

Most medical device companies must implement a Quality Management System except for the nonsterile ones under Class I. This system is in accordance to the requirements mentioned in the Directives. To meet these requirements most device companies apply the ISO 13485 which is a Quality Management System standard developed exclusively for medical devices. This system takes 3-9 months to be implemented. During this period, the company has to prepare the Technical File which includes all data related to the safety and efficacy of the device. This document also includes the other components as in Table 6.3.

**Table 6.3:** Components of EU Technical File for Medical Devices

| *Device description* | *Instructions for use* |
|---|---|
| Intended use | Packaging |
| Product specification | Labeling |
| Technical drawing | Clinical Data—Efficacy and safety |
| Risk analysis | Performance testing |
| Manufacturing documentation | Standards used |

All technical files except those for the Class I devices are audited by Notified Bodies (NB). The NBs are independent auditing bodies that are authorized by the government. After the audit and the review of the technical file, a CE Certificate is issued by the NB.

In India, a set of sterile medical devices are considered as drugs by the Drugs and Cosmetics Act and are regulated by the Drugs Controller General of India (DCGI). These devices include:

- Cardiac stents
- Drug eluting stents
- Catheters
- Intraocular lenses
- IV Cannulae
- Bone cements
- Heart valves
- Scalp vein sets
- Orthopedic implants
- Internal prosthetic replacements.

These products will not fall under the Schedule M-III which aims at regulating medical devices as a separate sector from drugs. According to Schedule M-III, the main regulatory body for medical devices will be the Central Licensing Approval Authority (CLAA), a branch of the CDSCO. All medical devices imported into or exported out of India will need to undergo a conformity assessment. They will need to carry an Indian Conformity Assessment Certificate (ICAC) issued by the CLAA. The regulatory standards for such assessment will be the Bureau of Indian Statistics (BIS) and International Organization for Standardization (ISO) specifications.

Besides this, the Indian parliament has two other pending proposals for regulation of medical devices. In 2006, the Medical Devices Regulation Bill (MDRB) was drafted. It aims to establish an Indian Medical Devices Regulatory Authority (IMDRA) as an independent government ministry to regulate medical devices. In 2007, another bill called the Drugs and Cosmetics Amendment Bill (DCAB) proposed the establishment of a Central Drug Authority (CDA) with a separate department that would have exclusive authority to regulate medical devices. With the approval of the Schedule M-III in June 2009, this guidance seems to be the most likely way in which medical device regulations in India will head in the coming years.

Apart from the above regulations, there are some other regulations being followed in different parts of the world, like the GHTF and the ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects - Part 1 and 2, Revised 2003). The ISO 14155 regulations are followed in EU and helps the Sponsors, Investigators and Monitors in the design and conduct of medical device clinical investigations or trials. They also help the national regulators and the Ethics Committees during their review of the Clinical Investigations Plan (CIP). The Part 1 of ISO 14155 mentions about the general guidelines required for the conduct of the clinical investigations of the medical devices. The Part 2 of this guideline deals with the procedure and the contents of the CIP.

## MEDICAL DEVICE SAFETY

The various regulations governing the effectiveness and safety of the medical devices ensure protection of the health of the patient. Such regulations require the various stakeholders - manufacturers, importers, exporters and users, to report all device-related safety issues.

In the US the latest system is the Medical Devices Reporting (MDR), which was effective on February 19, 1998 and recently amended on March 27, 2000. The reporting of the adverse events by the manufacturers in the US can be summarized in Table 6.4.

**Table 6.4:** Reporting of adverse events by manufacturers in the US

| *What to report* | *Report form #* | *To whom* | *When* |
|---|---|---|---|
| 30-day reports of deaths, serious injuries and malfunctions. | FDA 3500A | FDA | Within 30 calendar days from becoming aware of an event. |
| 5-day reports on events that require remedial action to prevent an unreasonable risk of substantial harm to the public health and other types of events designated by FDA. | FDA 3500A | FDA | Within 5 work days from becoming aware of an event. |
| Baseline reports to identify and provide basic data on each device that is subject of an MDR report. | FDA 3417 | FDA | With 30 calendar, and 5 work day reports when device or device family is reported for the first time. Interim and annual updates are also required if any baseline information changes after initial submission. |
| Annual certification | FDA 3381 | FDA | Coincide with firm's annual registration dates. |

(*Source:* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094529.htm)

**Table 6.5:** Reports about deaths, injuries, adverse events etc. by user facilities and distributors

| *Reporter* | *What to report* | *Report form #* | *To whom* | *When* |
|---|---|---|---|---|
| User Facility | Death | FDA 3500A | FDA and Manufacturer | Within 10 working days |
| User Facility | Serious injury | FDA 3500A | FDA and Manufacturer | Within 10 working days |
| User Facility | Semi-annual reports of death and serious injury | FDA 3419 | FDA | January 1 and July 1 |
| Distributor (includes importers) | Death and serious injury | FDA 3500 | FDA | Within 10 work days |
| Distributor (includes importers) | Death, serious injury and malfunction | FDA 3500A | Manufacturer | Within 10 work days |
| Distributor (includes importers) | Annual Certification | FDA 3381 | FDA | Annually |

Similarly, the user facilities and the distributor must also report to FDA and/or to manufacturer about the deaths, serious injuries, adverse events, and any malfunction as per the grid given in Table 6.5.

In EU, the safety reporting is based on the ICH GCP guidelines. The European regulators also follow the ISO 14155 regulations, but it has been observed that it is better to follow both the guidelines while conducting device trials. The compliance to both these guidelines ensures the easier acceptance of the data in the US. Many device sponsors prefer to create a hybrid set of operating procedures taking both the above guidelines into consideration.

The safety reporting need to be more aligned to the ICH GCP guidelines. All adverse events must be reported to the EC (Ethics Committees). This will also include lab values which so clinically significantly change from the baseline. As the ISO 14155 is silent over the adverse events reporting, it is better to follow the ICH GCP guidelines and ensure that all the adverse events are reported to the EC. It is a good practice to mention upfront in the protocol the nonreportable adverse events which are expected during the device implantation/administration process.

In EU, there is also a recent guideline on the Medical Devices Vigilance System, Dec 2009. The main purpose of this recent guideline is to enhance the protection of health and safety of patients on whom medical devices are used/administered. This guideline clearly specifies the reporting procedures

for the manufacturers and the users. It also defines the role of the regulatory agencies in EU in managing the safety reporting and the dissemination of such reports to the manufacturer.

In India, as per the proposed M-III guidelines, the performance of the device has to be closely monitored by the manufacturer once the marketing of the device begins. The reporting of any adverse event occurring postmarketing will be done to the CLAA. The reporting timelines will depend upon the type and severity of the adverse event, e.g. in the event of an unanticipated death or an unanticipated serious injury or an event that represents a serious public health threat, the manufacturer has to report it within 48 hours.

## CONCLUSION

The device regulations are different in various parts of the world. There are efforts to streamline them and make them uniform across the globe. They need to be harmonized at the earliest to ensure safety of the patients on whom these devices are used. The responsibility of safeguarding the health of the patients is to be equally shared by the manufacturer, regulators and also the patients. A concerted effort by all the stakeholders is necessary at the earliest to enhance the protection of the health of the patients.

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# CHAPTER 7 Clinical Development of Vaccines

## INTRODUCTION

Vaccination is an integral part of human health. Measured in terms of deaths prevented, vaccines against infectious disease are widely viewed as the most effective, and most cost effective medical technology ever developed.[1] Vaccination in a population apart from protecting vaccines exposed to the infectious agent can also change the exposure to infection for people who are not vaccinated. Vaccination has also helped eradication of many deadly diseases such as small pox and polio disease is on the verge of eradication with the help of mass vaccination programs throughout the world.

Early forms of vaccination were developed in ancient China and India as early as 200 BC. The history of clinical trials designed to demonstrate the safety and efficacy of new vaccines is also rich. In 1954, the largest medical experiment tested a vaccine to prevent poliomyelitis, one of the most feared childhood diseases. This was the Salk vaccine, named after Dr Jonas Salk.[2]

Similar to clinical development of drug products, there are four phases of clinical trials in vaccine development. All clinical trials should adhere to the standards described for good clinical practice (GCP) and guidelines for GCP already in place for trials of pharmaceutical products, also apply to vaccine studies. However, vaccines demand special consideration because:

- Vaccines are given to healthy individuals, mostly children and infants
- Vaccines are given to prevent disease; this limits tolerability of adverse events
- Vaccines are biological products which are highly complex substances derived from living materials, and sometimes comprising living organisms. They require specialized assays and testing to assure their quality and safety on a lot-to-lot basis.

## PHASES OF TRIALS

### Phase I Trials

Phase I trials are referred to early studies with human subjects. phase I trial is usually small scale and conducted in healthy, immunocompetent adults who are at low risk of the infection or complication against which the vaccine protects. The purpose of phase I trial is to explore the acceptable safety and reactogenicity of a candidate vaccine as well as to obtain preliminary

information on its immunogenicity of multiple dose levels of the vaccine under investigation.[3] During phase I studies, the dose and various methods of administration are also assessed with respect to safety and immunogenicity parameters. All phase I studies should be conducted in highly controlled research environments with adequate laboratory and medical support.

These studies are usually conducted as open label studies without randomized with a placebo or any control groups. But a control can be added, even in phase I, to allow at least some comparison of intercurrent common nonvaccine induced events. phase I studies are conducted in several different age or population groups because of differences in, for example, dose, safety, vaccine schedule, route of administration or disease risk. The age stratification can vary but usual practice is to evaluate the candidate vaccine safety in stratified age groups as below:

- Adult 18 to 45 years
- Extended adults age group 18 to 64 years
- Children and adolescents 12 to 18 years
- Children 5 to 11 years
- Young children 2 to 4 years
- Below 2 years of age.

A short period of evaluation in a clinical research center or hospital or extended observation in a clinic, day-care center or home environment is recommended for close monitoring of vaccinees. Less intensive phase I trials might involve daily visits by a research nurse to the home or day-care center or daily return visits by the subject to the clinic. Safety studies in special population like pregnant mothers, geriatric subjects are usually done in late phase studies.[4]

Phase I studies for live attenuated candidate vaccines (viral or bacterial) should be undertaken to make not only preliminary evaluations of dose ranges, immune responses, clinical signs of infection and reactogenicity (immediate, early and late) but also for information on shedding, reversion characteristics, transmission to contacts and genetic stability. Major safety concerns in the evaluation of a live attenuated vaccine include the possible shedding of the agent, transmission to contacts, potential genetic variability and reversion to a more virulent state. Therefore, such vaccines require intensive investigations in closely monitored clinical settings especially when they are used for the first time in humans during phase I studies.[4]

### Phase II Trials

Once phase I studies have been successfully completed with a satisfactory outcome, a candidate vaccine should then undergo phase II clinical evaluation. The main distinction between phase I and phase II studies is that phase II studies involve larger numbers of subjects, and are often randomized and well controlled. phase II vaccine trials are intended to demonstrate the immunogenicity of the relevant active component(s) and the safety profile of a candidate vaccine in the target population.

Ultimately, the phase II studies will define the optimal dose, initial schedule and safety profile of a candidate vaccine before the phase III trials can begin.

Phase II studies are undertaken to evaluate multiple variables associated with the host immune response such as age, ethnicity, gender and presence of maternal or pre-existing antibodies. In addition; they also assess the use for candidate vaccine in special population like geriatric and pregnant women. Other factors that are investigated to determine their influence on immune response includes:

- Dose per vaccination
- Sequence or interval between vaccine doses
- Total number of doses of vaccine
- Route of vaccine administration
- The duration of immunity, potential need for booster immunizations and qualitative aspects of the immune response.

In phase II studies for a live attenuated vaccine, continued active monitoring of earlier specific parameters associated with live vaccine are done. The duration of follow-up is determined by a number of factors that are identified in the phase I studies including the degree of shedding, transmission and potential reversion characteristics.

The evaluation of immune responses to vaccine antigen(s) is critical part of phase II clinical studies. Such studies are intended to further characterize immune responses elicited by a particular immunogen thought to be relevant to protection, such as level, class, subclass and function of the specific antibodies produced, as well as appearance and duration of adequate antibody titers. Other relevant information such as presence of neutralizing antibodies or cross-reactive antibodies, formation of immune complexes, cell-mediated immunity and any interaction that might affect the immune system (e.g. preexisting antibodies, concomitant administration of another vaccine or drugs) is also studied during phase II studies.

### Phase III Trials

The phase III studies[4] are large-scale clinical trials that are usually performed in large populations to evaluate efficacy and safety of formulation(s) of the immunologically active component(s). In large scale efficacy studies, thousands of subjects are evaluated and serological data are usually collected from at least a subset of the immunized population at predefined intervals.

When vaccines containing the same antigens are already in common use and/or the incidence of disease is very low, it may not be feasible to perform a formal study of protective efficacy. In such instances, the phase III trials, although involving larger numbers of persons than previous phases, are confined to the evaluation of immune responses and comparison with any recognized correlates of protection. Since phase III trials involve a larger number of subjects than were included in the earlier phases of development, thus they also provide expanded safety assessments.

The duration of follow-up in phase III study depends on the type of vaccine and factors such as, disease incidence, characteristics of immune response to vaccine, and anticipated and safety profile of the vaccine.

## VACCINE EFFICACY

The effectiveness of vaccine is the measure of protection provided by the vaccine in a specified population.

Vaccine effectiveness is affected by a number of factors, including:

- Vaccination coverage of the population
- Distribution of vaccine in population
- Immune status of the population
- Efficacy of vaccine in preventing disease and preventing colonization
- Correlation of strains used in vaccine production with circulating strains
- The incidence of disease due to strains not included in the vaccine following introduction of the vaccine in that population
- The heterogeneity in susceptibility, rates of exposure to infectious agents and protection conferred by the vaccination
- Time-related changes in protection caused by intrinsic properties of the vaccine like waning of efficacy, requirement for boosting, changes in vaccination coverage, and population characteristics (such as age distribution)

Studies of effectiveness measure effects of all above parameters in both direct and indirect protection (herd immunity).

When the result of intervention by a vaccine is described under normal circumstances in real world scenario, it is called as effectiveness of the vaccine. In usual practice and controlled conditions, it is difficult and time consuming to evaluate vaccine effectiveness hence, vaccine efficacy is the parameter which is usually measured in clinical trials. For evaluating a new vaccine, the protective efficacy of the vaccine against the target disease in humans is assessed.

Vaccine efficacy is the reduction in the chance or odds of developing clinical disease after vaccination relative to the chance or odds when unvaccinated. Efficacy of vaccines measures directly the protection induced by vaccination in the vaccinated population sample.

Efficacy is calculated as per the formula:

$$VE = (I_u - I_v)/I_u * 100$$

where $I_u$ = Incidence in Unvaccinated Population

$I_v$ = Incidence in Vaccinated Population

Two general approaches can be applied to assess vaccine efficacy; they can be:

- Experimental studies
- Observational studies.

## Experimental Studies

These are the studies which involve the investigator intervention by introducing some form of treatment to affect the outcome.

Randomized controlled trials (RCT) are the gold standards for the experimental or interventional studies. It is the method to assess both the association between vaccination and immune markers, and the association between markers and clinical end-points. The subject is allocated randomly to either receive the test vaccine in comparison to another vaccine that acts as a comparator or to placebo.

The comparator (a conventional vaccine already approved for the prevention of the disease) or placebo is called as the control group; therefore the name Randomized controlled trials. The choice and feasibility of blinded, randomized controlled trials depends on the vaccination strategy and on the demographic and epidemiological characteristics of the study population.

The following approaches may be used:

- Prospective cohort studies for population-based vaccination strategies
- Pre-exposure cohort studies in groups at risk of the target infection (e.g. vaccination for travellers).

Advantages of RCTs include:

- Avoid bias in dividing the trial subjects to one of the study groups
- It permits statistically valid comparisons to be made between different arms of a study
- It allows the detection of small differences between vaccines and comparators; this is particularly important when an active control is used
- RCTs may provide an early indication of likely long-term protection and the need for booster vaccination(s).

A double-blinded evaluation of disease outcome minimizes potential ascertainment bias and, therefore maximizes the chance that a difference in disease incidence observed between two equivalent groups is due to a true effect of the vaccine being evaluated. The unit of randomization is usually the individual included in the trial and this is ideally the unit of statistical analysis. In some situations, randomization is also done on the basis of clusters or groups, e.g. school, geographical or political region. It is important to specify the randomization procedures and to adhere to them. Failure to do so may lead to biased results. Generally, late phase clinical studies follow randomized controlled approach. Every effort should be made to use randomized well-controlled designs for phase III trials. However, such studies can be technically difficult and the decision to undertake them should be made on a case-by-case basis.

Types of randomization generally used in randomized controlled trials:

- ***Stratified randomization:*** The subjects are stratified by one or more of the important factors (for example stratified on the basis of demography) and a separate randomization list is used in each stratum.

- Stratified randomization prevents imbalance between treatment groups for known factors that influence prognosis or treatment responsiveness. As a result, stratification may prevent type I error and improve power for small trials (<400 patients), but only when the stratification factors have a large effect on prognosis. Stratification has an important effect on sample size for active control equivalence trials, but not for superiority trials.[5]
- ***Block randomization:*** The subjects are allocated in small blocks that usually consist of two to four times the number of groups. The subjects in each block are randomly assigned so that there are equal numbers in each group.
- ***Cluster randomization:*** The randomization is done on the basis of clusters or groups, e.g. school, geographical or political region.

  Randomization of groups or clusters rather than of individuals is preferred in the following situations:

  (a) When a vaccination program is to be conducted in a geographical area or community
  (b) When it is logistically easier to administer the vaccine to groups than to individuals
  (c) When the purpose of the vaccination is to reduce transmission of the infection, where the unit is the "transmission zone" (the area in which humans, vectors and intermediate hosts interact and share a common pool of pathogens).[4]

### Safety Evaluation in RCTs

When safety is the primary end-point in a clinical trial, the adverse event or reactogenicity (local or systemic) considered to be of primary importance should be the major focus in RCT study design. The safety profile should be representative of, and predictive for, the target population for which the vaccine is to be used in practice. For determining safety, the study must have sufficient power to provide reliable rates of common (>1/100 and <1/10) adverse events, and to detect less common, but not necessarily very rare (<1/10,000) adverse events. For evaluation of common local reactogenicity, approximately 300 subjects are selected for each comparison group. However, enrolment of more than 5000 subjects is generally done depending on the type of vaccine, the disease indication, and the target population; to provide reasonable assurance of safety prelicensure in RCTs settings. These numbers are based on a one-sided confidence interval when no adverse events are observed. They increase if one adverse event is observed. The investigation of uncommon or rare events already occurring in the study population requires long-term prospective population based surveillance studies.[4]

The efficacy of a new vaccine can most convincingly be demonstrated in a randomized, double-blind, placebo-controlled trial based on a clinical disease end-point. The placebo can be an inactive product or a vaccine for a different disease, believed to be ineffective in preventing the disease of interest.

This type of trial is called a superiority trial, because the vaccine must be sufficiently superior in efficacy to the placebo to be acceptable. High specificity of case definition is desired in superiority trials. The aim of these trials is to estimate efficacy with both a point estimate and the corresponding confidence interval (usually 95%). The sample size chosen for these trials depends on disease incidence rates in the study population, and on the anticipated level of efficacy of the vaccine that is considered to be clinically relevant.

There are, however, situations in which vaccine efficacy cannot be determined from cases of disease. For example incidence of a disease in a population may have been reduced to very low levels by widespread immunization with a previously licensed vaccine. When the serological parameters are known to correlate with clinical protection, evaluation of a new vaccine for the same disease is based on measures of the vaccine's immunogenicity. One or more immune response outcome variables thus serve as "surrogates" for determining efficacy. Since the comparator in this setting is typically the already-licensed vaccine, evaluation of the new vaccine is based on establishing its "noninferiority" to the licensed vaccine. Statistical inference of noninferiority is based on the appropriate confidence interval excluding a prespecified difference in immune response believed to be clinically meaningful. The size of sample required for establishing non-inferiority of immune response depends upon the variability in the immunogenicity measurements and on the level of efficacy of the comparator vaccine.

### Sample Size in RCTs

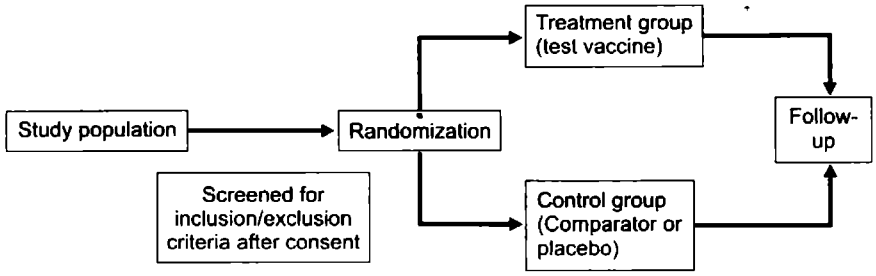
The number of subjects participating in a clinical trial must be sufficient to provide a reliable answer to the questions posed. The sample size in a trial of vaccine efficacy should be large enough to allow precise interval estimation of efficacy. Sample size is usually determined by the primary end-point chosen. Generally, the sample size should be large enough to ensure that the lower confidence limit for efficacy will be considerably greater than zero. A sufficiently high lower confidence limit is desirable to ensure a minimal level of vaccine efficacy.

The protocol of RCT should clearly explain calculations of sample size required for each primary end-point (immunogenicity, safety and efficacy) and the largest estimate should determine the number of subjects to be enrolled.

### Sample Size in Noninferiority/Equivalence Trials

The sample size should be such that, if a new vaccine is truly noninferior, there is a high probability that the appropriate confidence interval for the relative effect of interest will not exceed the predefined noninferiority criterion. Alternatively, for equivalence trials, there should be a high probability that both the upper and lower confidence intervals will fall within the predefined upper and lower equivalence margins. Methods of sample size calculation

**Flow chart 7.1:** Randomized controlled trial




specially designed for noninferiority/equivalence trials should be used. Noninferiority trials of vaccine efficacy based on clinical outcomes usually require much larger samples than placebo-controlled superiority trials or noninferiority trials based on immunogenicity measurements.[4]

Undersized superiority trials that give nonsignificant results will not generally allow any conclusions to be made regarding noninferiority or equivalence.

The criteria underlying the determination of sample size are based on methodological and statistical considerations, as well as on epidemiological and scientific judgment. Factors to be taken into account include the expected incidence of the disease and its prevalence (endemic spread, epidemic spread, or low-incidence disease). These factors may vary from product-to-product and from one setting to another.

The efficacy of the vaccine in the trial population is measured with the help of biomarkers that can be correlates or surrogates of protection (Flow chart 7.1).

A Biological Marker or Biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[6]

A biomarker changes due to disease, exposure to chemicals, or exposure to organisms. Biomarkers have always been important in clinical development and provide the most practical means of demonstrating that a candidate vaccine is safe and effective in a disease target population. Biomarkers in vaccine clinical trials phase I/II settings are used to evaluate efficacy and develop dose response relationship in and they generally help in stratifying study populations, select or deselect patients for inclusion in trials, conducting interim analysis of efficacy/safety and toward regulatory approval in phase III settings. Examples of biomarkers include safety biomarkers such as serum creatinine and blood chemistries, CBC, CXR, ECG; pharmacodynamic (efficacy) biomarkers such as blood glucose levels, urine or sputum cultures, pulmonary function tests, etc.

## Correlates of Protection

Correlates of protection are also useful, and are required for situations in which the conduct of clinical trials using prevention of disease as an end-point cannot be practically or ethically justified. Nevertheless, it is important to recognize that correlates of protection may be difficult or impossible to define.[4]

The following section describes a simple definition of correlates of protection. Immune correlates of protection can be population-based or individual-based.

Correlates of protection to an infectious organism are measurable signs that a person (or other potential host) is immune, in the sense of being protected against becoming infected and/or developing disease. A correlate of protection in vaccine efficacy trials is generally a laboratory parameter that has been shown from adequate and well-controlled trials to be associated with protection from clinical disease. An immunological correlate of protection is most useful if clear qualitative and quantitative relationships can be determined, e.g. a certain type and level of antibody correlate with protection.

A commonly used measure of population-based correlates of protection requires the identification of a level of antibody that is achieved by most of the subjects in a protected group (i.e. vaccinated) and is not achieved by the majority of a susceptible group (i.e. unvaccinated). The level of protection correlated with the antibody level of vaccinnees is the vaccine efficacy measured in the randomized controlled trial. For a population-based correlate it is only necessary to measure immunogenicity in a representative and statistically adequate sample of the vaccinated and unvaccinated phase III cohort.

The individual-based correlate of protection involves the measurement of preimmunization and at least one postimmunization antibody level(s) in all study subjects and relating this to whether they subsequently develop the disease. The objective is to identify a threshold level in a vaccine that predicts protection. For an individual-based correlate, it is necessary to measure postimmunization antibody levels in the entire study cohort.

Correlates of protection can be classified as:[7]

- *Absolute correlate:* A quantity of a specific immune response to a vaccine that always provides near 100% protection
- *Relative correlate:* A quantity of a specific immune response to a vaccine that usually (but not always) provides protection
- *Cocorrelate:* A quantity of a specific immune response to a vaccine that is one of two or more correlates of protection and that may be synergistic with other correlates.

We should understand that the correlate of protection induced by vaccination is not necessarily the same correlate that operates to close off infection. An excellent example of this principle is explained in a study

conducted by Chen S et al on measles vaccine. He showed that titers ≥ 200 mIU/ml of antibody after vaccination are protective against infection, whereas titers between 120 and 200 mIU/ml protect against clinical signs of disease but not against infection. Titers <120 mIU/ml are not protective at all.[8]

Examples of licensed vaccines with an identified correlate of protection are Hepatitis B, *Haemophilus influenzae* type b, diphtheria vaccine etc. However, identification of correlate is not always a requirement for licensure. For example, licensed vaccines without an identified immune correlate of protection are pertussis, typhoid and tuberculosis (BCG).

*Surrogate end-point* is a biomarker such as laboratory measurement or a physical sign intended to substitute for a clinical end-point. A surrogate end-point is expected to predict clinical benefit (or harm, or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.

A surrogate is especially useful if it is easily measured and highly correlated with the true end-point. Often the 'true' end-point is one with clinical importance to the patient, e.g. mortality or a major clinical outcome, while a surrogate is one biologically closer to the process of disease. In vaccine clinical trials, it is often not possible to perform the studies resulting in clinical end-point such as existence of infectious disease in subjects or the time duration to attain the clinical end-point is very large in the trial setting. Use of the surrogate can often lead to dramatic reductions in sample size and much shorter studies than use of the clinical end-point. Changes induced by a therapy on a surrogate end-point are expected to reflect changes in a clinically meaningful end-point.[9]

The primary surrogate markers to monitor vaccine efficacy have been either the antibody titer to vaccine antigens or the measurement of antibody function such as anti-viral neutralizing activity or in pertussis vaccine, proportion of subjects achieving seroresponsiveness to pertussis is generally measured. In recent years, the measurement of T-cell function in conjunction with or independent of antibody measurements have been used to assess vaccine efficacy.[10]

Immune responses should always be evaluated as part of a phase III clinical protection study with the aim of identifying immunological correlates of protection. For such an evaluation to be clinically meaningful, validated standardized assays are essential. Methods for the validation and standardization of immunological (antibodies and cell mediated) correlates of protection should be developed and are vital for ensuring comparability of data between one trial and another. To correlate humoral immune responses to a vaccine with protective efficacy, the qualitative and quantitative relationships should be determined.

Many immunogenicity studies of vaccines where the primary or secondary end-point is to determine the efficacy of the vaccine in a subject population employ randomized controlled trials.

Vaccine immunogenicity studies are generally classified into the following categories which are briefly outlined below.

### *Superiority Immunogenicity Study*

The objective of these Immunogenicity studies is to assess the superiority of immunogenicity of the vaccine under study as compared to a placebo or control. Superiority Immunogenicity studies are often conducted in early phases of vaccine development, which can also be performed to claim superiority of one vaccine as compared to another from a different manufacturer with respect to immune responses.[11] The purpose of these trials is to estimate the percentage reduction in the incidence rate of disease due to use of the vaccine. The point estimate of this percentage reduction can be obtained by various methods: As a ratio of risks, incidence rates, or hazards.[4]

### *Noninferiority Immunogenicity Study*

A noninferiority vaccine immunogenicity is designed to show that the use of a new vaccine gives a relative risk, relative incidence rate or relative hazard rate of a disease, infection, etc. when compared to the control, is not greater than a prespecified clinically relevant quantity.

In a noninferiority trial based on immune response, the relative effects of interest are

- Difference in proportions of subjects responding in a prespecified manner The trial for the same is designed to show that the proportion of subjects responding to the new vaccine is not less than the proportion of subjects responding in the control group by as much as a prespecified quantity (often 0.10)
- Ratio of geometric mean titers (GMT) or concentrations. For the evaluation of titers, the trial is designed to demonstrate that the ratio of the geometric mean titer (or concentration) of the new vaccine relative to the control is not less than some prespecified ratio.

### *Dose-response Immunogenicity Study*

During the development of a new vaccine, dose-response immunogenicity studies are often conducted to assess the immunologic responses across different dose levels of the vaccine. Generally phase II RCTs determine the dose response relation to different doses of candidate vaccine. An established dose response can help in determining the minimum effective dose and the safe dose. In addition, dose-response studies are useful in studying the kinetic of potency decay and in determining the release and end-expiry dose level and shelf-life of the vaccine.

### Two-sided Equivalence Trials/Consistency Lots Study

A two-sided equivalence trial, such as might be used to compare two vaccine lots, is designed to show that the outcome measure for one group is similar in both directions to that for another group. The reason that the evaluation of lot consistency is inherently two-sided is that there would be concern if an outcome measure for one lot were either too high or too low when compared to another lot. Such a finding might suggest that the two lots are not similar enough to be considered to be consistently manufactured. The lots are considered equivalent, or consistently manufactured, when a two-sided confidence interval for the appropriate effect for example ratio of geometric mean antibody concentrations or relative risk of adverse event falls entirely within pre-specified limits.[4] Before a vaccine can be licensed, the regulatory agencies require that evidence of clinical consistency in at least three lots of vaccine from the same manufacturing process be provided. Generally, vaccines from three consistency lots and a control vaccine are used for a typical clinical consistency lots study.[12]

### Bridging Study

These are the studies intended to support the extrapolation of efficacy, safety and immunogenicity data from one formulation, population, and dose regimen to another. The end-points for clinical bridging studies are usually the relevant immune responses and clinical safety parameters. The nature and extent of a bridging study are determined by the likelihood that vaccine efficacy may vary according to ethnic factors, manufacturing changes or changes in dosing schedule. An immunogenicity bridging study is usually designed as a noninferiority trial aimed to exclude a clinically significant difference in the immune response between the modified vaccine and the current vaccine.

### Combination or Multivalent Vaccine Study

A combination vaccine is defined as a vaccine that consists of two or more live organisms, inactivated organisms, or purified antigens combined either by the manufacturer or mixed immediately before administration (FDA, 1997). A combination vaccine is intended to prevent multiple diseases or to prevent one disease caused by different strains or serotypes of the same organism. Once the serological correlates of protection have been validated for each of the antigenic components, the efficacy of a new combination vaccine consisting of components already licensed and/or components with proven efficacy is evaluated using immunogenicity end-points.

Studies of combination vaccines are usually designed and analyzed (for efficacy or immunogenicity) as noninferiority trials, the aim being to demonstrate that the combination is comparable with the individual components. For establishment of efficacy of a combination vaccine, the

immunogenicity of all vaccine components in the combination or multivalent vaccine should be performed to rule out clinically significant differences in immune response rates and/or GMTs between the combined vaccine and the separate but simultaneously administered antigens.

### *Immunological Persistence Study*

The impact of a particular vaccination schedule is evaluated by the primary outcome measure of the clinical trial. In principle, all vaccines under development need a long-term evaluation plan. In most confirmatory clinical trials, this implies a follow-up period of at least 6 months subsequent to the last vaccination. However, this will depend upon the outcome measurement chosen (i.e. clinical end-point, immunogenicity or safety), the vaccination strategy and the novelty and/or type of the vaccine. Long-term follow-up is undertaken for the whole study population or in a relevant subset. In practice, it is recognized that the duration of vaccine-induced immunity will be considerably longer than the time span of the clinical studies. Thus, immunological persistence study is often conducted to collect data regarding immune responses over multiple years. Life table or time-to-event data analysis is then used to assess the cumulative immunological persistence rate for determination of long-term immunological persistence.[11]

## OTHER DESIGN FOR EFFICACY STUDIES

The designs other than double-blind randomized-well controlled trials to provide efficacy data are used only when fully justified. Several alternative types of study depending upon the incidence and epidemiology of the disease of interest, the characteristics of the population and the expected efficacy of the vaccine or prophylactic agent are considered. The possible alternative approaches include:

- Observational studies
- Secondary attack rate study, or household contact study (which can be randomized).

### Observational Studies

Observational studies of efficacy or effectiveness are usually part of phase IV post licensure studies. In observational studies, the investigator "observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice. Observational studies allow nature to take its own course; the investigator measures but does not intervene.

Observational studies are used primarily to identify risk factors and prognostic indicators and in situations in which randomized, controlled trials would be impossible or unethical.[13]

Phase IV clinical studies are generally set up as observational cohort or case control studies. Observational studies have several advantages and disadvantages (Tables 7.1 and 7.2).[14]

**Table 7.1:** Advantages of observational studies

- There are fewer restrictions on number of subjects/patients enrolled in the study. Often >30,000 patients are enrolled
- Since the number is large, the rare adverse events associated can be predicted
- Many outcomes can be studied together
- Greater timelines can be selected
- More relaxed inclusion or exclusion criteria as patients are enrolled without 'controlling' the therapy beyond normal medical practice
- Lower cost in retrospective studies
- Less affected by ethical considerations than RCTs if only using data that have already been collected in routine clinical practice.

**Table 7.2:** Disadvantages of observational studies

- Since there is no randomization, it may lead to potential bias
- If data have been collected for a reason other than the observational study, it is unlikely that all relevant information will have been rigorously collected
- If prospective, can be expensive
- Potential for confounding variables (i.e. inability to control for all other factors that may vary between two groups).

Observational studies can be prospective or retrospective. These types of studies are subject to different forms of bias (information and selection). In prospective studies, investigators recruit subjects and observe them prior to the occurrence of the disease outcome. Prospective observational studies compare the incidence of a disease with exposure to the substance. In retrospective studies, investigators review the medical records of subjects and/or interview subjects after the disease has occurred. Retrospective studies are particularly vulnerable to measurement error and recall bias because they rely on subjects' recollections of what they consumed in the past.[15]
Various types of observational studies include:

- Case control study
- Cohort study
- Ecological study
- Natural history study.

### *Case Control Study*

Case control study as an observational study in which the exposure to a particular risk factor (the vaccine in the case of vaccine studies) is determined retrospectively, and the effect of this exposure is compared between individuals (the cases) who experience an event (the disease, in vaccine studies) and individuals who do not (the controls).

The controls provide an estimate of the baseline or expected amount of exposure in that population. If the amount of exposure among the case group is substantially higher than the amount you would expect based on the control group, then disease is said to be associated with that exposure.

These studies are done to compare potential substitute end-points between subjects who developed the clinical outcome and those who did not.

A case control study was documented by Grassly et al[16] where efficacy of mOPV1 used in supplementary immunization activities from 2076 matched case-control pairs of confirmed cases of poliomyelitis caused by type 1 wild poliovirus and cases of non-polio acute flaccid paralysis in India was estimated. The effect of the introduction of mOPV1 on Indian population immunity was calculated on the basis of estimates of vaccination coverage from data for non-polio acute flaccid paralysis. In areas of persistent poliovirus transmission in Uttar Pradesh, the protective efficacy of mOPV1 was estimated to be 30% per dose against type 1 paralytic disease, compared with 11% for the trivalent oral vaccine. 76–82% of children aged 0–23 months were estimated to be protected by vaccination against type 1 poliovirus at the end of 2006, compared with 59% at the end of 2004, before the introduction of mOPV1.

### *Cohort Study*

Cohort study may also be called as a 'follow-up' study and is similar in concept to the experimental study.

It is a retrospective or prospective study in which the development of a disease or infection, or any other relevant event, is observed over time in a defined group of subjects.

In a cohort study the observer records whether each study participant is exposed to a vaccine or not, and then tracks the participants to see if they develop the disease of interest. This kind of a study is different from an experimental study because in a cohort study, the investigator only observes but does not determine the participants' exposure status. For follow-up at a time interval, the investigator compares the disease rate in the vaccinated and unvaccinated group. The unvaccinated group provides an estimate of the baseline or expected amount of disease occurrence in the community. If the disease rate is substantially different in the vaccinated group compared to the unvaccinated group, the exposure is said to be associated with illness.

The length of follow-up varies considerably. In an attempt to respond quickly to a public health concern such as an outbreak, relatively brief studies are carried out.[17]

Observational cohort studies in a clinical program for marketing approval are considered in those unusual situations in which a double-blind randomized controlled trial is not ethically justified or where the clinical end-point requires long-term follow-up (e.g. hepatitis B vaccination in neonates), or where the number of individuals is too large to follow-up.[4]

Cohort study was documented by Dine MS et al.[18] To examine the persistence of vaccine-induced antibody, participants of a vaccine study in 1971, with documentation of antibody 1–7 years after vaccination, were followed up in 1997–1999 to determine the presence and titer of measles antibody. Of the 56 participants (77% were 2-dose recipients), all had antibodies detected by the plaque reduction neutralization (PRN) antibody assay an average of 26–33 years after the first or second dose of measles vaccine; 92% had a PRN titer considered protective (>1:120). Baseline hemagglutination inhibition antibody titer in 1971 strongly predicted follow-up PRN antibody titer (P<.001). The author concluded that persistence of antibody in these primarily 2-dose recipients supported the current elimination strategy to achieve and sustain high population immunity with a 2-dose schedule.

### *Ecological Study*

Ecological studies are the type of observational studies where associations are assessed using different population groups, not at the individual level. For example, examining differences in disease rates between counties. Ecological studies are more prone to bias as there is no information about exposures experienced by the individuals in the group.

Example to provide more clarity on Ecological study is listed below:

Immunogenicity data for the pertussis components of the French diphtheria-tetanus-two component acellular pertussis vaccine (DTaP(2Fr)) obtained after primary series of immunizations were compiled from 75 study groups comprising 36 clinical trials or vaccination programs conducted between 1987 and 2006 by Vidor E et al.[19]

The clinical trials were conducted in 17 countries [Western Europe (France, UK, Germany, Spain, Belgium, Italy, Sweden), Central Europe (Turkey), North America (USA), South America (Chile, Argentina), Africa (Sénégal, South African Republic), and South East Asia (Vietnam, Thailand, Philippines, India)].Overall, these trials included nearly 10,000 subjects.

DTaP(2Fr) vaccine was administered either as a standalone vaccine or as the backbone of several combination vaccines that included IPV, HepB and/or PRP-T antigens. Most of the variability in responses was associated with differences in the schedules, and to a lesser extent the geographical region where the study was performed, suggesting the importance of ethno-ecological factors. However, the addition of other vaccine antigens did not affect the immunogenicity of the aP(2Fr) antigens. The immune responses to the PT and FHA antigens of the DTaP(2Fr) vaccine used in the Sénégal efficacy trial, which established its good efficacy relative to a highly effective DTwP vaccine, was in the middle of the range of titers observed during other studies using the 2–4–6 months schedule conducted with the same vaccine. The study concluded that the consistent immunogenicity of the DTaP(2Fr) vaccine is accompanied by effectiveness in controlling pertussis disease in the areas where it is used on a large scale with good vaccination coverage.

### *Natural History Study*

The course and outcome of the disease is followed up in individuals and groups in natural history studies. This kind of observation study of vaccines follows up individuals who developed infections and recovered later, in order to analyze the components of their immune response after recovery.

*Example of natural history study:*
Forty five previously infected subjects (23 chickenpox, 22 vaccinated) were tested for their varicella zoster virus (VZV)-specific antibody levels and for their lymphocyte stimulation responses to VZV antigen by Ndumbe et al.[20] Antibody was measured by both an enzyme-linked immunosorbent assay (ELISA) and an immunofluorescence assay (IF), while lymphocyte stimulation was detected by tritiated thymidine incorporation. Antibody was tested in 10 post-chickenpox and 9 vaccinated subjects. About 6 to 8 weeks after first exposure, the magnitude of the responses determined by both ELISA and IFT were much higher in the naturally infected than in the vaccinated group (P less than 0.001) with both test methods). There was no significant difference in the lymphocyte transformation responses in both groups of subjects. Thirteen post-chickenpox and 13 vaccinated subjects who had been infected at least 12 months previously were also tested. Total antibody levels were again significantly higher in the naturally infected than in the vaccinated group (P less than 0.001). One vaccinated subject had VZV-specific IgA and IgM in the serum. The magnitude of the lymphocyte transformation reaction was higher in the naturally infected than in the vaccinated group (P less than 0.01). Thus, the author concluded that antibody responses to VZV were better in naturally infected than in vaccinated subjects.

### *Secondary Attack Rate Study*[4]

A secondary attack rate study is a specific type of pre-exposure cohort trial that usually requires smaller sample sizes than other randomized controlled trials. This is the method of choice in studies of infections with a relatively high secondary attack rate in closed communities and/or susceptible populations. The unit to which the intervention is applied can be the individual, family (household) or community (environment) and the unit of randomization will correspond with this.

Data regarding the presence of infecting pathogens and their attack rates are essential in this kind of study. The follow-up period for subjects after contact with the index case can be short; but it should cover the assumed incubation period and infectious period of the index cases and secondary contacts. The inclusion period for new cases and controls and their contacts are set at a maximum of 6 months following the detection of the first case. Inclusion over a longer period may introduce bias in favor of vaccine efficacy, because the exposure to the infecting pathogen and thus the risk of infection will be reduced in the vaccinated groups or clusters compared with that in unvaccinated groups or clusters.

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# CHAPTER 8 Clinical Development of Anticancer Molecules

## INTRODUCTION

Around the world, tremendous financial and scientific resources are being invested in prevention, diagnosis, and treatment of cancer. Cancer is the second leading cause of death in Europe and North America. Discovery and development of anticancer agents are the key focus of several pharmaceutical companies as well as nonprofit government and nongovernment organizations, like the National Cancer Institute (NCI) in the United States, the European Organization for Research and Treatment of Cancer (EORTC), and the British Cancer Research Campaign (CRC).[1,2]

Traditionally, anticancer drug development has focused on DNA as a target, based on the fact that a high turnover of nucleic acid in cancer cells will provide a therapeutic margin. But the recent growth in molecular sciences and the advances in genomics and proteomics provide a better understanding of molecular basis of cancer and the use this information to discover and validate several potential new drug targets, leading to changes in the paradigms of anticancer drug discovery.[3] These shifting paradigms have not only resulted in the greater involvement of biological scientists in the drug discovery process but also required changes in the screening and clinical evaluation of drug candidates.

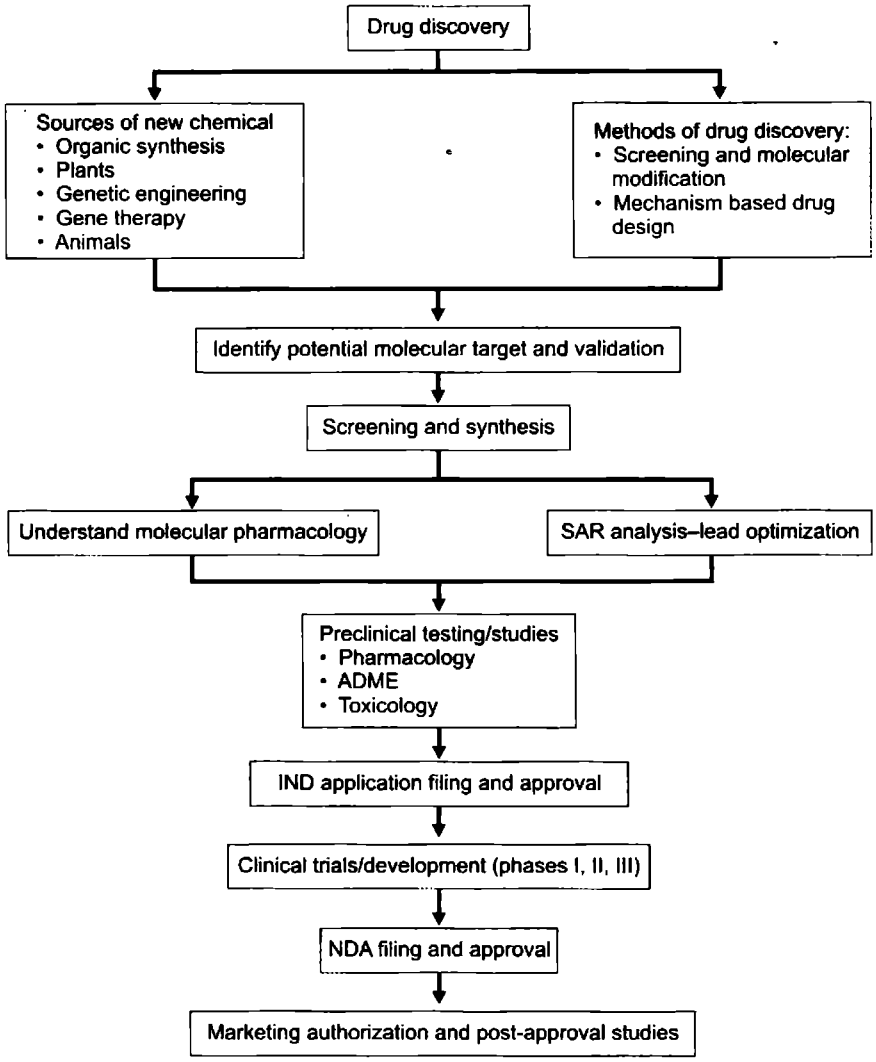
The new drug discovery and development process is typically divided into three major steps:

- Discovery
- Preclinical development
- Clinical development.

The transition from discovery to preclinical development is a continuum, and results of preliminary pharmacology and toxicology testing often contribute to lead drug candidate selection. The boundary between preclinical development and clinical trial is sharply defined by the filing of an investigational new drug (IND) (refer Table 8.1) application, which is required prior to initiation of the clinical trial.[4,5] The activities supporting an IND application are the subject of this chapter.

In this chapter we have presented the logical flow (Flow chart 8.1) of events from identification of cancer specific target to IND application and the molecule's development plan.[6]

**Flow chart 8.1:** Development process




## SOURCE AND TARGET IDENTIFICATION

Historically, drug for the treatment of cancer were discovered through testing of the cytotoxicity of compound on whole cells, organ(s). Whereas in modern times anticancer drug discovery typically starts with the identification of a molecular target either a protein or its RNA and DNA precursors.

Cancer cell differ from normal cells by following characteristics:

- Their ability to proliferate due to self-sufficiency in growth signals
- Insensitivity to growth inhibitory signals

- Evasion of apoptosis and senescence
- Timeline replicative potential
- Sustained angiogenesis and potential to invade tissue and metastasize.

The current strategy of controlling tumor growth selectively is to develop drugs that interfere with target, important in tumor angiogenesis, tumor invasive, tumor metastasis and cell cycle control apoptosis. Selection of individual target for drug discovery is usually based on information obtained from the academic literature and unpublished original research.[3]

Some of the ways for identification and validation of targets include:

- Indication of pathological deregulation, that is mutation or over, under expression in disease
- Confirmation of adverse clinical outcome correlating with the particular target locus
- Formation of a malignant phenotype by mutation or increasing or decreasing expression of proposed target
- Reversal of a malignant process by correcting the genetic abnormality, e.g. knockout, RNA interference, transfection, etc.

The evaluation of high throughput mutation screening and gene expression analysis will add to already large number of targets that are the focus of new anticancer drug development. Once a target has been validated, it can be inducted into the drug discovery process that includes screening, lead optimization, preclinical and clinical studies.[3]

## SCREENING OF ANTICANCER AGENT

There has been a positive change in the screening of new anticancer agents. Over the period of time, a general transition has been observed from the empirical drug screening of cytotoxic agents against uncharacterized tumor models to the target-orientated drug screening of agents with defined mechanisms of action.[7,8]

Commonly, the US National Cancer Institute (NCI) *in vitro* 60-cell line panel, hollow fiber assay, and subcutaneous xenografts are used for screening of anticancer agent.[9]

The aim of screening effort is to identify all the products that will produce antitumor effect matching the activity criteria already defined for taking the compound to the next stage in the preclinical development program. As we all aware about the fact that drug development is an expensive and lengthy process, hence one should select the screening method considering simplicity, swiftness, costeffectiveness and at the same time it should also be indicative of pharmacodynamic activity. Anticancer drug screening can be performed using various type of *in vitro* and *in vivo* tumor models.[7]

### The National Cancer Institute (NCI) Screen

In this unique screening method, the compound is tested against 60-cell line panel and dose response produced by given compound results in a biological response pattern. Further, this data would help in pattern recognition algorithms (i.e. COMPARE program. See: http://dtp.nci.nih.gov/docs/compare/compare.html).[10] Compare is the computer program and uses a simple algorithm for comparing the patterns of cellular responsiveness for each compound against the extensive database that has constructed from the large number of past agents tested in the screen. Using these algorithms, it is possible to presume mechanism of action of a test compound, or to determine that the response pattern is unique and not similar to that of any of the standard prototype compounds already exists in the NCI database. After this kind of agents are then tested against the sensitive cell line grown as subcutaneous xenografts in nude mice *in vivo*.[9-11]

Later, in review of database it has been found that a large number of agents tested against cell lines are inactive, hence the need for a method by which compound activity can be tested in short time.

Therefore, a three-cell line panel using three highly sensitive cell lines, MCF-7 (breast carcinoma), NCI-H460 (lung carcinoma), and SF-268 (glioma) has been introduced. The main advantage with using this prescreening method is to eliminate the inactive compound early and consequently it prevents from unnecessary and costly full-scale evaluation in the 60-line panel.[7]

Three end-points are used to determine compound activity and whether a compound will be considered for further evaluation. These are as follows:

1. $GI_{50}$ (concentration required to inhibit 50% of cells), total growth inhibition.
2. $LC_{50}$ (concentration required to kill 50% of cells).
3. Compounds, possessing disease specificity or that are COMPARE-negative, are also qualified for secondary *in vivo* screening.

The present human tumor cell line *in vitro* screen is technically simple, relatively fast, cheap, reproducible, and provides valuable indicative data of mechanistic activity and target interaction. However it also has some limitations. *In vitro* methods are susceptible to false-positive and false-negative results.

### Conventional Cellular Screen

The cellular screens mainly permanent human tumor cell lines are used for their everlasting nature and consequently controllable, reproducible growth behavior makes them suitable test systems. However, choice of detection method depends on the number of cell to be used and desired sensitivity. A variety of processes to determine cell growth are being used in screening laboratories. Initially, mostly used growth inhibition assays were developed

by Mossman and the NCI screening staff, specifically, the methylthiazoldiphenyl tetrazolium (MTT) assay. The yellow MTT dye reduced mitochondria into a purple formazan, which can be read with ultraviolet/visible light scanner. Its limitations are the use of large quantities of hazardous solvent, diethyl, which is required to dissolve the resulting formazan crystals and the varying number of mitochondria in cells.[7]

### Biochemical Screening Assays

Biochemical assays compared to cellular assays are "target-driven" and provide the means for evaluating high numbers of compounds. These screens are primarily employed in the pharmaceutical industry and institutions that harbor large compound libraries for systematic search of novel agents.[7,8]

An important advantage of biochemical screens is that they can be fully automated; thus, most steps can be performed by robot or computer systems such as dispensing of targets, addition of drugs and detection reagents, as well as compound library storage and management. Key requirements for target-oriented screening are:

1. The molecular target must be validated and is shown to be causally linked to disease initiation or progression.
2. The target required for *in vitro* assays must be made available in large quantities, may be by using recombinant DNA techniques.
3. Defined, pure compound libraries comprising hundred of thousands of structures derived from combinatorial approaches or collections of natural substances should be available.
4. Simple, cost-effective, highly reproducible assay and detection systems, which can be performed in microplate formats.

### Combination of Target and Cell Screen

Both cell and target-based screening procedures have clear advantages and disadvantages, while cell-based approaches will overlook the agents with certain defined modes of action.

They might, on the other hand, identify compounds as active with previously unknown targets and therefore allow for identification of novel mechanisms of action as well as the illumination of their interaction in certain pathways.[7]

Another advantage of compounds identified in cellular screens are their proven cell-permeable properties, which might be missing in a cell-free systems. In addition, ligand interactions might be more appropriate in the biological environment.

Considering these facts, a combination of rational biochemical and "more" empirical cellular screening systems would therefore be the most optimal methodology in new cancer drug discovery.

## Screening *In Vivo* Model

One of the key criteria for the strength of screening programs is their predictiveness of clinical response. Unfortunately, these analysis are very time consuming, as the process of preclinical and clinical development requires several years. As per reports on the correlation between compound efficacy against transplanted tumors and clinical activity was significantly better than the previously used mammalian cell and model organism (bacterial cultures). Therefore, the *in vivo* models are considered to be better indicators for evaluation of antitumor activity of molecule.[8]

### *Xenografts*

Xenograft tumors are generally established by the Sub cutaneous (s.c) inoculation of tumor cells into nude mice ($1.0 X10^7$ cells per mouse). Growth of solid tumors is determined using *in situ* caliper measurements irrespective of early or advanced stage. Generally, in xenograft the compound activity is determined by factor like tumor growth delay, optimal percent of T/C (T/C median treated tumor mass/median control tumor mass) or net log cell kill. For toxicity, the drug-related deaths and loss in body weight are used.[7-9]

### *Hollow Fiber Assay*

The hollow fiber assay involves the short-term *in vitro* culture (24-48 hours) of a panel of 12 cell lines inside hollow fibers, followed by *in vivo* implantation at both subcutaneous (s.c.) and intraperitonial (i.p.) sites of the nude mouse. The assay has potential to simultaneously evaluate compound efficacy against a maximum of six cell lines (three cell lines/fibers per site). Generally, the mice are treated with test compound at two different doses for up to 4-days, fibers excised and analyzed for cell viability using a modified MTT assay. In this method based on scoring system and optimal or near optimal treatment regimens compounds are considered active. This further confirms that the compound warrants further testing using xenograft model.[7,8]

### *Colony-forming Assay*

Another combined *in vitro/in vivo* testing procedure is the soft agar colony-forming assay, also termed tumor clonogenic assay (TCA). The TCA can either be used for sensitivity screening of patient tumor material *in vitro* predicting direct clinical response, or with fresh xenograft tissue for selecting the most appropriate *in vivo* model.

The assay was disease-orientated in concept and involved the growth on soft agar of colonies derived from freshly explanted human tissue. Compounds were tested against tumor colonies and activity defined by the growth inhibition of colonies. Salmon and colleagues compared *in vitro* results to the clinical responses of myeloma and ovarian cancer patients and the study showed clear correlations and unique patterns of sensitivity and

resistance. This study showed sufficient promise to warrant larger-scale testing to determine the efficacy of the assay for selecting clinically active agents and individualizing cancer treatment.[7,8]

However, the major limitation with this method is lack of reproducibility (unique sample material) and the elaborative assay procedure results in restriction of its application.

## IMPORTANCE OF BIOMARKERS IN ANTICANCER DRUG DISCOVERY

Biomarkers, typically genetic or biochemical parameters are used as characteristic indicators to measure outcomes. They have assumed increased importance in assessing drug toxicity effects in compound screens, in diagnostic assay development, and in clinical evaluations to monitor therapy and prognosis.[12]

Over recent years the role of biomarkers in anticancer drug development has expanded across a spectrum of applications ranging from research tool during early discovery to surrogate end-point in the clinic.

Tumor markers are endogenous proteins or metabolites whose amounts or modifications are indicative of tumor state, progression characteristics, and response to therapies. They are present in tumor tissues or body fluids and encompass a wide variety of molecules, including transcription factors, cell surface receptors, and secreted proteins. Broadly, cancer biomarker can be classified in following categories.

### Diagnostic Biomarker

Diagnostic biomarker is used to detect and identify a given type of cancer in individual. This type of biomarker is expected to have high level of diagnostic sensitivity and specificity especially if it is used in large screening trial.

### Prognostic Biomarker

Prognostic biomarker is commonly used, once the disease status has been established. They expect to predict the likely causes of disease, its recurrence and thus they have an important influence on the aggressiveness of the therapy.

### Stratification

These biomarkers are often DNA based and serve to predict the likely response to a drug before starting the treatment. It classifies patients as responder or nonresponder.

Such predictive classification is of major importance in designing further development plan. Thus, the role of chosen biomarker in early developmental stage facilitates the chances of success in clinics.[12]

## FORMULATION STUDIES

When the candidate molecule shows promise as a therapeutic agent, it must be characterized for its molecule's size, shape, strengths and weaknesses, preferred conditions for maintaining function. During development of formulation, the emphasis must be given to proper drug delivery parameters.[13] It is important to begin thinking ahead to clinical trials at this phase of the drug development process. Drug formulation and delivery may be refined continuously until, and even after, the drug's final approval. Developer determine the drug's stability in the formulation itself, and for all the parameters involved with storage and shipment, such as heat, light, and time and at the same time formulation must remain potent and sterile and it must also remain safe (nontoxic). At the first level of development, determination of basic pharmacology of the compound in animals is needed. Early stage pharmacology and drug delivery studies help to characterize the underlying mechanism of action of the compound.

## ANIMAL STUDIES

While a compound is being developed, large number of animal studies must be performed to provide some degree of assurance that the candidate drug not only is safe for use in human subjects, but also is also potentially efficacious and commercially viable. Although, we understand that such assurances never carry absolute certainty, sufficient information usually is obtained from *in vitro* assays assessing mutagenicity and *in vivo* studies assessing whole animal toxicology and pharmacokinetics. This can be used as a surrogate for evaluation purposes.

Some of these studies typically take several years to complete after initial identification from screening. Such evaluations are performed in candidate drugs that show biologic effectiveness and potential efficacy in treating human disease conditions.

### Pharmacokinetics and Toxicology Studies

In the case of chronic diseases such as cancer, the unique medical needs of patients have the potential to affect several aspects of drug design. The cancer patients require long-term treatment and, therefore, the preclinical toxicology program must include repeat-dose administration to animals with the dosing regimen expected in the normal clinical practice.

The general battery of preclinical pharmacokinetic and toxicology studies for anticancer drug generally includes efficacy, pharmacology, and experimental toxicology studies to define the dose, route and frequency required for subsequent studies. Using one or more pharmacological animal

models of the disease, the initial efficacy studies demonstrate that treatment with drug candidates has the desired therapeutic effect. Efficacy studies also help to identify the best drug candidates for further development.[14,15]

A number of studies are used to address the absorption, distribution, metabolism, and excretion (ADME) characteristics of the drug. Bioavailability studies are generally conducted *in vivo* on candidates intended to be administered by a nonintravenous route. Bioavailability results provide information on the percentage of drug that is absorbed by the body as defined by quantity in plasma. Pharmacokinetics (PK) studies provide information on the maximum attainable plasma concentration ($c_{max}$), the time after dose administration to $c_{max}$ ($t_{max}$), the mean residence time in the plasma, clearance, and other information used to characterize the body's effect on the drug.

Initial dose range-finding and toxicity studies include single and multiple-dose administration protocols with varied observation times. These earliest studies are intended to determine the maximum tolerated dose (MTD), identify observable signs of toxicity, and provide a rationale for setting dose levels in more complex definitive studies. Regulatory requirements almost always call for definitive studies in at least two laboratory animal species, one rodent (rat or mouse) and one nonrodent (rabbit, dog, nonhuman primate, or other suitable species). Preliminary toxicity, bioavailability, and PK studies should also include one or more rodent and non rodent species, including the species to be used in the definitive studies. The group sizes for the early range-finding studies may consist of only a few animals and one sex (one animal per dose level). Once a suitable dose range is identified, group sizes are increased to at least three per sex per dose level to allow for statistical comparisons. Only a few end-points are collected in these range-finding studies unless there are particular toxicity concerns.

Toxicology involves many steps and call for a complete integration of multiple discipline including chemistry, manufacturing and control (CMC) as well as clinical regulatory and project management in order to be successful while developing toxicological studies plan. The careful consideration is required for multiple sectors like clinical development plan, physiochemical properties, and pharmacokinetic and pharmacodynamic profile of the compound. Overall the toxicological plans need to support proposed clinical development plan.

For example, if 14 days of continuous drug administration is proposed for the phase 1 clinical trial, then animal toxicity studies of at least 14 to 28 days are typically required to support a clinical study of this length. Although usually occurring after phase 1 dosing, longer-term animal studies (for example, 60 days and longer) will be needed to support later stage human clinical trials. The frequency of dosing (for example, three times a week for 4 weeks) in the animal studies should also mimic the clinical dosing schedule.

## REGULATORY PROVISIONS FOR INVESTIGATIONAL NEW DRUG APPLICATION PROCESS

On the basis of these preliminary evaluations, sponsors then file an investigational new drug application (IND) with the Food and Drug Administration (FDA) in US, EMEA (Europe) and Drug controller General office (India) which will evaluate the preclinical and CMC information presented to determine, if the stated safety of the candidate drug is reliable and sufficient to allow testing in humans.[16, 17]

### IND Submission for US

With the filing of an IND, the FDA becomes involved in the drug development process. The Center for Drug Evaluation and Research (CDER) is the review body for the FDA in the area of drug approval, whereas the Center for Biologics Evaluation and Research (CBER) evaluates biologics (e.g. proteins).[4] The Federal Food, Drug, and Cosmetic Act (amended by the FDA Modernization Act of 1997) defines the subject of the IND as a new drug subject to the specific requirements of the drug regulatory systems of both CDER and CBER. Clinical trials with the candidate drug generally can begin after 30 days of IND filing although the FDA during these 30 days review the application and inform the sponsor that it is safe to proceed but they can also put the study on clinical hold after reviewing submitted data on animal pharmacology / toxicology studies, manufacturing information, and clinical protocols and investigator information. Key sections of IND application are mentioned in Table 8.1.

**Table 8.1:** Key components of an investigational new drug application (US)

| *Components* | *Descriptions* |
|---|---|
| Animal pharmacology and toxicology studies | Preclinical data providing information about experiments performed in experimental animals as well as *in vitro* studies that provide a toxicology profile |
| Manufacturing information | Information regarding the composition, manufacturing, and controls used to manufacture the candidate drug (information presented should ensure that the sponsor can adequately provide material for testing) |
| Clinical protocols and investigator information | Information on the manner and format of study ("study protocols") of the clinical evaluations proposed and on those who will be involved in the program (and their qualifications); commitments to obtain informed consent from research subjects, to have oversight and review of the clinical protocols by an institutional review board, and to adhere to regulations of the investigational new drug application |

### Types of Investigational New Drug

The most common type of IND is the commercial IND, submitted by companies with the ultimate goal of gaining marketing approval for a candidate drug.[17] There are, however, three types of noncommercial INDs:

- Investigator IND
- Emergency use IND
- Treatment IND.

*Investigator IND:* Typically the application submitted by a physician, an investigator IND proposes to study either an unapproved drug or a drug that is approved but for which the physician intends an indication or patient population different than that previously approved by the FDA. The overall responsibility to conduct and administration of such studies lies with the physician or researcher submitted the application.[17, 18]

*Emergency use IND:* The emergency use IND is employed by the FDA to authorize use of an experimental drug in an emergency situation when there is insufficient time to submit. A standard IND under the usual strict guideline. It can also be employed in situations in which patients do not meet the existing criteria for a specific study protocol or an approved study protocol does not exist.

*Treatment IND:* A treatment IND is submitted for use of a compound to treat a serious or life-threatening condition while the final clinical work is being performed and FDA review is taking place. The FDA reviews this information to determine the adequacy of information derived from experiments in animals and *in vitro* experiments alleging to show that there is reasonable safety in allowing administration of the drug to humans. The FDA also evaluates the clinical plan, to ensure that the study protocol(s) are designed in such a fashion that information regarding the safety and/or efficacy of the compound can be ascertained.[17, 18]

## Regulatory Provision in Europe

EU Directives 2001/20/EC and 2005/28/EC set out the new rules and regulations for the approval and conduct of clinical trials in Europe. A Sponsor submits a clinical trial application to the Competent Authority in each member state where the trials are to be conducted. The Competent Authority has 60 days to review and approve or reject the application. An application in prescribed forms and covers the proposed clinical trial protocol, manufacturing, and quality controls on the drug, and supporting data, most of the information sought is similar to the FDA ' s IND requirements.[19]

The major difference in EU is that a Qualified Person (QP)) has to certify that the investigational medicinal product (IMP) is manufactured according to GMP.

### Regulatory Provision in India

In India, the drugs controller general of India (DCGI) is responsible for granting the permission to conduct the clinical trial. The data required to be submitted along with application is mentioned in Appendix I of Schedule Y, which is similar to US IND format mentioned above. The major difference is the requirement of addition toxicity data of male fertility studies.[20]

## CLINICAL DEVELOPMENT OF ANTICANCER MOLECULE

Once IND approval has been granted, the drug classically enters into three sequential phases (I, II and III) of clinical trials, each representing a distinct set of goals and challenges. There is also phase 0 study before commencement of phase I.

Clinical development of drugs to treat cancer is different from that of other diseases for a number of important reasons. Some of these are self evident, but all have a significant influence on drug development in this therapeutic area.

Patients perceive Cancer as an immediate life-threatening event. In many cases this perception is correct and therefore there is a sense of urgency to initiate therapy and an understandable reluctance to take part in trials that involve a placebo of any sort. It is thus rare to conduct the "gold standard" double-blind randomized controlled trial that is common in other disease entities.

### Phase 0 Clinical Trials

Typically, the exploratory IND studies are clinical trials conducted early in phase I (hence, the term phase 0) that involve limited human exposure and have no therapeutic or diagnostic intent. The purpose of the phase 0 study is to assist in the go versus no-go decision-making process of a drug's fate earlier in the development process, using relevant human models instead of relying on sometimes inconsistent animal data,[15] thus, helping to confirm end-points such as mechanism of action, pharmacology, bioavailability, pharmacodynamics, and metabolic micro dose assessments. These studies of novel agents expose a small number of patients (10 or even less) to a limited duration (e.g. 7 days or less) and dose (in the range of one 100th of the dose required to yield a pharmacologic effect of the test substance with a maximum dose of $< 100$ μg).

They are conducted before the traditional phase I dose-escalation safety and tolerance studies. By not having the traditional phase I objectives of toxicity and dose finding, phase 0 studies can be conducted early in the development process and are actually considered more of a discovery, rather than development, tool. In early 2006, the FDA published "A Guidance for Industry, Investigators, and Reviewers for Exploratory IND Studies" as part of the agency's critical path initiative to streamline drug development and improve the understanding of drugs early in the clinical process.

The ethics of doing phase 0 trials must also be considered carefully. These trials have no therapeutic intent and often will require significant invasive procedures. They have finite treatment duration and, theoretically, are not in the range of efficacious dosing.

There is a responsibility on the part of the investigator to advocate for the patient's ability to be treated after phase 0 experience, either with conventional treatment or on another clinical trial, in as timely a fashion as possible.

## Phase I Clinical Trial of Anticancer Molecule

Phase I trials plays a pivotal role and is a major step forward in the introduction of a new anticancer drug in to the clinic.

The primary objective of a phase I is to determine an optimal dose for a given schedule and route of administration for a new drug. This dose is also known as the recommended phase II dose. The recommended phase II dose is typically defined as the maximum tolerated dose (MTD) for the given schedule route of administration.[21]

The MTD is defined according to toxicity criteria and thus accurate assessment of dosing related toxicity is essential in the conduct of early stage of clinic development. If the difference between toxic and effective dose is small (i.e. narrow therapeutic index, however, for certain compound the therapeutic index may be quite large) in which case alternate strategies can be for determining optimal dose needs to be considered such a Pharmacokinetic and pharmacodynamic based method.

Secondary objective of phase I trials usually includes evaluation of Pharmacokinetics parameter associated with the compound. The understanding of human pharmacology is critical in optimizing the use of a new anticancer drug.[21, 22]

### *Essential Element in Phase One Clinical Study*

The models generally used for phase I oncology trial is selected considering the toxicity associated with traditional cytotoxic drugs. They usually have antiproliferative side effects such as myelosuppression, mucositis, hair loss and teratogenic effects. Therefore, it is not possible to enroll normal volunteer as in other therapeutic areas. Thus, we almost always develop anticancer drug in patients with cancer. It is clear that few patients will volunteer for experimental therapy when standard care is available. The problem is then compounded by the need to use end-stage patients for our phase I studies in cancer.[21, 22]

### *Selection of Patients*

In view of toxicity associated with most of anticancer agents, we usually do not recruit normal healthy volunteers for phase I studies in these studies. Further, the cancer patients tend to have limited life expectancy, underlying

disease such as metastases, or organ specific toxicity (neuropathy, renal dysfunction, diarrhea), which affect the enrollment.[21,23]

In order to limit such problems we select patients within very careful entry criteria. They usually should have at least 3 month life expectancy to allow time to observe any side effects. They should have critical organ function (liver, renal) that is normal or near normal. This will help limit variable pharmacokinetics between patients and allow for some comparison to be made between animal pharmacokinetics (done with normal organ function) and the human experience. This requires a high degree of efforts during patient selection, as most people with advanced intractable cancer will have deranged organ function.

### *Starting Dose Selection*

At the start of the first phase I trial of an anticancer drug, we will have limited data on dosing in animal model systems. Usually this will have been derived from toxicity (lethality) experiments and will have been performed across a limited dose range. In the case of standard cytotoxics with narrow toxicity, there is fairly good correlation with human toxicology. The convention with such drugs is to employ as a starting dose 1/10th of the lethal dose in 10% of animals (LD10) in the most sensitive animal species and this has been shown to be generally safe if somewhat conservative.[21,24]

### *Schedule Selection*

Preclinical knowledge about the expected schedule of the new agent may not be precise. At most one will have some idea of an appropriate route of administration and a concept of whether the drug needs to be given often or as a single dose with time allowed for normal tissue recovery. The dilemma is then how often to give the new drug in early-phase studies? Considerations of mechanism of action, expected toxicities, and convenience will all have an influence here. Often sponsors and investigators try to avoid this issue by setting up studies with a variety of schedules; this does not usually solve the dilemma, but simply delays the decision-making process until the phase II plans are made.

### *Dose Escalation Methods*

The same dilemma applies in the case of dose escalation scheme. The most efficient phase I is that which reaches the MTD as quickly as possible, the temptation is to be aggressive with dose escalation. In the absence of toxicity at the previous dose, how much of an increase should be made for the next dose level? A variety of fairly arbitrary methods are utilized to try to overcome this dilemma. Traditionally dose escalation has been performed using a "modified" Fibonacci scheme; if level 1 is the starting dose X1, level 2 is X1 + 100%, level 3 is X2 plus 67%, level 4 is X3 plus 50%, and level 5 and above are Xn + 30–35%. The major limitation of this method is as follows:

a. More patients and months are required to determine the dose
b. Difficult to define accurately the relationship to the study drug
c. Too many doubling may lead to toxicity
d. Expose too many patients to subtherapeutic dose.

A widely practiced method to avoid this pitfall is to maintain drug dose doubling until the first drug-related adverse events are observed and then to employ the Fibonacci element.[21,24] Patient cohorts at least for the very early low doses to limit exposure of patients to doses that are too low to have a realistic expectation of efficacy. It is worth noting that although this aim may be achieved, the use of single-patient cohorts will not necessarily result in more rapid escalation through the doses.[25, 26]

As a result, alternatives approaches have been sought hence various statistics and pharmacokinetic-guided methods have been developed for phase I dose escalation, with their primary goal to shorten the duration of phase I trials and to enhance the accuracy of the phase II dose recommendation. Like the traditional modified Fibonacci, these methods use toxicity, and specifically DLT, as the end-point of the trial. As yet none have gain the popularity as the "modified" Fibonacci.

### *End-points*

The usual end-point for a cytotoxic phase I study is the occurrence of grade 3–4 reversible toxicity in the majority of patients treated at that dose level. Objective measures of blood parameters can be simply applied to predefine acceptable levels of toxicity. Subjective toxicity causes much more of a problem. A lethargy that one person might consider intolerable may be of little significance to a more stoical individual.

Even the apparently simple objective measures such as blood count parameters are under question now. The discovery and widespread use of hematological growth factors to support blood counts means that we could define MTD with and without such support (or even a cocktail of such "support" molecules). This has some merit in that we commonly define MTD in terms of nausea and vomiting despite maximal antiemetic support. Conceptually similar though these situations are, it is not yet widely accepted to perform initial phase I trials of drug plus growth factor.

It is also possible to influence such end-points by patient selection. Prior exposure to cytotoxics or extensive radiotherapy with fields encompassing marrow primes patients to experience myelosuppression. It is necessary to take account of this, usually by including a cohort of "good risk" patients at the end of the trial to ensure that the MTD has not been set too low.[21,24]

## ***Surrogate End-points***

The scheme outlined above has been shown over the years or development of "cytotoxics" to be fairly efficient. Individual drugs or clinical circumstances require that the basic plan be altered slightly to take such factors into account.

A good example is the situations when acute toxicity is not dose limiting but a cumulative effect such as neuropathy is expected to be the DLT.
The surrogate end-point would be able to define rapidly and efficiently that the target had been affected in the appropriate tissue in the manner and extent that one would predict.[21,23,24,27]

## Phase I Study of New Biological Entity (NBE)

There is a basic difference in one of the objectives of phase I study of cytotoxic molecules and biological molecules. Finding out MTD may not be relevant in biological agent development. In primary objective in phase I of NBE is to find out the optimal biological dose (OBD). Optimal biological dose is defined as the maximum dose at which biological activity is maximally stimulated. Hence in the development of NBE the identification of parameter responsible for predicting the treatment of the disease, becomes inevitable. The identified parameter will help in the assessment of response.

## Phase II Clinical Trials of Anticancer Agent

Phase II oncology studies usually focus on a particular type of cancer with efforts to test the safety of the drug, and initial evaluation of efficacy in targeted patients.[5]

Phase II Clinical trial also provide additional opportunity to gather more information about the molecule such as:

- To add and expand pharmacokinetic data
- Increase the experience with toxicity through larger patient populations treated with multiple cycles of drugs
- Perform biological and imaging studies that enhance the understanding of the drug's action.

Phase II trials are performed to increase the probability to show the clinical response and consequently the risk of unnecessary exposes the patients to inactive treatment. To fulfill the aim to provide a better treatment to patients the utmost consideration should be given while selecting the objective, patient population and study design.[28]

### *Primary Objective*

The primary objective of phase II cancer clinical trials is to assess the anti tumor activity generally measured by the degree of tumor shrinkage using various different criteria that are often referred to as objective tumor response. For objective tumor response, WHO and miller, et al has suggested the criteria in initial stages based on 2D measurement of tumor. In 1994, the European Organization for Research and Treatment of Cancer (EROTC) the NCI (US) and Canada clinical trial group set up a task force to review the above criteria for evaluation of response in solid tumors. Later on a guideline was proposed with a new method called Response Evaluation Criteria in solid tumors (RECIST) based on 1D tumor measurement to evaluate the antitumor activity.

The reason for using the antitumor activity as primary end-point for phase II cancer trial is that it can be observed in a considerably shorter period of time as compared to usual survival end-points used in late phase studies.[28,29] Patients typically have a poor prognosis and therefore the probability of new agent's effectiveness will be low: Phase II trials are also performed for new treatment regimens to pilot their feasibility and obtain a preliminary estimate of their efficacy. These pilot studies can be performed in different patient sub groups and are conducted for a variety of reasons.[5]

Some pilot phase II studies are conducted to demonstrate the feasibility of a regimen that is believed to be more efficacious than standard therapy. In many of these studies, standard therapy is considered in some way to be inadequate and in certain situations there is a lack of standard therapy, which makes the way to use novel agents or treatment approaches ethically acceptable providing a treatment option, that otherwise would not have been existed. These pilot phase II studies may be conducted in newly diagnosed patients, sometimes selecting patient subgroups, which may be anticipated to have a worse prognosis, such as those presenting with metastasis disease.

However, the patients with good performance status according to ECOG criteria and minimal prior chemotherapy are a good option.

### *Study Designs in Phase II Trial*

The greatest variability exists in the design of phase II studies, as multiple approaches can be utilized to obtain information on efficacy. The most common framework for phase II trials is the "hypothesis-testing framework", in which the null hypothesis (H0) is compared with an alternative hypothesis (H1). H0 generally states that response rate is, at most, equal to a predefined level (P0), which is usually the minimum acceptable rate of activity or the response rate achieved with standard treatment. H1 states that the true response rate is at least equal to a target value P1, which is defined as P0 plus $\delta$, where $\delta$ is the amount by which it is hoped response to the new treatment will exceed P0 and the respective agent can be tested further in larger population in subsequent phase III study.[30]

In the most traditional phase II study design, a new treatment is given as a single therapy to a patient for whom no standard therapy exists.

However, the clinical trialists as well as the statisticians identify several limitations associated with this approach, even though this design is more suitable to justify the size of the trial using hypothesis testing. After the trial is complete the preferred analysis would usually be summarization of the data in terms of estimates and measures of uncertainty.

The main limitations of single arm design are as follows:

- Accuracy of Tumor response rate due to limited information on historical response rate

- Variability in patients mainly because of disease assessment and supportive care
- Possibility of bias in patient selection leads to inconsistency in response rate assessment.

In view of above limitations, it is very difficult to estimate the unbiased anti tumor activity of new agent based on the tumor response rate. Therefore to overcome these limitations many researchers proposed the several randomized design for phase II trial of anticancer agent. The main advantage by using randomized phase II trial is elimination of bias through evenly distribution of known and unknown factors, which influence the tumor rate assessment. In general the simple randomization procedure is followed during the phase II trial. Initially, the patients satisfying inclusion and exclusion criteria are randomly assigned to respective treatment. Primarily, below mentioned study designs are in practice.

### *Randomized Phase II Trial*

Simon et al suggested and explored the uses and characteristics of a randomized phase II selection design in which Patients are randomized to two or more experimental agents or regimens The regimen that results in the highest observed response rate is selected for further study. Sample sizes are given that assure 90% probability to select the best study arm, so long as the true expected response rate exceeds that of any other arm by at least 15% (in absolute terms; e.g. 35% vs 20%).[30] Appropriate uses of this design include selection among new agents administered singly as well as among new combination regimens, especially if the regimens all have a common core regimen to which various new agents are added.

### *Randomized Phase II Design Including Reference Standard Treatment Control Arm*

"Herson and Carter" introduced the phase II design including a simultaneously randomized standard-treatment control arm. The EORTC has advocated use of this design and applied it in selected phase II trials. In this design, the standard treatment control arm is not directly compared with the experimental arms, due to the statistical constraints resulting from the small sample sizes.[30]

In this design the standard-treatment control arm acts as a check for whether the historical control patients, against which the experimental arms are being judged, are comparable to the patients entering the phase II trial. If the standard-treatment control arm does substantially worse than expected, failure of an experimental arm to improve on historically based standards does not necessarily imply an actual lack of benefit. Conversely, if the standard treatment control arm does significantly better than expected, apparent improvement for an experimental arm is called into question.

### *Combined Phase I/II Design*

In the clinical development plan, sponsors sometimes also plan combined phase I/II clinical trial to accelerate the development of the molecule. Phase I/II trials combine a phase I and a phase II trial of the same treatment into a single protocol. First, the phase I part of the trial is done—to determine the maximum tolerable dose (MTD). Then, more patients are treated at the MTD, in the phase II portion of the study, to further evaluate safety and/or efficacy.[28,30]

### *Combined Phase II/III Randomized Design*

There has been increasing interest in the conduct of clinical trials that aim to select the best of a small number of treatments and provide a valid comparison of this selected treatment with a control, while also stopping recruitment to inferior treatments as quickly as possible. Traditionally, this aim has been met by conducting a phase II clinical trial in which the selection is made, followed by a separate phase III clinical trial to compare the selected treatment with the control. The advantage of conducting a single trial to achieve both objectives is that phase II patients are included in the phase III analysis, thus reducing the total resources required and potentially accelerating the drug development process.

Seamless phase II/III designs are aimed at interweaving the two phases of full development by combining them into one single, uninterrupted study conducted in two stages. In the dose-finding example above, one (or more) dose(s) are selected after the first stage based on the available data at interim, and are then observed further in the second stage. The final analysis of the selected dose(s) includes patients from both stages and is performed such that the overall type I error rate is controlled at a prespecified level regardless of the dose selection rule used at interim. The adequacy of the dose selection at interim is obviously a critical step for the success of a seamless phase II/III trial.

## Phase III Trials of Anticancer Molecule

Phase III anticancer trials are large, randomized, multicentric, lengthy and expensive attempt with the objective to confirm clinically important benefits of molecule against an established standard of care. The classical phase III trials include:

- A control group receiving standard therapy
- A broad selection of patients so that results can be applied in the community
- The measurements of end-points that have direct relevance to patients such as TTP, survival, or relief of symptoms.

In comparison with early clinical trials, phase III trials require large number of patients and are considerably more difficult to execute. As such, they are much more expensive to complete. Regardless of their multiple

**Table 8.2:** Benefits and drawbacks of phase II trials in oncology ·

| *Benefits* | *Drawbacks* |
|---|---|
| Eliminate the possibility of bias | Highly expensive |
| Allows more number of patients and more data | Difficult to conduct due to complexity |
| Produces data on delayed or infrequent toxicities | Ethical considerations |
| May be best suited to evaluate molecularly targeted agents | May introduce delays in drug approved |
| Permit pivotal trial design for determination of marketing approval | Historically high rate of failure |

challenges, phase III trials provide the most reliable source of efficacy data, and their results are the most important criteria for approval by any regulatory agency. The majority of the approved indications were based on the results of phase III trials.

The phase III trials give a high degree assurance as it excludes the selection bias, more number of patients, broad eligibility criteria, and variety of patient participation, all of which allow the collection of accurate results. The large numbers of patients enrolled in phase III trials also provide data on rare or delayed toxicities that may not be apparent in a smaller group of selected patients.[5]

As mentioned above sections the phase III trials, on one hand emphasizing their power through size and randomization and on the other hand their costs, ethical concerns, and complexity (Table 8.2). Even more fundamental, and at times more perplexing than the design and execution of phase III trial, is the selection of experimental treatments to be tested. There are limited resources available to support the high commitment level, effort and money required of these trials.[5]

### *Criteria for Go/ No Go Decision*

It is apparent that there is no standard or ready to use formula for making the important phase III "go/no go" decision. These choices are difficult, because each agent in developmental phase has something unique in its pharmacological characteristics, treatment potential, toxicity profile, and strategic role in the sponsor's portfolio. The underlying cancer biology on which the treatments are based is often partly understood. Taking the decision even more challenging is the fact that several predictions about the future need to be made, including regulatory trends and changes in the standard of care for the disease the agent is intended to treat.

The criteria with which to answer this question can be grouped into five important considerations unique to each agent in question.[5,30]

### Criteria for Phase III Decision

1. Novelty of mechanism of action and preclinical evidence for activity.
2. Pharmacokinetic properties shown in developmental (phase I and II) trials.
3. Activity and toxicity in developmental studies.
4. Potential role of the molecule in treating a disease either alone or in combination.
5. Commercial value to the sponsor and opportunity in respective market segment.

### End-points Used in Anticancer Trials for Regulatory Approval

It is generally acknowledged that the aim of treatment is to improve quality of life and survival. Hence, there should be sufficient evidence available to demonstrate that the selected end-point can provide a valid and reliable measure of clinical benefit in the targeted patient population.[30]

Generally, the following end-points are being used to establish the clinical benefit:

- Overall survival benefit
- Progression-free survival
- Response rates (complete and partial)
- Beneficial effects on disease symptoms
- Quality of life.

*Survival benefit:* Traditionally, in oncology drug development process, survival is considered to be the gold standard for drug approval. Although improvement in disease-free survival may also be acceptable when the proposed indication is used in the adjuvant setting. This is an unambiguous end-point as this is free from investigator bias or interpretation. It is an end-point that can be assessed easily and without reliance on tumor measurements.

*Overall survival (OS):* The length of time a patient is alive after enrolling in the study or beginning treatment.

*Progression free survival (PFS):* This end-point measures the length of time from starting treatment/randomization to worsening of the patient's disease (including death).

In majority of cancer trials the both PFS and OS are measured, particularly in cancers that are difficult to treat. The main difference between PFS and OS is that PFS is a direct measure of comparing two treatments where as OS can be affected by the use of subsequent therapies, which can make the interpretation of particularly OS, more challenging. PFS is a clinically meaningful end-point that is important to physicians and patients. It is also not affected by the use of subsequent therapies, therefore offers a good way of comparing two treatments.[30]

*Response rate (RR):* The percentage of patients whose cancer shrink or vanish after treatment. Types of potential responses are illustrated in Figures 8.1A to C.

- *Complete response (CR):* When a tumor goes away entirely due to treatment
- *Partial response (PR):* When a tumor undergoes major shrinkage due to treatment (typically 30% shrinkage compared to baseline)
- *Stable disease (SD):* When no new tumors appear and there is little change in the size of the known tumors
- *Disease control rate:* The percentage of patients who have a partial or complete response to an investigational treatment plus those whose disease stabilizes
- *Duration of response:* Measured from the time that measurement criteria are met for complete or partial response until the first date that recurrent or progressive disease is documented.

*Quality of life:* Quality of life is supposed to measure how patient feels and perform day-to-day functions. Though quality of life is certainly important in the broad sense, unfortunately, there is no unambiguous physical measurement or definable property, which corresponds to "Quality of Life". Quality of life is, therefore, measured using a brief questionnaire in which patients rate their ability to function in various ways and enjoy life. Patients typically fill out the questionnaire several times during the course of the trial.

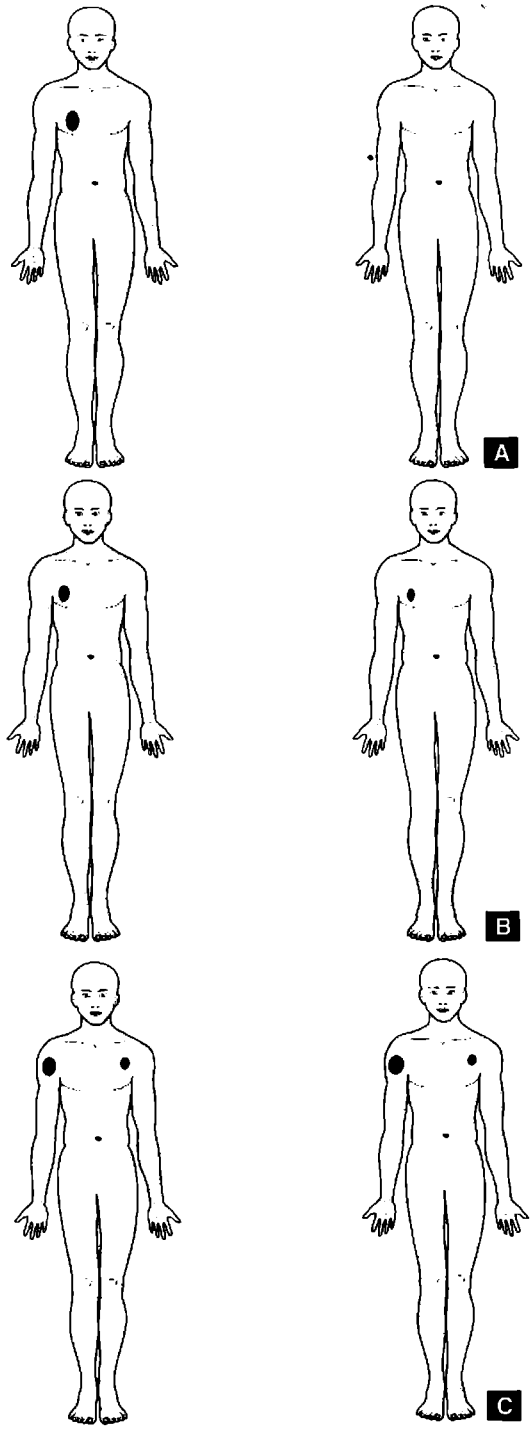
Quality of life is typically measured in phase III trials or Adjuvant Trials and it is typically a secondary end-point, less important than survival related end-points.

The most commonly used questionnaire is called the Functional assessment of cancer therapy (FACT) scale and there are specialized FACT questionnaires for several different types of cancer (which tend to affect quality of life in different ways).[31]

## Regulatory Approval for Marketing in India, Usa and Europe

If results from clinical trials conducted for the molecule are favorable and meet the set end-points, sponsor may choose to submit an application to applicable regulatory authority such as Food and Drug Administration (USA), EMEA (Europe), Drug Controller General (India) for the marketing authorization.

Through a new drug application a sponsor acquires the rights to manufacture and market the product in the respective country. The application incorporates, references, and contextually includes the prior regulatory submission, annual update reports, and other submissions that together make up the complete dossier for approval. All the data submitted to regulatory agencies are subjected to review. As it is the final step before market authorization the review requirements are much more stringent and time consuming than with any other submission. Every regulatory has their own set of format for application and the deviation, if any, from the specified format will ultimately result in delay.




**Figs 8.1A to C:** Types of potential response: (A) Complete response (CR); (B) Partial response (PR); (C) Stable disease (CD)

### Approval Timeline and Types of Approval in USA

Generally, the new drug approval process is a lengthy process and takes around 8–9 years from synthesis to market. In view of this, regulatory agencies primarily FDA has shortened the timeline through expedited approval process for drugs that treat serious diseases and no standard treatment is available. This facilitates the faster availability of drugs to patients especially when the drugs are the first available treatment or have advantages over existing treatments.[32] The Food and Drug Administration (US FDA) has developed three distinct and successful approaches to making such drugs available as quickly as possible.

#### Fast Track Approval

Any drug being developed to treat or prevent a disease with no current therapy available; obviously it is directed at an unmet medical need. If there are existing therapies, a fast track drug must show some advantage over available treatment, such as:

- Showing superior effectiveness
- Avoiding serious side effects of an available treatment
- Improving the diagnosis of a serious disease where early diagnosis results in an improved outcome
- Decreasing a clinically significant toxicity of an accepted treatment.

#### Accelerated Approval

Considering the fact that obtaining data on clinical outcomes take a long time, FDA instituted the Accelerated Approval regulation, allowing earlier approval of drugs to treat serious diseases, and that fill an unmet medical need based on a surrogate end-points.

The accelerated approval is granted under subpart 'H' applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.

The main condition associated with approval of a drug based on such end-points that the anticipated clinical benefit needs to be proven by post marketing clinical trials.

#### Priority Review

This is also intended for the molecule addressing an unmet medical need, refers shortened timeline for regulatory approval after reviewing a complete application.

#### Orphan Drug Approvals

This kind of approval is available for drugs used to treat disease, which are rare and affecting fewer people.

All these approaches are intended to make therapeutically important drugs available to the patients as early as possible. There is no compromise in the standards for the safety and effectiveness of the drugs, which are made available through this process.

### Approval Process in European Union

Similar to the US requirements, there are two regulatory steps to go through before a drug is approved to be marketed in the European Union. These two steps are clinical trial application and marketing authorization application.

There are approximate 27 member states in the European Union clinical trial applications are approved at the member state level, whereas marketing authorization applications are approved at both the member state and centralized levels.[19]

### Approval Process in India

In order to launch the new drug in Indian market the sponsor will be required to submit an application with drug controller general (India) .The application has to state what the drug is intended to do, along with scientific and clinical evidence for its efficacy and safety. It should also provide details of chemistry, manufacture and control of the drug, and the data to show that the drug has a consistent quality. Applicant must submit accurate claims so that the drug is promoted for its intended use.[20]

### Postmarketing Surveillance/Phase IV Studies

After the approval the continuous evaluation of a new drug, as it reaches the general population including various types of patients is of ever-increasing concern for regulatory agencies. The studies or research for evaluation of performance of a drug after marketing approval is known as "postmarketing surveillance," or phase IV studies. Often when a new drug comes to market, a phase IV trial is implemented to further evaluate the safety and efficacy of the drug.

Phase IV trials are performed in the postmarketing period in order to collect more data with respect to phase IV clinical trials encompass the detection, assessment, understanding, and prevention of drug-related problems. Both regulatory authorities and the sponsoring company may require phase IV studies for competitive purpose to find a new market for the drug.[5] Postmarketing studies are generally conducted for following reasons:

- Improving treatment strategy
- Specification of indication, improvement of diagnostics to establish the indication
- Use in patients with comorbidity
- Exploration of effect modifiers
- Detection and enumeration of unexpected or rare side effects and delayed effects

- Interactions with concomitant therapies, in particular, drug interactions
- Risk/benefit ratio in different subgroups.

Phase IV trial may also be required as a part of qualification set forth under accelerated condition. There is no standard design for phase IV studies due to diversity in objective. Based on the objective and requirement design can be selected.

## CONCLUSION

Anticancer drug Development has come a long way. From empirical based discovery to target based discovery, from cytotoxic agents to biologic agents, from MTD to OBD, from taking all cancer patients to selecting the patients based on the biomarkers, leading to personalized therapies. Still there is a long way to go. There is a need to develop more effective and safer drugs, more efficient and cost effective ways to develop the new molecular entities and better ways to accelerate the drug development process without affecting the quality of data.

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# CHAPTER 9 Role of Pharmacovigilance in Clinical Research

## INTRODUCTION

The concept of pharmacovigilance or monitoring of drug safety dates back much before to 150 years ago, however findings published in 1893 in *The Lancet* confirmed for the first time the establishment of a reporting system for suspected adverse drug reactions (ADRs).[1] These findings which were based on the reports presented during a commission set up by *The Lancet* in which doctors in Britain and its colonies were invited to report anesthesia related deaths, eventually triggered and bolstered the concept of monitoring of drug safety amongst the medical community and later on beginning of the concept of 'pharmacovigilance'.

Pharmacovigilance, a French word, was described as 'a discipline involving detection, evaluation and prevention of undesirable effects of medicines'. This was derived from the Greek *'pharmakon'* meaning a drug or medicine and from the Latin *'vigilans'* meaning watchful or careful.[2] The UK MHRA (Medicines and Healthcare products Regulatory Agency) referred it as 'a technical term used for identifying and responding to risk/benefit issues emerging for authorized medicines as used in clinical practice and including the effective dissemination of such information to optimize the safe and effective use of medicines.[3] World Health Organization (WHO) defines pharmacovigilance as 'the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem.[4]

## PHARMACOVIGILANCE: INTERNATIONAL STATUS

The foundation of World Health Organization (WHO) International Drug Monitoring Program was laid during 20th World Health Assembly in 1971. The current international system of pharmacovigilance is based on a report published in 1972 and accordingly the national pharmacovigilance centers work in collaboration with WHO.[5-7]

The WHO Collaborating Center for International Drug Monitoring is based in Uppsala, Sweden (The Uppsala Monitoring Center) and supports and coordinates the WHO International Drug Monitoring Program. The WHO center provides active support to the pharmacovigilance centers in developing countries. The Center collects the pharmacovigilance data from national

pharmacovigilance centers, maintains an international database, evaluates the efficiency and problems of ongoing national pharmacovigilance programs and takes measures to further strengthen them with technical and financial support. In 2000, WHO Uppsala Monitoring Center has provided guidelines for setting up and running a pharmacovigilance center. In 2002, WHO publication 'The importance of Pharmacovigilance' provided the guidelines for implementation of pharmacovigilance program at international level. The efforts of developing and implementing new legislation and qualitative requirements have led to the establishment of The Council for International Organizations of medical Sciences (CIOMS) and International Conference on Harmonization (ICH). These organizations along with national regulatory authorities and pharmaceutical industry have been instrumental in development of pharmacovigilance worldwide.

## PHARMACOVIGILANCE: THE CURRENT SYSTEM IN INDIA

In India, a formal drug safety monitoring system was proposed for the first time in 1996. The proposal of adverse drug reaction monitoring system of 1986 consisted of 12 regional centers each covering a population of 50 million. More concrete efforts of drug safety monitoring in India began in 1997, in cooperation with WHO Uppasala Monitoring Center. Under this program, three adverse drug reaction monitoring centers were identified including a National Pharmacovigilance Center at All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centers at Mumbai and Aligarh. This program leads to launch of a more ambitious National Pharmacovigilance Program (NPP) sponsored by WHO and funded by World Bank on January 1st, 2005. The objectives of NPP are to involve a large number of healthcare professionals in the process, inculcate the culture of reporting adverse drug reactions and to be a benchmark for global drug monitoring.

The NPP particularly solicits reports of:

- All adverse events suspected to have been caused by new drugs and 'drugs of current interest' (List published by CDSCO from time to time)
- All suspected drug interactions
- Reactions to any other drugs which are suspected of significantly affecting a patient's management, including reactions suspected of causing:
  - Death
  - Life-threatening reactions (real risk of dying)
  - Hospitalization (initial or prolonged)
  - Disability (significant, persistent or permanent)
  - Congenital anomaly
  - Required intervention to prevent permanent impairment or damage.

The NPP consists of a Pharmacovigilance Advisory Committee located at Central Drugs Standard Control Organization (CDSCO), New Delhi and two zonal centers—South-West zonal center (Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and

the North-East zonal center (Department of Pharmacology, AIIMS, New Delhi). The Mumbai zonal center collects information from three and New Delhi zonal center from two regional centers. Each regional center in turn collects information from 24 peripheral centers. To further support the NPP, implementation of Schedule Y from *Drugs and Cosmetics Act* has made it mandatory to report all Serious adverse events (SAEs) including Suspected unexpected serious adverse reactions (SUSARs) from clinical trials.

## IMPORTANT AREAS OF PHARMACOVIGILANCE

The discipline of pharmacovigilance remains a dynamic clinical and scientific discipline. The priority areas of pharmacovigilance at national and international level have been outlined by WHO and include the following:

### Detection of ADRs

- Detection and accurate diagnosis of ADRs by healthcare providers and patients
- Active surveillance of specific drug(s) through epidemiological methods such as case control studies, record linkage and epidemiological studies
- Consideration of special activities and expertise required for the detection of safety concerns related to vaccines, biological, veterinary medicines herbal medicines, biotechnology products and investigational drugs
- Improvement of signal detection systems by facilitating the rapid availability of ADR data that may have international relevance
- Revisit the definitions of terms used within the field of pharmacovigilance including the definitions of specific ADRs to ensure reliability and universal understanding of data obtained through ADR reporting systems
- Develop and implement ADR detection systems that could benefit populations with restricted access to healthcare.

### Assessment of ADRs

- Further development of automated signal detection systems used in spontaneous monitoring programs
- Improvements in assessment of drug safety concerns that are of international relevance
- Foster collaborative links both at local and international level that could allow countries to assess and respond appropriately to drug safety crises
- Consider methods by which information on local patterns of drug use can be integrated with pharmacovigilance information during assessment of benefit and harm at a national level.

### Prevention of ADRs

- Improves access to reliable and unbiased drug information at all levels of health care
- Improves access to safer and more effective medicines for neglected diseases prevalent in developing communities
- Integrate pharmacovigilance activities into rational drug use among health professionals and the public
- Integrate pharmacovigilance activities into national drug policies and the activities arising from these (e.g. standard treatment guidelines, essential drugs lists, etc.)
- Further incorporation of pharmacovigilance principles into clinical practice and academic medicine
- Encourage the principles of product stewardship among the various partners in health care
- Improve regulation and pharmacovigilance of traditional and herbal medicines
- Develop systems which assess the impact of preventive actions taken in response to drug safety problems.

### Communication

- Improve communication and collaboration between key partners in pharmacovigilance both locally and internationally
- Adoption of the principles of good communication practice in pharmacovigilance and drug regulation
- Development of communication in different countries and regions and the sharing of mutual experience
- Development of a better understanding of patients, their expectations of medicines and their perception of risk associated with the use of medicines
- Development of sustained and active relationships with the media in order to facilitate effective and accurate communication of drug information to the public
- Harmonization of drug regulatory and pharmacovigilance activities by incorporating the wider international community in the development of harmonization policies.

## PHARMACOVIGILANCE METHODS

As per the ICHE2E[8] guidelines, the pharmacovigilance method can be categorized as:

- Passive surveillance
  - Spontaneous reporting
  - Case series
- Stimulated reporting

- Active surveillance
  - Sentinel sites
  - Drug event monitoring
  - Registries
- Comparative observational studies
  - Cross-sectional study (survey)
  - Case-control study
  - Cohort study
- Targeted clinical investigations
- Descriptive studies
  - Natural history of disease
  - Drug utilization study

Spontaneous ADR reporting and drug event monitoring is also known as *Hypothesis Generating Methods*, as these are used as tools in pharmacovigilance for generating initial suspicions. Case control studies, cohort studies and randomized controlled trials are known as *Hypothesis – Testing Methods* as these aim to prove whether any suspicions that may have been raised are justified.

## Passive Surveillance

### *Spontaneous Reports*

"A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g. WHO, Regional centers, Poison control center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.[8]

*This type of report is voluntary in nature (voluntary reporting), i.e. it may be initiated by the healthcare professionals or consumers as and when they become suspicious of any adverse reaction by any medication.*

These forms are generated by the concerned regulatory authority or the organizations working under the aegis of the government regulatory authorities; these are either provided on the websites or distributed to the healthcare professional through various training programs conducted by the personnels working in the area of pharmacovigilance or distributed by the sponsors which in most of the cases is a pharmaceutical company or a medical device manufacturing company. These filled forms are then notified to the central authority (country's governmental body) which is usually the drug regulatory authority (e.g. DCGI, i.e. Drug controller General India for India; USFDA for United States of America; TGA, i.e. Therapeutic and Goods Administration for Australia; MHRA for UK; BfARM for Germany ; AFFSAPS for France, etc.).

In India, the form used for the spontaneous reporting is known as "Suspected Adverse Drug Reaction Reporting Form" generated by CDSCO

(Central Drug Standard Control Organization) working under the aegis of Directorate General of Health Services (DGHS), Government of India.

In the United Kingdom, the form used for the spontaneous reporting is known as "Yellow Card". This has been used for the purpose of spontaneous reporting since 1964. The form is available separately for the patients (patient reporting form) and for the healthcare professionals (healthcare professional reporting form).

In the United States, the "Med Watch" form is used in two different categories:

- *Form FDA 3500—Voluntary Reporting:* for use by health professionals, consumers and patients
- *Form FDA 3500A—Mandatory Reporting:* for use by IND reporters, manufacturers, distributors, importers, user facilities personnel.

Similar forms are provided in the FP10 prescriptions pads, the British National Formulary and other sources.

### *Case Series*

Case report describes the particular outcome or experience of a person who has been exposed to a drug. These reports are useful for generating hypotheses about the effects of the drug and may lead to further studies to test these hypotheses. A case series, reports on two or more people with common exposure to a drug, or a common outcome.

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome.[9,10] Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

## Stimulated Reporting

Stimulated reports are those that may have been motivated, prompted or induced and can occur in certain situations, such as notification by a Health Care Professional Communication (HCPC), public advisory, literature report, publication in the press, or questioning of healthcare professionals by MAH representatives. These reports should be considered unsolicited in nature and as a form of spontaneous reporting. Data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but can be used to estimate reporting rates.

## Active Surveillance

In active surveillance, the number of adverse events are collected via a continuous preorganized process. An example of active surveillance is the

follow-up of patients treated with a particular drug through a risk management program.

The various methods to get the comprehensive data through active surveillance are depicted below.

### *Sentinel Sites*

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system.

### *Drug Event Monitoring*

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at prespecified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events and reasons for discontinuation can be included in the questionnaire. [11-14]

### *Registries*

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry).

Exposure (drug) registries address populations exposed to drugs of interest (e.g. registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women.

## Comparative Observational Studies

### *Cross-sectional Study (Survey)*

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study.

### *Case-control Study*

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases.

### *Cohort Study*

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient.

### Targeted Clinical Investigations

When significant risks are identified from preapproval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction.

### Descriptive Studies

These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

### *Natural History of Disease*

This type of study includes the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest.

### *Drug Utilization Study*

These studies describe how a drug is marketed, prescribed and used in a population and how these factors influence outcomes, including clinical, social and economic outcomes.

## BENEFIT-RISK ASSESSMENT IN PHARMACOVIGILANCE

Benefits should be described and wherever possible, quantified in a way that is comparable to the quantification of risks. Evaluation of benefit must include the following points:

- Prevalence and incidence of disease
- Nature of disease: Fatal, disabling, self-limiting, associated morbidity and mortality
- Purpose of therapy: disease prevention, treatment, cure, prevent disease progression, reduce risk from subsequent disease, reduce disabling symptoms
- Nature of therapy: first or second line therapy, orphan drug, reported adverse effects and therapeutic responses, duration of therapeutic benefits
- Characteristics of population requiring treatment
- Quality of data.

A multifactorial approach is required to determine the qualitative profiles of different adverse reactions. The main points to consider in risk evaluation include the following:

- Nature, severity and duration of ADR
- Dose and duration of treatment
- Preventability, predictability and reversibility of the reaction
- Possibility of a class effect
- Possible effect of concomitant treatment
- Possible correlations with factors like demographics and concomitant diseases
- Supporting evidence from clinical trials or animal studies.

The adverse reaction that dominates the overall risk profile (carries the most weight) is referred to as the risk driver or dominant risk.

## CRISIS MANAGEMENT IN PHARMACOVIGILANCE

In Pharmacovigilance "crisis" is defined as the "the event which occurs when new information, which could have a serious impact on public health, is received for a marketed product and which requires an immediate action".

The crisis is usually provoked by spontaneous reporting and is most likely to occur in a country with a strong and well-developed pharmacovigilance system in place. At the time when crisis is identified, the information may not be public however if it becomes public handling of situation with effective communication is crucial as the public confidence is at risk. Immediate measures need to be taken to initiate a pharmacovigilance investigation to either confirm or disprove the signal.

### Planning for Crisis Management

The precrisis conditions are the major players in deciding the course of action during crisis and postcrisis impact. Thus it is important that all organizations think widely well beyond their territory and establish good working relation and communication channels with other supporting organizations which can provide crucial help not only during detection of crisis but also in handling the situation.

#### *Precrisis Planning*

The collection of information and evidences as quickly as possible and its subsequent analysis is vital for the recognition of an upcoming crisis. Therefore, adequate preparation and planning to facilitate early and accurate recognition of an upcoming event is the first step in the crisis management. The organizations must equip themselves with:

- Availability of appropriate sources of information at all times
- Availability of efficient communication channels to obtain as much information as possible without delay
- Availability of staff, which is well informed about their roles and responsibilities at all times, so as to channelize the information correctly
- Availability of a very efficient system of documentation of all information

- Availability of a group of trained managers for prioritizing, analyzing, assessing the information and quick risk identification
- Availability of cooperation from all stakeholders
- Availability of efficient communication channels to ensure confidence among all stakeholders.

### *Postcrisis Review*

Crisis planning is a dynamic process and preparedness of the organization at times of no crisis is of immense help during the periods of crisis. Case histories must be written which can be reviewed later by experienced professionals and their opinions can be utilized by making necessary amendments in the existing system or by adding new dimensions to the existing system. All possible technical skills must be utilized with utmost intelligence keeping in mind the emotional sensitivities and at no cost the importance of overall critical review can be undervalued. Following activities are essential to further support the crisis management system:

- Create a document of organizational profile giving details of core activities, number of staff, office locations, years in existence, product details and annual productivity figures. This document can be used to provide information to people and groups outside the organization
- A document of simple organization chart showing names, contact details and responsibilities of key persons and their deputies
- A document showing details of management of previously experienced crisis situations
- Continued in-service training of staff to maintain the awareness and abilities to respond during crisis.

## CLINICAL TRIALS: ASPECTS OF SAFETY MONITORING

Clinical trials are voluntary research studies, conducted in people that are designed to answer specific questions about the safety and/or effectiveness of drugs, vaccines, other therapies, or new ways of using existing treatments. During drug development process (clinical trials phase I to III) pharmacovigilance (Fig. 9.1) include continuous monitoring and evaluation of all adverse events with or without a causal relationship to the Investigational medicinal product (IMP)* and any adverse drug reaction to concomitant medication to ensure the safety of the participants (subjects) and a continual assessment of the risk and the benefit. The basic framework for pharmacovigilance during clinical development process is presented in Figure 9.1.

Pharmacovigilance has a role during clinical development, in view of the number of drugs that have been withdrawn or have had warnings added to their labels due to hepatotoxicity In the case of troglitazone (an antidiabetic

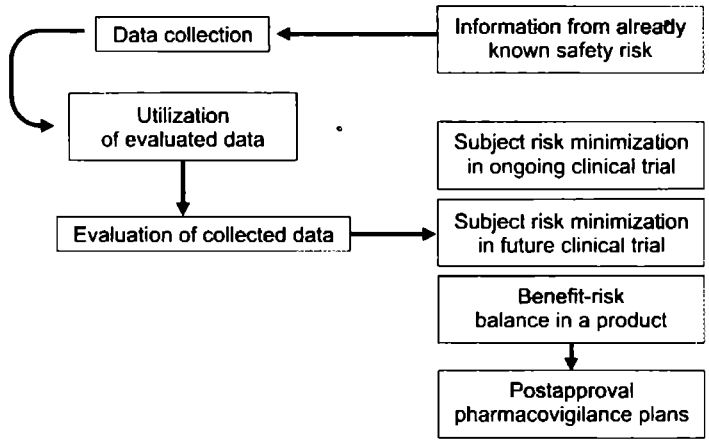


**Fig. 9.1:** Pharmacovigilance framework during clinical development

drug, voluntarily withdrawn from the market by the license holder in 2000), it was reported that 1.95 percent of patients treated with troglitazone in clinical trials developed elevations of aminotransferases that were greater than three times the upper limit of normal.[15]

## ROLE OF PHARMACEUTICAL INDUSTRY

Pharmaceutical industry has the prime responsibility towards the improvement of patient care (or clinical trial subjects) and safety related to the use of medicines, investigational products (during clinical trial) from the start of drug development (clinical research process) and thereafter throughout the lifetime of the drug. Pharmaceutical companies develop novel monitoring systems which are efficient for their contribution to the detection of new safety signals ("reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously"). Other agencies, viz. competent (regulatory) authorities (US FDA, EMEA, UK MHRA, TGA, Health Canada, MCCA), WHO (World Health Organization collaborating center for international drug monitoring (in Uppsala), CIOMS (Council for International Organization of Medical Sciences)—working groups play an advisory role in harmonization of pharmacovigilance practices for the improvement of patient care and drug safety. Erice Declaration[16] on communicating drug safety has improved communication and exchange of information between the industry, regulatory authorities and the public. Communication on drug safety has more recently been further supported by the establishment of the community database (Eudravigilance Database) in December 2001, in London.

**Drug Recalls**

Recalls are actions taken by a firm to remove a product from the market. Recent drug recalls are lised in Table 9.3. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority. These can be categorized in following types:

- *Class I recall:* A situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death
- *Class II recall:* A situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
- *Class III recall:* A situation in which use of or exposure to a violative product is not likely to cause adverse health consequences
- *Market withdrawal:* Occurs when a product has a minor violation that would not be subject to FDA legal action. The firm removes the product from the market or corrects the violation. For example, a product removed from the market due to tampering, without evidence of manufacturing or distribution problems would be a market withdrawal
- *Medical device safety alert:* It is issued in situations where a medical device may present an unreasonable risk of substantial harm. In some case, these situations are also considered recalls.

**Investigational Medicinal Product (IMP)**

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use [ ICH E6].

## DRUG DEVELOPMENT PROCESS

For the introduction of drug or any therapeutic or any biological compound for the first time in the country for human use (which is also called as the registration process), a process, viz. clinical trial process which is regulated by the specific regulatory guidelines (e.g. ICH GCP, USFDA guidelines, etc.) has to be undertaken. WHO defines clinical trial process as " for the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials .[15] Clinical Trials Directive (2001/20/EC)[17] defines clinical trial as "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s) and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism

and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.[17]

Pharmaceutical companies or the drug companies with robust research and development (R & D) facilities continuously analyze thousands of compounds, to choose the compounds of therapeutic value (Fig. 9.2). This usually takes six to seven years of preclinical testing (a first stage of drug development involving synthesis and purification testing in the lab and animal testing) during which thousands of compounds are tested before entering into the second stage that requires filing of an IND (investigational new drug application) to the appropriate regulatory authority which is also termed as FDA (Food and Drug Administration, e.g. US FDA in USA). If the IND is approved by the FDA and by an Institutional review board, the manufacturer may begin the first phase of development. The IND stage consists of three phases.

- *Phase I:* In this healthy individuals are recruited to determine the drug's basic pharmacokinetic properties and safety profile in humans
- *Phase II:* During this phase, the drug is administered to the patients for first time in the indication it is meant for
- *Phase III:* The preliminary evidence gathered in phase II that a drug is safe and effective for use in the intended indication and recipient population is confirmed in phase III.

After the completion of phase III, the manufacturer or the pharmaceutical company files or submits a New Drug Application (NDA) to the FDA for review of the efficacy, safety and tolerability data generated during phase I to phase III. NDA review typically lasts for one to two years, thereby bringing total drug development and approval (i.e. the IND and NDA stages) to approximately nine years. During the NDA stage, the FDA consults advisory committees made of experts from the different scientific discipline (clinical

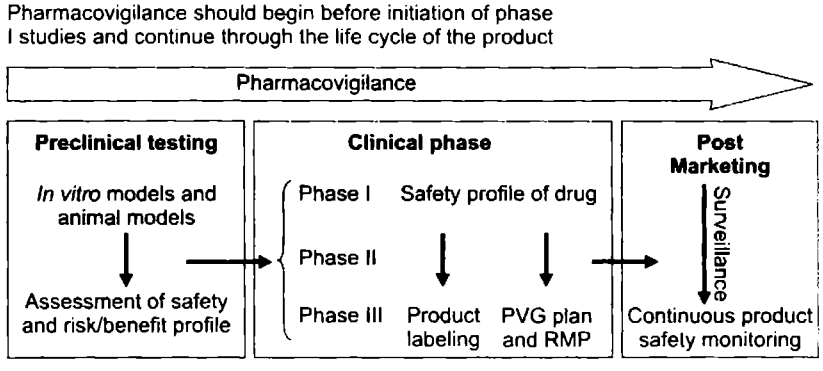


**Fig 9.2:** Drug development process and pharmacovigilance

pharmacologist, biostatistician, field expert, viz. cardiologist/endocrinologist/oncologist/rheumatologist) to obtain a broader range of advice on drug safety, effectiveness and labeling. Once approved, the drug is marketed with FDA regulated labeling often called as therapeutic indication'. During marketing of the drug in 'real world' clinical practice where prescribing decisions of the prescribers does not follow strict eligibility criteria specified during subject enrollment in controlled clinical trials, FDA gathers safety information on the continuous basis as the drug is used and adverse events are reported.

Clinical trial process as discussed above involves many stakeholders (Fig. 9.3), viz. sponsors, regulators (government agencies), investigators, monitors, ethics committees or Institutional review boards (IRBs), participants and a myriad of other public and private entities as discussed earlier in this chapter whose involvements greatly affect the clinical research process. During the conduct of clinical trials, it becomes imperative to assess the safety and tolerability profile of investigational new drugs (INDs), so the responsibility for monitoring the safety (a pharmacovigilance process) of study subjects during clinical trials is shared between trial sponsors, researchers, ethics committees and drug regulators. In lieu of its pharmacovigilance role in clinical trials the sponsor has the obligation to carry out various risk management activities during the clinical trial process. These risk management activities include: modifications in protocol due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion criteria, intensification of monitoring); restrictions in study population or indications; changes to the informed consent document relating to safety issues; formulation changes for safety reasons; addition of a special reporting requirement; issuance of a communication to investigators or healthcare professionals; plans for new safety trials.

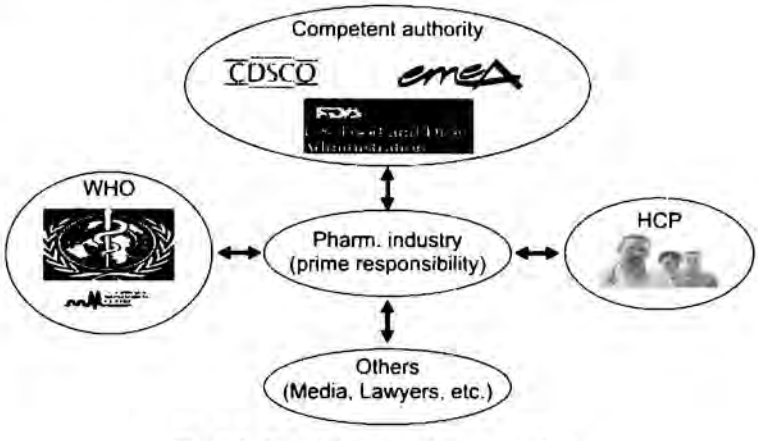


**Fig. 9.3:** Stakeholders in pharmacovigilance

Here it should be noted that since contract research organizations (CROs) and/or site management organizations (SMOs) are contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions, so the pharmacovigilance roles and responsibilities as defined for sponsors for clinical trials will be applicable for them also. To carry out some or the other functions, a sponsor has to execute specific legal "agreements" and "arrangements" with the other stakeholders as defined earlier in order to ensure safety for the subjects participating in clinical trial. As part of delegation of responsibilities as defined in the contractual agreement, a sponsor may transfer any or all of the pharmacovigilance tasks and functions, to another person(s) or organization, but the ultimate responsibility for the fulfillment of all pharmacovigilance obligations and the quality and integrity of these pharmacovigilance functions always resides with the Marketing authorization holder. It becomes imperative for the sponsor of the clinical trial to ensure that detailed and clear documented contractual arrangements for meeting pharmacovigilance obligations between the sponsor and the other stakeholders are in place. The contracted person(s) or organization should implement quality assurance and quality control and accept to be audited by or on behalf of the sponsor.

Now, for the understanding of role of pharmacovigilance in clinical research the roles and responsibilities of various stakeholders have been presented below.

### Sponsor: Pharmacovigilance Responsibility

As per ICH-GCP (ICH E6) a sponsor is "an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial".[18]

For a sponsor, it becomes essential to use and adopt pharmacovigilance procedures to monitor adverse reactions occurring in clinical trials to ensure the immediate termination of any clinical trial in which there is an unacceptable level of risk. The sponsor has the prime responsibility to ensure the safety evaluation of the investigational medicinal products on the continuous basis (on going safety evaluation). In order to ensure ongoing safety evaluation sponsor is not only required to evaluate the safety of IMP when the trial finishes but also to continuously assess any problems when both serious and nonserious ADRs are reported. As per regulations, sponsor is responsible for the immediate notification of finding from the clinical trials that could adversely affect the health of subjects or if the findings could create an impact on the further conduct of the trial. For such findings sponsor

has the prime responsibility of notifying to all concerned investigator(s), the Ethics committee and competent authorities (regulatory authorities). In Europe, a sponsor has to notify to concerned investigator(s), the Ethics committee and competent authorities (regulatory authorities) of each concerned Member State in order to ensure whether the findings could alter the competent authority's authorization to continue the trial in accordance with Directive 2001/20/EC.[17]

From sponsor's perspective its pharmacovigilance role in clinical research commences at the first stage during preparation of various essential documents, viz. protocol, investigator brochure, case report forms (CRF). In the next stage during the commencement of clinical trial, sponsor or its designated representatives report the occurrence of adverse events in a clinical trial as per the applicable regulatory guidelines and other company specific standard operating procedures or as per specifications mentioned in the 'pharmacovigilance section of the protocol'. The importance of incorporation of pharmacovigilance section or safety section in the essential documents has been discussed below.

### Protocol: Pharmacovigilance and Safety Reporting Section

ICH E6 defines protocol as "a document that describes the objective(s), design, methodology, statistical considerations and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents".[18]

Experts in the regulatory bodies and members of the ethic committees critically review and examine each and every section of the protocol and imparts much emphasize on the 'pharmacovigilance and safety reporting section' of the protocol as this remains a key section in guiding the proper recording and reporting of safety issues occurring in a clinical trial to ensure safety of study subjects. The basic rules for what does or does not need to be recorded in the CRF or reported to the sponsor are usually mentioned in the protocol.

Following guidance should be provided in "pharmacovigilance and safety reporting" section of the protocol:

- A definition of the adverse event (AE)/serious adverse event or reaction (SAE/SAR).
- A definition of the expectedness and unexpectedness of adverse event or reaction (AE).
- Specifications of the safety parameters to be studied as per the protocol along with methods and timings for recording and analyzing.
- Standards for expedited reporting with reporting time frames.
- Declaration from the principal investigator (PI) that PI will ask the study subjects during each scheduled visit or unscheduled visit (if any) about experience of any events or hospitalizations, disability or incapacity since their previous visit.

- The study subjects shall be provided with a contact address or telephone number of the PI or of any research personnel designated by PI to expedite the reporting of adverse events.
- In case of occurrence of serious adverse event in a blinded clinical trial the management for blinded therapy cases should be given in detail with clear responsibilities of breaking the blinding of code. During the conduct of clinical trial maintenance of blinding is advantageous till the final study analysis. However in circumstances where a serious adverse reaction is judged to be reported in an expedited manner then it is advocated that the sponsor should break the blind for that specific patient only.
- A clear statement for adverse drug reactions that are not deemed to be reported to the sponsor unless they are considered to be occurring at greater frequency or with greater severity than might be expected as defined in the Summary Product Characteristic (SmPC) or any other reference safety information. For example, in case of a licensed medicines or the approved pharmaceutical product this might include a list of known ADRs as present or documented in the SmPC. A copy of SmPC or any other reference safety information should be added as an appendix to the protocol with an accompanying statement in the 'Pharmacovigilance and Safety Reporting' section of the protocol as follows:
  "Adverse drug reactions listed under 'undesirable effects' section in the SmPC are not deemed to be reported to the sponsor unless they are considered to be occurring at greater frequency or with greater severity than might be expected as defined in the summary product characteristics (SmPC)".
- A statement for serious adverse events that may not deemed to be recorded and reported as per expedited reporting requirements should be clearly mentioned. For example, deaths due to disease in a study where death is a primary endpoint, as in case of death from stroke in a stroke trial. Other examples include the case of hospitalization for an event that is an endpoint as in case of myocardial infraction, AIDS event and cancer recurrence.
- In regard to therapeutic failures and defining the adverse events it should be explicitly mentioned in the protocol that if the disease under investigation worsens during a clinical trial then it will be considered as an AE or not. In some cases if the disease entity under investigation worsens during a clinical trial, then it is not considered as an AE rather, it is considered as a disease progression. The progressed disease, however, may cause a new symptom, which may be considered as a new AE. For example, if a patient's pancreatic cancer spreads during a trial and the new metastases result in increased pain, the worsened pancreatic cancer detected by restaging CT would not be considered as an AE. The new pain may be reported as an AE and in such cases the investigator should provide an attribution indicating that the pain is unlikely with the result of the study therapy.

- A statement regarding confirmation of reporting to sponsor in case of occurrence of a pregnancy or a follow-up till outcome in a female participant or in the female partner of a male participant should be provided. This is important for the drugs where there is a paucity of safety information concerning fetal exposure and fetal development.
- A risk assessment statement should be provided in the protocol.
- Recording and reporting of poststudy events that occurred after the patient had completed a clinical study (including any protocol required post-treatment follow-up) should be clearly mentioned.
- The name and contact details of the sponsor's pharmacovigilance representative who in most of the cases is qualified personnel for pharmacovigilance (QPPV) should be included for the purposes of reporting of SAE/SARs/SUSARs.

**Risk Assessment Statement in the Protocol**

The risk assessment statement in the protocol ensures that an appropriate deliberation has been imparted by clinical investigators to potential safety issues in clinical trials that apply to investigational medicinal products/comparator products/noninvestigational medicinal products (products which are not the entity for investigation such as rescue medication provided for preventive, diagnostic or therapeutic reasons to ensure that adequate medical care is provided for the subject participating in clinical trial).

Previous knowledge about the benefit/risk profile (frequency and severity of the adverse drug reaction) of the investigational medicinal product plays an important role for risk assessment. The risk is usually less in clinical trials that involve the licensed or marketed drugs that have been used or prescribed in large number of patients and whose patient characteristics in whom the drug has been prescribed resemble those of clinical trial subjects. In such instances, it becomes appropriate that the investigators record known adverse drug reactions in the CRF but not report them to the sponsor unless they occur with unexpected frequency or severity.

In case of licensed drugs that are designated 'black triangle' by the drug regulators, it is necessary that sponsor should explicitly specify in the protocol that investigators need to report all SAEs to the sponsor and that unexpected events be considered potential SUSARs.

For investigational medicinal products tested in preliminary phases, viz. phase I and II studies ('first-in-man') where there is no information on safety profile, sponsor should explicitly mention that the investigators will record all adverse events in the CRF and will notify the sponsor for the adverse events that qualify the criteria for 'seriousness'.

## Investigator Brochure (IB)

As per ICH GCP 'Investigators Brochure' (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects'.[18] As an essential document,

it has an important pharmacovigilance role as in addition to providing the investigators and other trial related staff about the information that facilitate their understanding of the rationale for dosage, dosage frequency/interval, drug administration methods it provides procedures for safety monitoring. In clinical research, expedited reporting is made on the basis of 'expectedness' and 'unexpectedness' of the serious adverse reaction. During the clinical trial since the main purpose of expedited reporting is to make regulatory bodies, principal investigator or investigator (s), IRBs and other appropriate people aware of new, important information on serious reactions, so investigator brochure acts as an important source document to define the 'expectedness' and 'unexpectedness' of the adverse drug reaction. "Expected adverse drug reaction" is one, the nature or severity of which is consistent with information in the relevant source documents. "Unexpected adverse drug reaction" is one, the nature or severity of which is not consistent with information in the relevant source documents. Investigator brochure prepared and furnished as per the ICH guidelines by the sponsor serves as the source document for a medicinal product in a country where it is not yet approved for marketing. Like the "undesirable effects" section of the SmPC where the adverse drug reactions are listed for the marketed product, the summary of adverse drug reactions is tabulated for the investigational product in investigator brochure. The summary in terms of severity and frequency of these adverse drug reactions in the investigator brochure serves as information mentioned in the above definitions of expected and unexpected adverse drug reaction.

**As per section 7.3.6 of ICH GCP, "...The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s)....."**

### Case Report Form (CRF)

A case report form is "a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject".[18] During the clinical trial process all adverse events and serious adverse events reported at a trial visit are recorded unless otherwise specified in the protocol (Tables 9.1 and 9.2). For routine data collection study protocols clearly define how adverse events will be identified, managed, reported and recorded in the case report form. From the pharmacovigilance perspective nonserious adverse events are also recorded and reported if their occurrence is important to safety monitoring in a clinical trial or if they are believed to be adverse reactions critical to the evaluation of

**Table 9.1:** Adverse event page in case report form

| **Adverse Event Form** | | | | |
|---|---|---|---|---|
| **Is there any adverse event experienced by the subject?** *(If yes, kindly complete the adverse event form)* | | | | Yes ❑ No ❑ |
| **Adverse Event Description** | | | | **Adverse Event Number** [__I__] |
| **Is this an initial report or follow-up report?** *(Kindly tick whichever is applicable)* | | Initial Report ❑<br>Follow-up report ❑ | | |
| **Date of onset (DD/MM/YY)** | | [__I__]-[__I__]-[__I__] | | |
| **Severity** | Mild ❑ | **Moderate** ❑ | **Severe** ❑ | **Life-threatening** ❑ |
| Mild = No interference with usual activities; Moderate = Significant interference with usual activities; Severe = Prevents usual activities; Life-threatening = Endangering life/risk of death | | | | |
| **Frequency** | Isolated ❑ | Intermittent ❑ | Continuous ❑ | Not Applicable ❑ |
| **Study Medication Adjustment** | | **None** ❑ | **Dose modified/ interrupted** ❑ | **Discontinued** ❑ |
| ***Relationship to Study Medication** | **Certain** ❑ | **Probable/Likely** ❑ | **Possible** ❑ | |
| | **Unlikely** ❑ | **Conditional/ Unclassified** ❑ | **Unassessible/ Unclassifiable** ❑ | |
| ** To confirm the possible relationship of the study treatment to the suspected reaction, please go through the standard description of above-mentioned terms (viz. certain, probable/likely, possible, unlikely, conditional/unclassified, unassessible/unclassifiable) on page no. X of CRF named 'Instructions to fill AE / Intercurrent illness form and SAE form'.* | | | | |
| *Outcome* | **Resolved with no sequelae** ❑<br>**Resolved with sequelae**<br>**Specify**_____ | | **Date of Resolution** [__I__]-[__I__]-[__I__] | |
| | **Unresolved/ongoing at final contact** ❑ | **Death** ❑ | **Unknown** ❑ | |

drug safety. Predictable adverse reactions are also recorded if they are mentioned in the protocol as guiding decisions about adjustment of dosage. In addition to recording other data elements, e.g. compliance with treatment regimen, significant laboratory tests and diagnostic procedures, medical history and physical examination findings, safety data is recorded in case report forms using adverse drug event questionnaires and extensive checklists of symptoms organized by system organ class. Since detection of adverse reactions during clinical trials requires careful and systematic evaluation of study participants before, during and after exposure with the investigational product so a quality control mechanism is also undertaken to ensure the accuracy and integrity of data. As per ICH-GCP, the definition of quality assurance stands as "all those planned and systematic actions that are

**Table 9.2:** Serious adverse event page in case report form

| **1. Patient Details** | | |
|---|---|---|
| Patient initial: [__I__I_ ] | Hospital/OPD record number (if any): [__I_ _I__I__I_ I__] | |
| Age: [__I__] yrs | and/or | Date of Birth: [__I__]-[__I__]-[__I__] |
| Male / Female | (if female)<br>Confirmed Pregnancy: Yes No Test not done<br>If 'Yes' then weeks of gestation: [__I__] weeks | |

| **2. Suspected Drug(s)** | | | | | |
|---|---|---|---|---|---|
| Generic name with dosage form and strength | Indication | Daily dose and regimen (specify units) | Route | Duration of Therapy | |
| | | | | Starting date and time | Stop date and time |
| | | | | | |

| **3. Other treatments (prescription or nonprescription medications/nondrug therapy)** | | | | | |
|---|---|---|---|---|---|
| Generic name with dosage form and strength/name of therapy | Indication | Daily dose and regimen (specify units) | Route | Duration of therapy | |
| | | | | Starting date and time | Stop date and time |
| | | | | | |

| **4. Details of the Suspected adverse drug reaction(s)/Description** | | |
|---|---|---|
| 'Specific Diagnosis' for the reaction/event: | Associated signs and symptoms (if any): | |
| Full description of the reaction/event along with body site/system involved: | | |
| Intensity/severity of reaction: Mild and moderate and severe and life-threatening and | | |
| Mild = No interference with usual activities; Moderate = Significant interference with usual activities; Severe = Prevents usual activities | | |
| Criteria for reporting the event as an SAE—the adverse event resulted in (please tick as applicable):<br>Death<br>A life-threatening experience<br>Inpatient hospitalization or prolongation of existing hospitalization<br>A persistent or significant disability/incapacity<br>A congenital anomaly/birth defect<br>A condition that required intervention to prevent permanent impairment or damage | | |
| Start date and time<br>[__I _]-[__I__]-[_ I__]<br>[_ I__]:[_ _I__] hrs | Stop date and time<br>[__I_ _]-[__I _]-[__I__]<br>[__I _]:[__I__] hrs | Ongoing at final contact |
| 'Dechallenge and Rechallenge' done: Yes No<br>If 'Yes' please provide details: | | |
| Setting: Hospital/Nursing home/Clinic/Outpatient/Others _ _____ | | |

*Contd...*

*Contd...*

| **5. Outcome** |
|---|
| Resolved with no sequelae/Resolved with sequelae/Unresolved at final contact/Death/ Unknown |
| Results of specific tests/investigations/treatments that may have been conducted/ given (if any): |
| In case of death (please mention cause of death) |
| Possible relationship of the study treatment to the suspected reaction: **Unrelated/Unlikely/Possible/Probable/Likely** |
| Post-mortem/autopsy done: **Yes/No**<br>If 'Yes', findings (if any): |
| Any other relevant information to facilitate the assessment of the case: |

| **6. Details about the investigator** | |
|---|---|
| Name: | Profession (speciality): |
| Address: | Telephone No.: |
| Date of reporting the event to the Licensing authority:<br>[__I__]-[__I_ _]-[_ _I__] | Date of reporting the event to the Ethics Committee overseeing the site:<br>[ _I_ ]-[_ I__]-[__I _] |

established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)".[18] The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and safety data are generated, documented (recorded) and reported in compliance with the protocol, GCP and the applicable regulatory requirement(s).

Based on CIOMS VII, an adverse event of special interest (serious or non-serious) is one of scientific and medical concerns specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g. regulators) might also be warranted.

## Safety Update Report

During the drug development process (clinical development) of an investigational drug it becomes imperative that the periodic analysis of safety information which is crucial to the ongoing assessment of risk to trial subjects should be carried out. Presently, drug regulatory authorities (Food and Drug Administration) in some countries or regions require submission of a periodic report or development safety update report (DSUR) to themselves and to

other interested parties or stake holders (e.g. ethics committees) at regular intervals or defined timelines. These reports mainly present safety profile of an investigational drug and actions proposed (viz. early termination of the trial, ongoing status, addition of any extra visit for patient for evaluation of safety, etc.) or being taken to address safety concerns. ICH E2F[19] guidelines on development safety update report (DSUR) describe a common standard for annual clinical trial safety reporting among the ICH regions to provide an additional level of assurance of protection for clinical trial subjects. As per the guideline, the main objective of a DSUR is:[20]

- To summarize the current understanding and management of identified and potential risks
- To describe new safety issues that could have an impact on the protection of clinical trial subjects
- To examine whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the product's safety
- To provide an update on the status of the clinical investigation/ development program.

A DSUR needs to be submitted annually to regulatory authority as long as the sponsor conducts clinical trials with the investigational drug or as long as it is suitable for reporting in the purview of local safety requirements. The details pertaining to the format and presentation of the contents[16] of the development safety update report has been appended as *Annexure II*. An executive summary (a concise summary of the important information contained in the report) of the safety update report should be provided for periodic submission of safety information on an investigational drug to ethics committees, institutional review boards, or investigators. This should serve as a "stand-alone" document suitable for submission to ethics committees and other stakeholders, if required by local regulations. Information on the following should be included in the executive summary of this report:

- An introduction
- Information about investigational drug (viz. mode of action, class, indications, dose, route of administration)
- An estimated cumulative clinical trial exposure
- Number of countries (if any) in which marketing authorization is sought for
- Overall safety assessment summary
- A summary or a cumulative list of important identified and potential risks
- Actions taken for safety reasons including significant changes to IB
- Conclusion.

The executive summary should be supplemented with line listings of serious adverse reactions (only those terms that were used in defining the case as serious) as warranted. In the line listing following data elements should be present: study ID (protocol number), case ID/subject number,

country, gender, age, serious ADR, outcome, date of onset, time of onset, suspect drug, daily dose, route of administration, formulation, dates of treatment, treatment duration, comments. During presentation of safety data from clinical trial, it becomes important that the report should also include adverse reactions of special interest** within the line listings and adverse events of special interest in summary tabulations. The basis for selection of such events/reactions should be explained.

Certain adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database and those that are integral, i.e. linked to efficacy endpoints, can be excluded from the summary tabulations and line listings, but such exclusions should be explained in the report in an explicit manner (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint or disease progression in cancer trials).[20]

Here it should be noted that the main focus of the DSUR is on the presentation of data from clinical trials of investigational drugs including biologicals, with or without a marketing approval and information such as safety findings, serious adverse reactions line listings, can also be provided in Periodic Safety Update Reports (PSURs) for marketed products that are utilized in ongoing clinical trials. In a DSUR, the safety information from all ongoing clinical trials that the sponsor is conducting or has completed during the review period must include:[20]

- Clinical trials conducted using an investigational drug whether with or without a marketing approval, i.e. human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (phase I – III)
- Clinical trials conducted using marketed drugs in approved indications, i.e. therapeutic use trials (phase IV)
- Other therapeutic use of an investigational drug
- Comparability trials conducted to support changes in the manufacturing process of medicinal products.

Here it should be noted that, other findings (e.g. safety findings from clinical research studies or clinical trial conducted by a codevelopment partner in a licensing agreement, significant safety findings from non clinical studies, or appropriate safety findings from noninterventional studies or safety issues reported with the compassionate use) that can impact safety and welfare of clinical trial subjects should also be included in the report.

In a safety update report, the primary focus should be on the investigational drug (s) and information on comparators is provided only where relevant to the safety of trial subjects. This report should be concise and able to provide information to assure regulators that sponsors are adequately monitoring and evaluating the safety profile of the investigational drug. It should not contain initial notification of any significant new safety issues, as these should have been communicated to regulatory authorities via expedited reporting.

In the situations when drug development program or a clinical trial is executed or carried out in mutual collaboration with public enterprises (hospitals, academia, research institutions) or private institutions/business partners (contract research organization/site management organization) or other parties then a written agreement should (as discussed previously in the beginning of this chapter) be placed thereby clearly detailing the responsibilities for preparation and submission of the safety update report. The same principle applies in the conditions where the sponsor delegates the responsibility of preparation of the safety update report to a third party, e.g. a contract research organization or an organization specialized in drug safety management aspects.

In special situations, e.g. when a sponsor is in a formal codevelopment or licensing relationship with one or more partners, or more than one partner is a sponsor of a clinical trial(s) of the investigational drug, then an arrangement to prepare a single safety update report should be made. Written agreements should be made in place thereby, stipulating the method of exchange of safety data, i.e. how safety data will be exchanged so that a single safety update report can be produced by one sponsor on behalf of all parties. Additionally, multiple sponsors can make an agreement for preparation of separate safety update report for the same investigational drug under the situations where different indications, routes of administration, or formulations are being investigated by different sponsors for same investigational drug. For this a rationale for preparation of separate development safety update report should be provided in each report.

In case of clinical trials involving a fixed dose combination product, a single safety update report should be prepared.[20]

Safety information received during the reporting period of preparation of safety update report is assessed on the basis of 'reference safety information'. As discussed earlier also the 'investigator brochure' acts as the 'reference safety information'. The Investigator's brochure (IB) at the start of the reporting period serves as the 'reference safety information' for the safety update report for an investigational drug whether or not the drug has a marketing approval. The safety information (adverse event) received during the conduct of clinical trial is compared with this 'reference safety information' (IB). While preparing the report, the version number and date of the generation of IB should also be mentioned in the report. It should be noted that if the revisions have been made in the IB during the reporting period and these revisions has not been previously submitted to the relevant regulatory authority then the sponsor must provide a copy of the revised version of the IB as an attachment to the safety update report. In situations, e.g. noncommercial sponsors conducting a clinical trial with a marketed product, where an IB is not required for the trial by local regulations, the applicable local product label (in EU this is Summary of Product Characteristics (SmPC), in Japan this is Japanese Package Insert and in the US this is US package insert) or another suitable document is used as the 'reference safety information'.[20]

A concise summary of key safety findings that gets arised (if any) from marketing experience of investigational drug in any country should be provided in the safety update report during the reporting period. This becomes important if the findings resulted in changes to the labeling or amendments to the product's risk management plan. A summary should be provided for major safety findings from nonclinical *in vitro* and *in vivo* studies initiated or completed during the reporting period. The examples of such studies include carcinogenicity, reproduction, or immunotoxicity studies. In the safety update report, the impact of the outcome from such studies on the clinical safety of the investigational drug should be discussed.

In case of clinical trials conducted with advanced therapy products (e.g. tissue engineered products, cell therapy products and gene therapy), subjects are followed even when the trials get completed. In such cases, information from long-term follow-up of subjects should be presented in the safety update report.

As a part of pharmacovigilance activities during clinical trials, it is deemed necessary that a sponsor makes periodic review of worldwide scientific literature for any new safety information that may arise during the conduct of clinical trial. For this, reviews are generally made into specific sites, viz. PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), scopus (http://info.scopus.com/) and other database, e.g. cochrane database. Any new and significant safety findings from nonclinical studies, clinical trials or any new safety information on drugs of the same class that have been published during the reporting period is incorporated in the safety update report. During the reporting period if changes are introduced in the manufacturing process and/or formulation of an investigational drug, then any key safety issues arising from such changes are also mentioned in the safety update report. Lack of efficacy should be reported in the safety update report for clinical trials with vaccines, or clinical trials where the investigational product is intended to treat serious or life-threatening illness. In case of vaccine failure the reporting becomes important from the view of possible signals of reduced immunogenecity in a sub group of vaccines, waning immunity and strain replacement.[20,21]

During drug development process, it is the prime responsibility of sponsor to continuously evaluate the risks that may arise due to the use of investigational product in clinical trial subjects. For evaluation of risks in clinical trials, any significant differences in the nature and severity of adverse drug reactions from previously identified reactions and identification of risk factors should be considered. For example, increase in frequency of expected adverse reaction as very common (≥10%), common (≥1% and <10%), uncommon or infrequent (≥0.1% and < 1 %), increase in severity (to moderate or to severe), changes in outcome and issues related to risk factors are considered for risk evaluation. These issues allow for consideration of further preventive measures in subjects. For evaluation, an emphasis should be given on signs, symptoms and evidences (based on the laboratory values) of

previously and newly identified clinically significant hepatic and renal toxicity, bone marrow toxicity, immunogenecity and hypersensitive reactions, CVS effects, CNS toxicity and reactive metabolites.

As per Article 17 of Directive 2001/20/EC of the European parliament on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use:

1. a. The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned and to the Ethics Committee and in any case no later than seven days after knowledge by the sponsor of such a case and that relevant follow-up information is subsequently communicated within an additional eight days.
   b. All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.
   c. Each Member State shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.
   d. The sponsor shall also inform all investigators.
2. Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.[14]

### Pharmacovigilance Responsibility of Investigator

As per ICH E6, an investigator is 'a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator'.

Article 2 of Directive 2001/20/EC of the European Parliament defines an investigator as 'a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator.[22]

During the conduct of clinical trial, investigator ensures that adequate medical care will be provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. To ensure safety of trial subjects and to eliminate an immediate hazard during the conduct of clinical trial, an investigator may implement a deviation or a change in the protocol (from the preapproved protocol) without prior approval/favorable opinion of IRB/IEC. The amended protocol along with the implemented changes or deviation should be submitted to:

- The IRB/IEC for review and approval/favorable opinion
- The sponsor for agreement and if required
- The regulatory authority(ies).

*Directive 2001/20/EC* of the European parliament on implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[17] explicitly describes in its *Article 16* about the pharmacovigilance role of investigator related to the notification of adverse events. As per this directive:

1. The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.
2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.
3. For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.
4. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request.

In blinded clinical trials [where investigator(s), monitor, subject(s) and in some cases, data analyst(s) being unaware of the treatment assignment(s)], pharmacovigilance role of investigator gets extended to the management of blinded therapy cases. For example, in case of double blinded trials occurrence of serious adverse events require a decision of breaking of the code for a specific patient to ensure the patient safety. Methods of breaking the blinded codes are predefined in the clinical trial protocol. If the blind is broken by the investigator, then it is believed that the assigned treatment for that patient will also be known to the sponsor.

Although it is advantageous to retain the blind for all patients prior to final study analysis, however it should be noted that from the pharmacovigilance and reporting purposes the maintenance of blinding has many disadvantages that outweigh the advantages. Some of the key disadvantages have been described below:

- By retaining the blind, there is always unnecessary filling of cases related to the placebo and comparator (usually a marketed product)
- At the time many weeks or months after reporting to regulators when the blind is eventually opened then it must be ensured that company and regulatory data bases are revised
- It is not appropriate to notify the relevant parties (CRO, IRB) of the new information that has been updated in a blinded fashion in investigator's brochure especially in case of new and possibly related serious adverse events to the medicinal products
- It should be noted that breaking of the blind for a single patient has no significant implication on the analysis of the final clinical investigation data. Source: [ICH E2A]

In Europe, documentation of adverse event and reporting in clinical trials has been harmonized by implementation of the Clinical Directive 2001/20/EC into national law. This has been made statutory or compulsory that serious unexpected suspected adverse reactions (SUSAR) from clinical trials must be reported to competent authorities and ethics committee (IRB) no later than 7 days in case of deaths and life-threatening adverse reactions and 15 days for all others. The aim of this directive is to identify and concentrate on SUSAR for the study and analyses of safety signals. This allows for annual review and revision (Directive 2001/28/EC) of the product information (Investigator brochure or Summary of product characteristics (SmPC) by the pharmaceutical industry (Manufacturing authorization holder). Additionally, ADRs associated with use of concomitant medication administered in clinical trials, where the sponsor is not the marketing authorization holder (MAH), should be reported either directly to competent authorities (regulatory authorities) or to the MAH of the concomitant medication so that regulatory requirements can be met and the serious adverse drug reactions can be reported to the competent authorities within 15 days.[23]

### Pharmacovigilance Responsibility of Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

ICH E6 defines an ethics committee as an 'independent body (a review board or a committee, institutional, regional, national or supranational), constituted of medical professionals and nonmedical members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the trial subjects'.

To fulfill its responsibilities towards the protection of rights safety and well-being of the human subjects an IRB/IEC reviews the essential documents, viz. trial protocol(s)/amendment(s), written informed consent form(s) (and consent form updates), Investigator's Brochure (IB) and available safety information about the investigational medicinal product.

IRB/IEC should be promptly reported for:

- All adverse drug reactions (ADRs) that are both serious and unexpected
- Any changes or deviations in the protocol to eliminate immediate hazards to the trial subjects
- Any changes creating an increase in the risks to subjects and/or changes in the protocol that are affecting the conduct of the trial
- Any new information that may adversely affect the safety of subjects or the conduct of the trial.

### Management of Case Safety Reports during the Conduct of Clinical Trials

As stated earlier in this chapter, standard operating procedures are implemented by the sponsor to ensure necessary quality standards for data collection or recording, evaluation, validation, reporting and archiving of the adverse drug reaction related information. In order to implement the pharmacovigilance responsibilities in clinical research sponsor has to maintain a detailed record of all adverse events that are reported to him by the investigator during the conduct of the clinical trial. A detailed analysis for the seriousness, causality and expectedness has to be performed by the sponsor on the individual case safety reports (ICSRs) that are received from the investigator. For causality analysis, either the WHO causality assessment scale[24] or the Naranjos probability scale (NPS) are utilized. In a clinical trial, an investigator makes an assessment on the adverse event since he/she has the opportunity to see the subject reporting the adverse event. From the sponsors perspective all the adverse events collected from all the sites (multicentric trial) need to be assessed so that sponsor can broadly depict the nature and occurrence of the adverse event from the pooled analyses of all participating sites. This helps the sponsor to provide additional information in comparison to that received by the individual investigator. This provides the rationality for a causality review to be conducted by both the investigator and the sponsor. In case a significant safety issue has been identified by the sponsor either on the receipt of an individual case safety report (ICSR) or upon review of aggregate data (pooled analyses) as stated above, the sponsor is required to issue as soon as possible a communication to all investigators. It should be noted that causality reported by the sponsor on the investigational medicinal product cannot be overruled by sponsor. In such circumstances, sponsor may comment ('sponsors section' on comments in ADR report) regarding the disagreement. The opinion from both investigator and sponsor should be submitted with the report.

## RISK INFORMATION DURING CLINICAL TRIALS

Risk assessment for a product involves making assessment for both existing risk information and any questions regarding safety which are evaluated against the product's demonstrated benefits. A product may be less acceptable if the product has demonstrated fewer benefits and higher levels of risks. For elucidating maximum information from clinical trials a careful attention should be paid by sponsor to the overall design of the safety evaluation.

During preapproval phase, databases do not have sufficient population size to detect all safety issues that might occur with the product once marketed in full population. Henceforth, it can not be expected to identify all risks associated with a product even from large clinical development programs. It is likely that during drug development more serious adverse events will be

detected with larger and more comprehensive preapproval database. The appropriate size of a safety database supporting a new product will depend on a number of factors:

- Whether the database represents a new treatment or is similar to available treatment
- Whether the alternative therapies are available and the alternative therapies are safe as compared to the new product
- The intended population and condition being treated
- The intended duration of use.

During preclinical or human clinical pharmacology studies if signals of risk that warrant additional clinical data to properly define the risk are identified, then a larger safety database may be appropriate. In case of life threatening diseases where there are no alternative satisfactory treatments, then in such circumstances safety databases are usually smaller than for products intended to treat diseases that are neither life-threatening nor associated with major, irreversible morbidity 21 CFR 312.82(b) provides that for drugs intended to treat life-threatening and seriously debilitating illnesses, end-of-phase I meetings can be used to agree on the design of phase II trials "with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing."

For products intended for long-term treatment of non-life-threatening conditions, (e.g. continuous treatment for 6 months or more or recurrent intermittent treatment where cumulative treatment equals or exceeds 6 months), the ICH and FDA have generally recommended that 1500 subjects be exposed to the investigational product (with 300 to 600 exposed for 6 months and 100 exposed for 1 year).[25] Many adverse events (e.g. hepatotoxicity, hematologic events) do not appear with single doses or very short-term exposure. Hence for chronic use products, the ICH guidance E1A, FDA recommends that the 1500 subjects include only those who have been exposed to the product in multiple dose studies.

The E1A guidance describes a number of circumstances in which a safety database larger than 1500 patients may be appropriate. These circumstances include the following:

- When there is concern that the drug would cause delayed adverse events
- When there is a concern that drug would cause adverse events that increase in severity or frequency over time
- When there is a need to quantitate the rate of occurrence of an expected specific low-frequency adverse event. For example, serious adverse event identified in similar products.

In addition to the considerations provided in E1A, other circumstances in which a larger database may be appropriate include the following:

- The proposed treatment is for a healthy population (e.g. the product under development is for chemoprevention or is a preventive vaccine)
- An effective alternative to the investigational product is already available and has been shown to be safe.

## CONSIDERATIONS FOR RISK ASSESSMENT

### Risk Assessment during Clinical Trials

Risk assessment strategies can be adapted as per the following situations:

- If a product is intended to be chronically used (particularly when it has a very long half-life) and/or has dose-related toxicities. In such cases it would be useful to examine whether a lower or less frequent maintenance dose would be appropriate.
- If a product's proposed dosing includes a proposed titration scheme, the scheme could be based on specific studies to define how titration is best performed and the effects of titration on safety and efficacy.
- When a drug has the potential for adverse effects which are not likely to be detected or readily reported by patients without special attention, then additional testing or specific assessments within clinical trials are appropriate. For example, for a new drug with recognized CNS effects (especially sedating effects), sponsors should conduct an assessment of cognitive function, motor skills and mood. Similarly, since many antidepressants have significant effects on sexual function, new antidepressants should be assessed for these effects. Since routine adverse event monitoring and safety assessments tend to underestimate such effects then the use of targeted safety questionnaires or specific psychometric or other validated instruments is often important for such assessments.
- If a product is to be studied in pediatric patients, special safety issues should be considered (e.g. effects on growth and neurocognitive development if the drug is to be given to very young children/infants; safety of excipients for the very young; universal immunization recommendations and school entry requirements for immunization).
- In circumstances when earlier safety data signal an unusual or important concern then in such cases a sponsor may consider reserving blood samples (or any other bodily fluids/tissues collected during clinical trials) from some or all patients in phase III studies for possible assessments at a later time.

### Medication Errors during Clinical Trials

Medication errors are defined as any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not.[26] Medication errors can occur at any stage of the medication use process. Some medication errors, especially those involving parenteral products, have been detected in clinical trials prior to marketing. The occurrence of medication errors can be minimized by assessing, prior to marketing, common sources of medication errors. Such errors may arise because of the product's inherent properties or because of the inadvertent contribution of the proposed proprietary name, the established name, the

proposed labeling (e.g. container, carton, patient/consumer labeling, or professional package insert) and the proposed packaging. During clinical trials, improper dilution or improper administration techniques, may result in nonoptimal dosing. These should be carefully examined as warning signs that the product could be subject to dosing errors that may warrant changes in labeling, packaging, or design. If errors are not observed in trials, then careful consideration should be given during development to the implications of the design of the product, its packaging and any device used to administer or deliver the product. For example, when a concentrated product that requires further dilution prior to intravenous administration is being developed then packaging is important. Packaging such a product in a syringe would make it possible to inject the product as a bolus without proper dilution, increasing risks to patients. Similarly, when developing a product that is administered or delivered by a device, the implications of mechanical failure of the device should be examined. Any such occurrences seen or considered during product development should be documented, reported and analyzed for potential remedial actions (e.g. redesign of the device or modification of instructions for use).

## OUTCOME AND IMPACT OF PHARMACOVIGILANCE SYSTEM ON CLINICAL TRIAL

Clinical studies conducted in the form of postauthorization safety studies or other postmarketing studies conducted to further evaluate the safety concerns have identified potentially dangerous adverse drug reactions. Most of the recalls/drug withdrawals and other advisories have been issued on the basis of results from controlled clinical trials. For example, results from SCOUT study showed an increased risk of serious, nonfatal cardiovascular events, such as stroke or heart attack, with sibutramine compared with placebo. Other large controlled clinical trials[19,22,27-29] have shown that the COX-2 selective agents (Vioxx, Celebrex and Bextra) may be associated with an increased risk of serious cardiovascular events (heart attack and stroke). Additionally, preliminary results from a long-term clinical trial suggested that long-term use of a nonselective NSAID, naproxen which was sold as Aleve, Naprosyn and other trade names and generic products may be associated with an increased cardiovascular risk compared to placebo. These advisories and recalls forms the basis for understanding of role of pharmacovigilance during the clinical trial process (clinical research) especially at the time when continuous advancement and introduction of new treatment approaches worldwide has widened pharmacovigilance concerns to include traditional and complementary medicines, herbals, medical devices, blood products, biological and vaccines. European regulations governing the pharmacovigilance process during clinical trial are appended as *Annexure I*.

Significant measures and steps have been taken to effectively deal with the adverse drug reaction and withdrawing the potentially harmful drugs from the market (Table 9.3). For last 35 years there have been continued instances of drug recalls (removal of prescription or over-the-counter medication from the market). Most recent recalls include the drug withdrawals of sibutramine (2010), efalizumab (2009), rimonabant (2008) and lumiracoxib (2007) from the worldwide market because of the various risks associated. These drug withdrawals from the market have been described as below:[29-32]

### Sibutramine (January 2010)

Sibutramine-containing medicines were authorized in the European Union (EU) since 1999. They were available in the European Union under the following names: *Afibon, Ectiva, Lindaxa, Meissa, Meridia, Minimacin, Minimectil, Obesan, Reductil, Reduxade, Sibutral, Sibutril, Siluton, Sitrane, Zelium and Zelixa.* This

**Table 9.3:** Recent drug withdrawals

| *Market authorization holder* | *Drugs* | *Type of drug* | *Date withdrawn* | *Primary health risk* |
|---|---|---|---|---|
| Parke –Davis | Rezulin (troglitazone) | Antidiabetic | 3/21/2000 | Liver failure |
| Janssen Pharmaceutica | Propulsid (cisapride monohydrate) | Gastrointestinal | 7/14/2000 | Torsades de Pointes |
| GSK | Lotronex (alosetron hydrochloride) | Gastrointestinal | 11/28/2000 | Ischemic colitis |
| Bayer | Baycol (Cerivastatin) | Lipid lowering | 08/08/2001 | Rhabdomy-olysis |
| Organon Inc | Raplon (Rapacuronium) | Neuromuscular blocker | 03/27/2001 | Fatal bronchospasm |
| Merck | Vioxx (Rofecoxib) | Anti inflam-matory | 09/30/2004 | Myocardial infarction |
| Shire | Adderall XR | ADHD | 02/09/2005 | Stroke |
| Pfizer | Baxtra (Valdecoxib) | Anti inflam-mtory | 04/07/2005 | Cardiovascular malfunction, severe rash |
| Eli Lilly | Permax (Pergolide) | Anti Parkinsonism | 03/29/2007 | Heart valve damage |
| Bayer | Trasylol (Aprotinin) | To control bleeding during heart surgery | 11/06/2007 | Increased mortality |

was used to promote weight-loss in obese patients and in overweight patients who also have other risk factors such as type-2 diabetes or dyslipidemia (abnormal levels of fat in their blood), together with diet and exercise.

A review was initiated on the use of Sibutramine under Article 107 of the Community code relating to medicinal products for human use (Directive 2001/83/EC). This type of procedure is initiated in cases where a Member State considers the need for a regulatory action (withdrawal, suspension or changes to the marketing authorization) of a decentralized authorized medicine as a result of the evaluation of safety data). It provides for a harmonized European approach because the CHMP is asked to prepare an opinion on whether or not the regulatory actions should be implemented throughout the European Union. In January 2010, the European Medicines Agency (EMEA) finalized a safety review of medicines containing sibutramine. The review was initiated because data from the Sibutramine Cardiovascular Outcome Trial (SCOUT) showed an increased risk of serious, nonfatal cardiovascular events, such as stroke or heart attack, with sibutramine compared with placebo. The SCOUT trial, in which nearly 10,000 patients were enrolled for up to six years, was designed to determine the impact of weight loss with sibutramine on cardiovascular problems in a large group of overweight and obese subjects with known or high risk for cardiovascular disease.

The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the risks of these medicines are greater than their benefits and recommended the suspension of marketing authorizations for these medicines across the European Union. As per recommendations, doctors should no longer prescribe, and pharmacists should no longer dispense the medicine. Patients taking sibutramine should make an appointment with their doctor at the next convenient time to discuss alternative measures to lose weight. Patients who wish to stop treatment before seeing their doctor can do so at any time. The CHMP noted that the use of sibutramine was not in accordance with the prescribing information for most of the patients enrolled in the SCOUT study, as sibutramine is contraindicated in patients with known cardiovascular disease. The treatment duration in the study was also longer than normally recommended. However, because obese and overweight patients are likely to have a higher risk of cardiovascular events, the Committee was of the opinion that the data from the SCOUT are relevant for the use of the medicine in clinical practice. The Committee also noted that the data from available studies show that the weight loss achieved with sibutramine is modest and may not be maintained after stopping. The CHMP was therefore of the opinion that the benefit of sibutramine as a weight-loss aid do not outweigh the cardiovascular risks.

### Efalizumab (Sept 2009)

In 2004 Efalizumab was granted a marketing authorization valid throughout the European Union for the medicinal product Raptiva (efalizumab). The

drug was approved for the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporin, methotrexate and PUVA. On 19 February 2009, the Committee for Medicinal Products for Human Use (CHMP) issued an opinion recommending the suspension of the marketing authorization for Raptiva in all Member States in which the product was marketed, as its benefits in the treatment of psoriasis were modest, while there was a risk of serious side effects, including the occurrence of progressive multifocal leukoencephalopathy (PML). As a condition for lifting the suspension, the CHMP recommended that new evidence should be provided to identify a subgroup of patients for which the benefits of Raptiva would outweigh the risks. On 12 May 2009, EC (European Commission) was notified by the Marketing Authorization Holder for Raptiva (Serono Europe Limited) of its decision to voluntarily withdraw the marketing authorization for the product, as it did not intend to conduct the clinical trials necessary to fulfil the requirements for lifting the suspension. On June 9, 2009 the European Commission issued a decision to withdraw the marketing authorization for Raptiva. Pursuant to this decision the European Public Assessment Report for Raptiva will be updated to reflect that the marketing authorization is no longer valid.

### Rimonabant (October 2008)

Rimonabant (Acomplia) was authorized in the European Union (EU) since June 2006 as an adjunct to diet and exercise for the treatment of obese patients or overweight patients with associated risk factors. Warnings about psychiatric side effects, in particular depression, were included in the product information since Acomplia was first authorized. The product information for Acomplia was continuously updated to include further contraindications The warnings were upgraded on these concerns to manage the risks associated with the use of Acomplia. In July 2007, the CHMP recommended contraindicating Acomplia in patients with ongoing major depression or who are being treated with antidepressants. Furthermore, in May 2008, the CHMP recommended updating the product information to reflect the fact that depression may occur as a side effect of Acomplia in patients who have no obvious risk factors apart from obesity itself and to advise prescribers to monitor patients for signs and symptoms of psychiatric disorders, particularly depression, after the start of treatment.

The CHMP considered that the new data from postmarketing experience and ongoing clinical trials indicated that serious psychiatric disorders may be more common than in the clinical trials used in the initial assessment of the medicine. The CHMP was also of the opinion that these psychiatric side effects could not be adequately addressed by further risk minimization measures. In addition, the CHMP noted, that the effectiveness of Acomplia

in clinical practice is more limited than was expected on the basis of the clinical trials, because available data indicate that patients generally take Acomplia only for a short period. Following the assessment of the available information on the benefits and risks of Acomplia including data from studies completed since it was granted marketing authorization, the CHMP confirmed that there is an approximate doubling of the risk of psychiatric disorders in obese or overweight patients taking Acomplia compared to those taking placebo. It was concluded that the benefits of Acomplia no longer outweigh its risks and the marketing authorization should be suspended across the European Union (EU). Consequently, in October 2008 The European Medicines Agency (EMEA) recommended the suspension of the marketing authorization for Acomplia (rimonabant) from Sanofi-Aventis.

### Lumiracoxib (December 2007)

Lumiracoxib is a nonsteroidal anti-inflammatory drug (NSAID) that belongs to the group 'COX-2 inhibitors'. It is used for symptomatic relief in the treatment of osteoarthritis of the hip and knee. Lumiracoxib was authorized in the European Union in Austria, Belgium, Czech Republic, Cyprus, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Latvia, Lithuania, Luxembourg, Malta, Nederland, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom (UK) under the trade names Prexige, Stellige, Hirzia and Frexocel. The review of lumiracoxib was conducted under Article 107 of the Community code relating to medicinal products for human use (Directive 2001/83/EC). As discussed earlier in this chapter, this type of procedure is initiated in cases where a Member State intends to withdraw, suspend or change the marketing authorization of a nationally authorized medicine as a result of the evaluation of new safety data. It provides for a harmonized European approach because the CHMP is asked to prepare an opinion on whether or not regulatory action should be implemented throughout the European Union.

The European Medicines Agency (EMEA) has recommended the withdrawal of the marketing authorizations for all lumiracoxib-containing medicines, because of the risk of serious side effects affecting the liver. Finalizing a review of available information on the safety of lumiracoxib, which concentrated on worldwide data on liver side effects, the Agency's Committee for Medicinal Products for Human Use (CHMP) concluded at its December 2007 meeting that the risks of lumiracoxib-containing medicines are greater than their benefits. The liver safety of lumiracoxib was monitored continuously since its launch in 2005. In August 2007, the product information was updated with contraindications for patients with potential liver problems and advice to doctors that they should frequently monitor patients treated with lumiracoxib for liver reactions. More spontaneous reports of serious liver problems were received since then, which increased the concerns regarding hepatic safety for

lumiracoxib. In addition, the CHMP considered that the proposed measures to reduce the risk for liver reactions cannot assure adequate patient safety and are not considered realistic given the approved clinical indication. The CHMP therefore recommended that the marketing authorization for these medicines should be withdrawn in all European Union (EU) Member States where they are approved. The Europe-wide review was started on 15 November 2007 following assessment of reports of serious liver injury by the United Kingdom. The CHMP was asked to give a scientific opinion on whether the marketing authorizations for lumiracoxib should be revoked (withdrawn), suspended or changed across the EU. On 19 November 2007 the United Kingdom suspended the marketing authorization of this medicine. Similar regulatory action was taken in Germany, Cyprus and Belgium. Consequently, the CHMP recommended the withdrawal of the marketing authorizations.

*For details on other recalls made in last 5 years reader may visit the website http://www.fda.gov/Safety/Recalls.*

Other precautionary statements (black box warning) or public health advisory (ies) due to discovery of potential hazards during their use have also been included to various drugs. The examples include:

- New safety information (severe, life-threatening and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure,) added to the 'WARNINGS and Boxed Warning for VIRAMUNE'
- New warning for Strattera, a drug approved for attention deficit hyperactivity disorder (ADHD) in adults and children. The labeling is being updated with a bolded warning about the potential for severe liver injury
- Public health advisory describing revisions to the *Warnings, Dosage and Administration, Clinical Pharmacology and Precautions* sections of the labeling of crestor (rosuvastatin calicum)
- Public health advisory concerning the use of nonsteroidal anti-inflammatory drug products (NSAIDs), including those known as COX-2 selective agents.[26]

## SUMMARY

Continuous advancement and introduction of new treatment approaches facilitated by clinical trials has widened pharmacovigilance concerns and the importance of understanding the safety issues during the drug development process (clinical research for traditional and complementary medicines, herbals, medical devices, blood products, biological and vaccines). The standards that are needed to be applied for the qualitative analysis and reporting of safety data in clinical trials should be same as that required for reporting of efficacy data. Safety update reports should specify the number and type of specific adverse events in each study group along with the number of patients withdrawn from the study because of each adverse event.

**ANNEXURE I**

## Pharmacovigilance (safety monitoring) in Clinical Trials: European Regulations

European regulations governing the pharmacovigilance process during clinical trial are listed below:

| | |
|---|---|
| Directive 2001/20/EC | Directive 2001/20/EG of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities' (L121, pp34-44) |
| ENTR/CT 3<br>Brussels April 2004 | Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. A guidance written in request of Article 18 of Directive 2001/20/EC |
| ENTR/CT 4<br>Brussels April 2004 | EudraVigilance Clinical Trial Module—Detailed guidance on the European Database of Suspected Unexpected Serious Adverse Reactions. A guidance written in request of Article 17.3(a) of Directive 2001/20/EC |
| ENTR/CT 5<br>Brussels April 2004 | Detailed Guidance on the European Clinical Trials Database (EudraCT Database). A guidance written in request of Article 11 of the Directive 2001/20/EC |
| E2A CPMP/ICH/377/95 | ICH Topic E 2 A : Clinical Safety Data Management: Definitions and Standards for Expedited Reporting |
| F2BMCPMP/ICH/287/95 | Data Elements for Transmission of Individual Case Safety Reports (ICSR) (2002). E2B (M) Data Elements for Transmission of ICSR (2004 Q and A) |
| E2B/M2 CPMP/ICH/285/95 | Maintenance of the Clinical Safety Data Management including the Maintenance of the Electronic Transmission of ICSR Message Specification |
| E2F (EMEA/CHMP/ICH/309348/2008) | Note for guidance on development safety update report |
| E6 (R1)CPMP/ICH/135/95 | ICH Topic E 6 (R1) Guideline for Good Clinical Practice and note for guidance on Good Clinical Practice |
| CIOMS Working Group V | Current Challenges in Pharmacovigilance: Pragmatic Approaches |
| CIOMS Working Group VI | Management of Safety Information from Clinical Trials |

**ANNEXURE II**

### Format and Presentation of Development Safety Update Report

#### Format

As per ICH E2F 'Guidance on Development Safety Update Report' (EMEA /CHMP/ ICH/309348/2008) the format and content of the 'Development Safety Update Report' should follow the table of contents as provided below. For each heading where information is available, the information should be presented concisely; when no information is available, this should be stated. Guidance on the content of each section is provided in ICH E2F 'Guidance on Development Safety Update Report' (EMEA/CHMP/ICH/309348/2008). It should be noted that the section numbers below reflect the numbering in the DSUR.

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14. Overall Safety Assessment
14.1. Evaluation of the Risks
14.2. Benefit-risk Considerations
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Appendices to the DSUR

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CHAPTER

# 10 Data Management in Pharmacovigilance

## INTRODUCTION

Pharmacovigilance being a sensitive subject, it is quintessential that a robust data management system is there in place at any pharmacovigilance department so that the stringent regulatory guidelines and global industry norms are adequately followed. A very intensive team effort is required for the successful outcome in the data management operations in pharmacovigilance. Many steps are involved in the processing of individual adverse event/suspected adverse reaction report cases, all requiring high and complex degrees of technical skill and judgment to ensure that the information is properly documented, reviewed, understood, and placed in proper perspective relative to a developing or already established benefit-risk profile for the product. Some of the important things that need to be adequately addressed in any pharmacovigilance department are source of report, triage of cases, validation of a case report, case entry and review in safety database, strategy to seek follow-up information and archival. Generation of line listings and summary tabulation for the periodic reports from the safety data base is also one of a very important activity of the data management.

## SOURCE OF REPORT

The source of a report can be a significant factor for the evaluator. Awareness of the "environmental" factors contributes to an understanding of the quality and value of the information for assessing a case. The nature, amount and even feasibility of any required follow-up will also be highly dependent on the source.[1]

Adverse events may arrive in a company from multiple sources. The traditional sources of adverse experience information are clinical trials and spontaneous reports (voluntary, unsolicited communications on marketed products). Adverse experience(s) may also be received from various other sources, including internet reports, solicited reports from patient support programs, surveys, epidemiologic studies, disease registries, regulatory and other databases, and licensor and licensee interactions. Standard operating procedures must be in place to ensure proper handling of these adverse

events (AEs) and that these AEs arrive in a timely manner (usually 1-2 days) in the drug safety department if they first arrive elsewhere in the company.

## Unsolicited Sources

### *Spontaneous Reports*

A spontaneous report is an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional center, Poison control center) that describes one or more adverse drug reactions (ADR) in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Consumer adverse reaction reports should also be handled as spontaneous reports.[2] Regulatory authorities might require medical confirmation for the purpose of expedited reporting. Even if reports received from consumers do not qualify for regulatory reporting, the cases should be retained. Even in the absence of medical confirmation, any ADR with significant implications for the medicine's benefit-risk relationship should be submitted on an expedited and/or periodic basis. These reports should be included in the PSURs in an appendix or as a statement indicating they have been reviewed and do or do not suggest new findings.[2]

Post marketing spontaneous reports are always considered to have an implied causal relationship to the drug. If an event is considered not to be drug related, it should be retained in the company database but not reported.

### *Literature*

Each Marketing Authorization Holder (MAH) is expected to regularly screen the worldwide scientific literature by accessing widely used systematic literature reviews or reference databases. The frequency of the literature searches should be according to the applicable local regulatory requirements. The publication reference(s) should be given as the report source; additionally a copy of the article might be requested by the local regulatory authority to accompany the report. All company offices are encouraged to be aware of publications in their local journals and to bring them to the attention of the company safety department as appropriate.[1]

If the product source, brand, or trade name is not specified, the MAH should assume that it was its product, although the report should indicate that the specific brand was not identified. If multiple products are mentioned in the article, a report should be submitted only by the applicant whose product is suspected. The suspected product is identified as such by the article's author.[3]

### *Internet*

The internet is a rapidly growing medium for communication and transmission of information (e-mail and websites).

MAHs should regularly screen websites under their management or responsibility for potential ADR case reports. MAHs are not expected to screen external websites for ADR information. Nowadays, MAHs utilize their websites to facilitate ADR data collection, e.g. by providing ADR forms for reporting or by providing appropriate contact details for direct communication.[2]

*Other Sources*

If an MAH becomes aware of a case report from nonmedical sources, e.g. the lay press or other media, it should be handled as a spontaneous report. For the determination of reportability, the same criteria should be applied as for other reports.[2]

### Solicited Sources

Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, postapproval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous. For the purpose of safety reporting, solicited reports should be classified as study reports and therefore, should have an appropriate causality assessment by a healthcare professional or an MAH. Signals may arise from solicited reports so they should be reviewed on an ongoing basis.[2]

### Contractual Agreements

The marketing of many medicines increasingly takes place through contractual agreements between two or more companies, which may market same product in the same or different countries/region. It is very important that explicit licensing/contractual agreements be made between two or more companies specifying the processes for exchange of safety information, including timelines and regulatory reporting responsibilities. Safety personnel should be involved in development of any agreements from the beginning. Processes should be in place to avoid duplicate reporting to the regulatory authority, e.g. assigning responsibility to one company for literature screening. Every reasonable effort should be made between the contracting partners to minimize the data exchange period so as to promote compliance with MAH responsibilities. The time frame for expedited regulatory reporting is generally 15 calendar days from the first receipt of a valid case by any of the partners.[2]

### Regulatory Authority Sources

Individual serious unexpected adverse drug reaction reports originating from foreign regulatory authorities are subject to expedited reporting to other

authorities by each MAH. Resubmission of serious ADR cases without new information to the originating regulatory authority is not usually necessary, unless otherwise specified by local regulation.[2]

### Call Centers[4]

A call center is a centralized office used for the purpose of receiving and transmitting a large volume of requests by telephone. A call center is operated by a company to administer incoming product support or information inquiries from consumers. Many multinational companies (MNCs) have their own drug safety call centers or they have outsourced this activity to specialized call centers which provide service to pharmaceutical companies with a complete postmarketing surveillance solution including adverse event monitoring and reporting, drug information services and product complaint management. Specialized drug safety call centers are rapidly increasing medium of collecting ADRs, product complaints, medical inquiries, etc.

Call centers are usually set up to receive calls from consumers, patients, physicians and other healthcare providers. They usually cover questions about the products, requests for reimbursement, reporting of AEs and product quality defects and problems. The call center must be set up in such a way as to ensure that all AEs and quality complaints are captured and sent to the appropriate departments for handling (e.g. the AEs to drug safety and the quality complaints to manufacturing quality). Standard operating procedure (SOP) must be in place to ensure the proper handling of AEs and quality complaints.

## TRIAGE OF CASES

Once the complaint is received at pharmacovigilance department of a pharmaceutical company, it must be properly classified for processing. The report should be date stamped upon entry into the pharmacovigilance department. For electronic reports, presumably whatever system is used automatically date stamps the information. As a general principle, this should be done within 24 hours of receipt. The initial triage should be to determine whether the report needs urgent processing in order to be transmitted to the regulatory authorities or business partners. The triage is done by drug safety associates to make an accurate determination. For difficult or controversial cases, the triage personnel may request assistance from the drug safety physician. Triage or case assessment should be standardized and trainable. Triage should cover, at the least, the following (Fig. 10.1):

- Adverse drug reaction(s)
- Product quality complaint(s) associated with adverse drug reaction(s)
- Product quality complaint(s)
- Medical inquiries
- Legal.

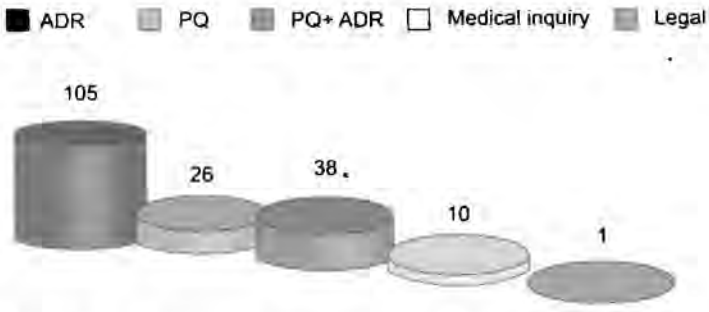



**Fig. 10.1:** Example of triage management on a particular day at safety department of an organization

ADRs can further be triaged using the following criteria:

- Serious or nonserious
- Expected or unexpected
- Causality (especially for SAEs from clinical trials).

Triaging of cases is also useful for those cases that do not have the minimum data elements for an ADR case reporting at the time of initial receipt. Usually, at this moment, a "Unique Identifier Number" is allotted to all the cases irrespective of the source or medium of receipt of the case and then is triaged. Some companies log all cases into a spreadsheet or database to track them and ensure that they are not lost in transit within the safety department. After triage, each case should be assigned to the appropriate department (e.g. safety, medical, product quality, legal, etc). As a general practice, pharmaceutical companies develop SOPs on triaging, handling and prioritizing the cases related to medicinal products.

## VALIDATION OF A CASE REPORT

Accurate, complete, and bonafide information is very important for MAHs and regulatory agencies identifying and assessing adverse drug reaction reports. Both are faced with the task of acquiring sufficient information to help ensure that the reports are authentic, accurate, as complete as possible and nonduplicative.

The minimum information[5] required for expedited reporting purposes is:

- An identifiable patient
- The name of a suspect medicinal product
- An identifiable reporter
- An event or outcome.

Information related to patient and reporter is very important not only to provide at least some assurance that the case can be regarded as valid (real people), but to assist a company or regulatory agency to ensure that the case does not represent duplicate reporting on the same patient from the same or other sources.

A case meeting minimum criteria is considered sufficient to inform a company or a regulator to the possibility that an adverse reaction to a drug has occurred. Some companies treat reports without all four minimum case criteria as "incomplete cases" that are tracked in a database, follow-up efforts attempt to obtain further information to confirm the existence of a valid case. When follow-up attempts yield no information (and the minimum case criteria remain unfulfilled), they may not required to be reported but should be kept in the database as "incomplete cases".

### Identifiable Reporter

It is generally assumed that a reporter is a person who describes a suspected ADR to a pharmaceutical company (usually MAH), to a health care system or to an institution authorized to handle ADR information for pharmacovigilance purposes. Ideally, the reporter will have the most knowledge about the patient. In most instances, this is likely to be a health professional involved in the care of the patient. However, the consumer/patient or other nonhealthcare professional may also be a reporter of such case information, sometimes with access to medical details, although he/she may not necessarily be able to make a medical judgment about the information. In addition, companies receive reports from health care professionals who may have no direct healthcare responsibility for the patient and have no direct knowledge of medical details.

ICH guideline E2B[6] refers to the "primary source" of a report as the person who provides the facts of the case, for a publication this would be the investigator or first author. However, any party that provides useful information on a case should be considered a "reporter".

All parties supplying case information or approached for case information should be identifiable, not only the initial reporter (the initial contact for the case), but also others supplying information. In the absence of qualifying descriptors, a report referring to a definite number of patients should not be regarded as a case until the minimum four criteria for case reporting are met. For example, "Two patients experienced..." or "a few patients experienced" should be followed up for patient identifiable information before regulatory reporting.

### Identifiable Patient

With respect to adverse event reporting, some level of patient identifiability is necessary in order:

- to be certain that the same patient is not the subject of duplicate reports or is recorded in multiple files
- to help establish authenticity of a case report in order to avoid scientific errors or fraud, and
- to allow follow-up communication with the health professional or patient if more evidence of confirmation is warranted, or out of medical treatment necessity.

As per E2D guidelines,[2] "One or more of the following should automatically qualify a patient as identifiable: Age (or age category, e.g. adolescent, adult, elderly), gender, initials, date of birth, name, or patient identification number. In addition, in the event of second-hand reports, every reasonable effort should be made to verify the existence of an identifiable patient and reporter". Local data privacy laws regarding patient and reporter identifiability might be applied.

### Criteria for Seriousness

In accordance with the ICH E2A guideline,[5] a serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or results in prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for acute gastroenteritis that do not result in hospitalization, or development of drug dependency or drug abuse.

### Criteria for Expectedness

Expectedness of the event refers to events that may or may not have previously been observed and documented. As defined in the E2D,[2] "An ADR whose nature, severity, specificity or outcome is not consistent with the term or description used in the local/regional product labeling (e.g. Package insert or Summary of product characteristics) should be considered unexpected". To ensure proper classification and specificity of ADR terms, ideally three conditions should be fulfilled:

- Case reports must be sufficiently well documented
- there must be no ambiguity regarding the nature, severity and outcome of the event and
- there must be no ambiguity regarding the section(s) in the Reference safety information (RSI) where the appropriate information is placed.

## CASE PROCESSING IN SAFETY DATABASE

Safety database (organized collection of data) is designed to support safety surveillance for:

- Drugs (IND and marketed products)
- Devices
- Vaccines.

Most of the organizations use a safety database for processing ADR reports. Generally a case in a safety database flows from data entry to quality review followed by medical review and distribution and submission to regulatory agencies/partners. These steps are described in detail in the following sections.

### Data Entry

After triaging, the case should be entered into the computerized safety database. If a case number (also called a "manufacturer control number" or "medical reference number") has not been assigned to the case at the triage, it is assigned now (Fig. 10.2).

Many software companies are into the business of developing safety databases which fulfill the criteria of 21 CFR Part 11[7] (e.g. Relsys, Oracle, Aris Global, Clintrace, etc). Many pharmaceutical companies develop their own safety databases. Although all the safety databases contain almost similar fields, some differences may lie in the user friendliness, management, view, speed, and output reports. For user friendliness, the front end of these software are made in such a way that end user or the data entry personnel can enter data very easily and more accurately. For example, at the time of data entry, initial screen generally have fields which cover the details of patient, reporter, adverse event/report, suspected medicinal product (to fulfill the criteria of minimal reporting). These systems generally require additional mandatory fields like date of receipt of ADR, source country, type of source (e.g. literature, spontaneous report, clinical trials). These data fields are

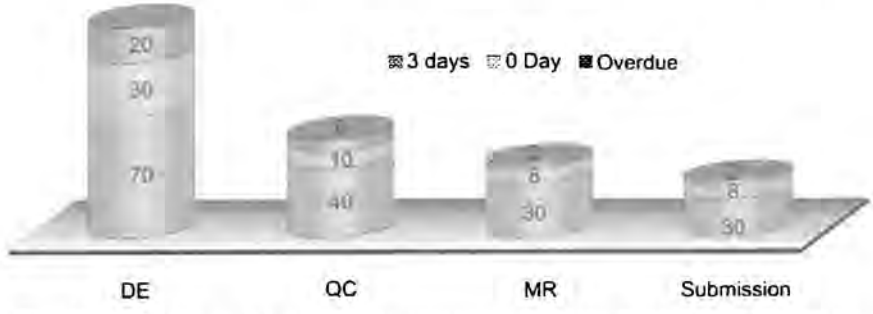



**Fig. 10.2:** Workflow status of cases present in a safety database which can be viewed on the screen of a pharmacovigilance manager on a particular day

required to build the reporting rules based on the local regulations of each country. Once the case with minimum information for reporting is entered, the case is saved and manufacturer control number is assigned (auto-generated by the database). Generally, the databases are designed in such a manner that information related to case can be entered easily and stored in a structured manner. For example, information can be divided into following fields:

- *Subject:* In this window, data entry personnel can enter data related to subject like name or initials, height, weight, gender, age or age group, date of birth, pregnancy, last menstrual period date, etc.
- *Suspect drug:* In this window, data entry personnel can enter data related to suspected medicinal product like name, start date, end date, duration of exposure, formulation, dose and dosage form, indication for which suspect drug was administered, route of administration, batch number, lot number, manufacturer's details, etc.
- *Event*: Which includes fields like, reporter's verbatim, company's verbatim, MedDRA terms, event onset date, event end date, criteria for seriousness, duration of event, whether any therapy was given for treatment of event, etc.

Field related to reporter's information may include reporter's name, contact address, phone number, e-mail id, whether reporter is a health care professional or not, secondary or tertiary reporter, etc. Reportability or submission fields may include country where the case is reportable, schedule of reports, including due date of submission, date of submission etc.

Sometimes data entry is easy, sometimes it is not. Some companies have an initial review by a medical professional who highlights items for data entry, other companies have the source documents sent directly to the data entry group (nonmedical professionals) and have medical review only after it is completed. MedDRA[8] coding of AEs, medical history and other required MedDRA fields are done either by the drug safety group or by a dedicated coding group. Drug coding using a standardized dictionary (e.g. WHO DD[9]) is also done.

### Data Review and Quality Checks

After data entry, a drug safety specialist reviews the data entry against the source documents and prepares or reviews the case narrative. Any changes or additions to the case are made at this time. A clear methodology on the quality check should be developed so that it is done in a standardized and repeatable way. The quality review should look at content, grammar and format. Follow-up information should be requested when the initial case is incomplete or unclear. It is almost always required that follow-up queries be sent to the reporter to complete the case data. In general, for serious cases, at least 2 diligent follow-ups are done. For nonserious cases at least 1 follow-up

is done. Follow-up data should be entered into the database using a similar procedure to the one used for initial data. Care must be taken to ensure that the data are not mistaken for a new case but rather are clearly identified as follow-up to a case already received.

## Medical Review

After quality review of the case, all cases should be reviewed by the drug safety physician/medical reviewer. The purpose of careful medical review is to ensure correct interpretation of medical information. Preferably, information about the case should be collected from the healthcare professionals who are directly involved in the patient's care. Regardless of the source of an ADR report, medical reviewer should carefully review the report for the quality and completeness of the medical information. The medical review should generally cover the medical content of the case with particular attention paid to the narrative, the suspect and concomitant drugs (including dosages), the past medical history and coding. The review should also include, but is not limited to, the following considerations:

- Is a diagnosis possible?
- Have the relevant diagnostic procedures been performed?
- Were alternative causes of the reaction(s) considered?
- What additional information is needed?

ADR terms should be used consistently and in accordance with recommended standards for diagnosis, if possible. The report should include the verbatim term as used by the reporter or an accurate translation of it. When a case is reported by a consumer, his/her description of the event should be retained, although confirmatory or additional information from any relevant healthcare professionals should also be sought and included.

It is generally not the role of the physician to do a source document quality review unless he or she needs to refer to the source documents for clarification of a medical point.

### *The Role of Narratives*

The objective of the narrative is to summarize all relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, and ADR(s) including the outcome, laboratory evidence (including normal ranges) and any other information that supports or refutes an ADR. The narrative should serve as a comprehensive, stand-alone "medical story". The information should be presented in a logical time sequence; ideally this should be presented in the chronology of the patient's experience rather than in the chronology in which the information was received. In follow-up reports, new information should be clearly identified. Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units. Key information from supplementary records should be included in the report and their

availability should be mentioned in the narrative and supplied on request. Any relevant autopsy or post-mortem findings should also be summarized in the narrative and related documents should be provided according to local regulation and if allowed by local data privacy laws. Terms (e.g. AEs/ADRs, indication, and medical conditions) in the narrative should be accurately reflected in appropriate data fields.

### Case Closure/Completion

A case is never really closed as new information could arrive weeks, months or even years later, requiring the case to be updated. But for practical purposes, once the above steps are concluded and follow-up requested, a case may be considered closed or completed for operational purposes. As and when follow-up arrives, the case can be reopened and processed.

### Distribution and Submission

Cases are next distributed to Regulatory department and to other companies with whom safety exchange agreements are in place for submission to regulatory authorit(y)ies. Cases may also be sent to subsidiaries or affiliates worldwide for their submission to local agencies— often with a cover letter in the local language and, in some instances, with a translation of the case itself into the local language if English is not accepted.

### Tracking and Metrics

It is critical that all cases reports be tracked so that none is submitted late to the regulatory authorities, subsidiaries or business partners. Hence, safety department should maintain a track of all the cases received at organization. This is done in spreadsheets or using a safety database. In general, tracking reports should be electronic and generated automatically from the drug safety database. Most modern drug safety databases have a tracking function with customizable reports. Manual tracking on spreadsheets is time consuming and usually unsatisfactory once AE volume grows and the staff becomes large. The tracking of cases should base on the workflow step (i.e. whether the case is at initial entry, or QC or medical review or at submission).

Each drug safety specialist and manager should be aware of status of all the cases (like number of pending cases, workflow step, and, in particular, the deadlines for each case). The manager can reallocate cases or other work to ensure that the time-critical cases are handled appropriately in the case of absence, vacation, or overload of his or her staff. Similarly, non expedited cases that need to be completed for aggregate reports (e.g. PSURs, ASRs, etc.) should be tracked so that they are completed by the time of data lock.

## Timelines

The timing, sequence and duration of each step in the processing of an AE should be clearly defined in the standard operating procedures. Generally, based on the type of reports, following timelines are followed:

- *7 Day reporting:*[10-12] Rapid reporting of the death/life-threatening clinical trial cases for submission to the regulatory authorities within 7 calendar days from first receipt by anyone in the company. 7 day reporting timelines for such cases are applicable for US, Europe and many other countries but it may vary in different countries as per the applicable local regulations. This usually means completing the case within approximately 5 days and attempting to get whatever follow-up information is needed immediately.
- *14*[13]*/15-Day*[10-12] *Reporting:* These are serious cases for which reporting must be done by calendar day 14/15 but preferably sooner to allow quality review, transmission to business partners. Again the timelines in different countries may vary as per the local applicable regulations. Many companies develop workflow such that all cases are completed by, say, calendar day 10 after initial receipt. Completion dates tend to range from 8 to 12 days in companies, though most companies pick one time frame for all cases and stick to it. This makes for simpler processing and tracking within the drug safety group.
- *Processing of other serious cases* that are not expedited reports. These cases do not have to be sent to the regulatory authorities within 15 calendar days. Rather they are included in NDA periodic reports (every 3 months or yearly),[14] IND annual reports,[15] and PSURs.[3] Thus there is usually the potential for a longer time frame for processing if needed. However, this is not always the case in practice.
- Serious cases that are to be sent to subsidiaries, business partners, and others may require rapid processing also if contractual arrangements require this. Many companies exchange all serious cases within 10 calendar days whether expedited or not.
- Sometimes a case is not an expedited report in one country but is an expedited case in other countries (e.g. the local labeling or reporting regulations are different there). This case must be transmitted to the subsidiary or business in time to meet 15-day reporting rules. It is often the situation, especially in large multinational companies, that the sending company (e.g. drug safety in the home office) is not able to know whether any particular serious case is an expedited report or not. Thus, many companies process these cases as if they were expedited reports and use a completion date of 8 to 12 calendar days (as noted above).
- *Nonserious cases* may be processed more slowly (e.g. 30 days) because they are not reportable at all or are reportable only in aggregate reports. Nevertheless, it is wise to screen nonserious cases rapidly upon receipt, especially if they come from "less than reliable sources," to ensure that

no serious cases are misclassified (presumably not intentionally) as nonserious cases. This could lead to late expedited reports.

- Similarly, the *"other" cases*, such as literature, legal and media, should be processed as appropriate for the company's needs. It is a general rule of thumb that the process should be kept as simple as possible and that "exceptions to the rule" be kept limited. As few as three fundamental procedures could serve: 7 day cases, all serious cases, and all nonserious cases.
- *Product quality complaints related cases* should be forwarded to the respective departments for their inputs.
- Medical inquires should be handled by medical department. Usually these queries should be immediately answered to the consumers by Medical experts or consumers should be provided with appropriate available literature article as soon as possible.

Most of the databases have the capability to set reporting rules based on various criteria (like seriousness, expectedness, causality, workflow step). Timelines for AE cases in the database should be built in accordance with the country specific regulatory timelines. Database should automatically generate a reminder to the concerned individual telling him or her of the timing and due date for each case. The due dates would be updated as needed (e.g., it is determined to be or not to be a 15-day expedited report or a case is upgraded from non serious to serious). Attention must be paid to weekends and holidays in calculating due dates. Each person in the workflow knows when his or her task is due and the manager is able to track the case through each step to ensure its completion. Figure 10.3 shows the workflow of individual cases in a Pharmaceutical company.

## FOLLOW-UP INFORMATION

The information from ADR cases when first received is generally incomplete. Ideally, comprehensive information would be available on all cases, but in practice efforts should be made to seek additional information on selected reports, including second-hand reports.

To optimize the value of follow-up, the first consideration should be prioritization of case reports by importance. The priority of cases for follow-up should be as follows:

- Serious and unexpected
- Serious and expected
- Nonserious and unexpected.

In addition to seriousness and expectedness as criteria, cases "of special interest" also deserve extra attention as a high priority (e.g. ADRs under active surveillance at the request of the regulators), as well as any cases that might lead to a labeling change decision.

Follow-up information should be obtained, via a telephone call and/or site visit and/or a written request. The company should provide specific

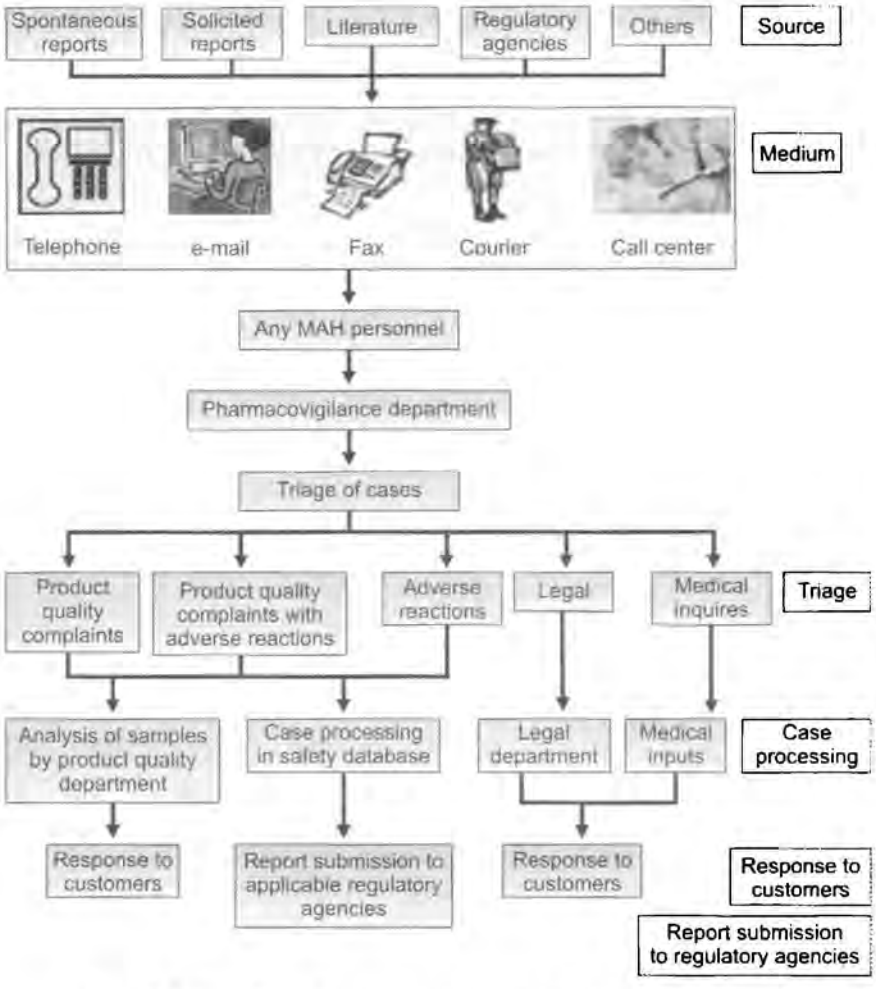



**Fig. 10.3:** Workflow of cases received at pharmaceutical company

questions it would like to have answered. Follow-up methods should be tailored towards optimizing the collection of missing information. Written confirmation of details given verbally should be obtained whenever possible. In exceptional circumstances, if requests for information have been refused by the reporter, a regulatory authority might be able to assist an MAH in obtaining follow-up data (Fig. 10.3).

To facilitate the capture of clinically relevant and complete information, use of a targeted questionnaire/specific form is encouraged, preferably at the time of the initial report. Ideally, healthcare professionals with thorough pharmacovigilance training and therapeutic expertise should be involved in the collection and the direct follow-up of reported cases (particularly those of medical significance). For serious ADRs, it is important to continue follow-up and report new information until the outcome has been established or the

condition is stabilized. How long to follow-up such cases is a matter of judgment.

It is important that at the time of the original report, sufficient details about the patient and reporter be collected and retained to enable future investigations, within the constraints imposed by local data privacy laws.

### Pregnancy Exposure

MAHs are expected to follow-up all pregnancy reports from healthcare professionals or consumers where the embryo/fetus could have been exposed to one of its medicinal products. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a fetus could have been exposed (e.g. if medicinal products taken before the gestational period should be considered).

## LINE LISTING AND SUMMARY TABULATIONS FOR PERIODIC SAFETY UPDATE REPORTS AND ANNUAL SAFETY REPORTS[16]

Safety related data is generally available with pharmacovigilance department, which can be generated from the safety database. This includes the following:

- Line listing for the reporting period
- Line listing for late breaking information
- Summary tabulation.

Pharmaceutical companies should have SOPs on the preparation of PSURs and generation of line listing and summary tabulations from database. Usually, pharmaceutical companies have templates for PSURs (or they refer E2C or Volume 9a for templates) including line listings and summary tabulations. As the regulations may vary from country to country, the template for PSUR is subjected to the requirement of a regulatory authority and hence may vary. One such template is shown in Table 10.1 for line listings and summary tabulation in Table 10.2.

**Table 10.1:** Template of line listing

| *Body SOC* | *Country* | *Age* | *Sex* | *Treatment* | *Treatment* | *Daily* | *Dosage* | *Onset* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|
| Case ID/ | | (years) | | | | dose | form | Date | |
| Pat. ID | | | | Start Date | End Date | and formulation | | | |
| Adverse event | | Reporter's verbatim (preferred term) | | | | | | | |
| Seriousness | | | | | | | | | |
| Concomitant medications | | | | | | | | | |
| Comments | | | | | | | | | |

**Table 10.2:** Template of summary tabulation

| *Preferred Term* | Serious | | Nonserious | | Cumulative | Serious |
|---|---|---|---|---|---|---|
| | unlisted | listed | unlisted | listed | unlisted | |

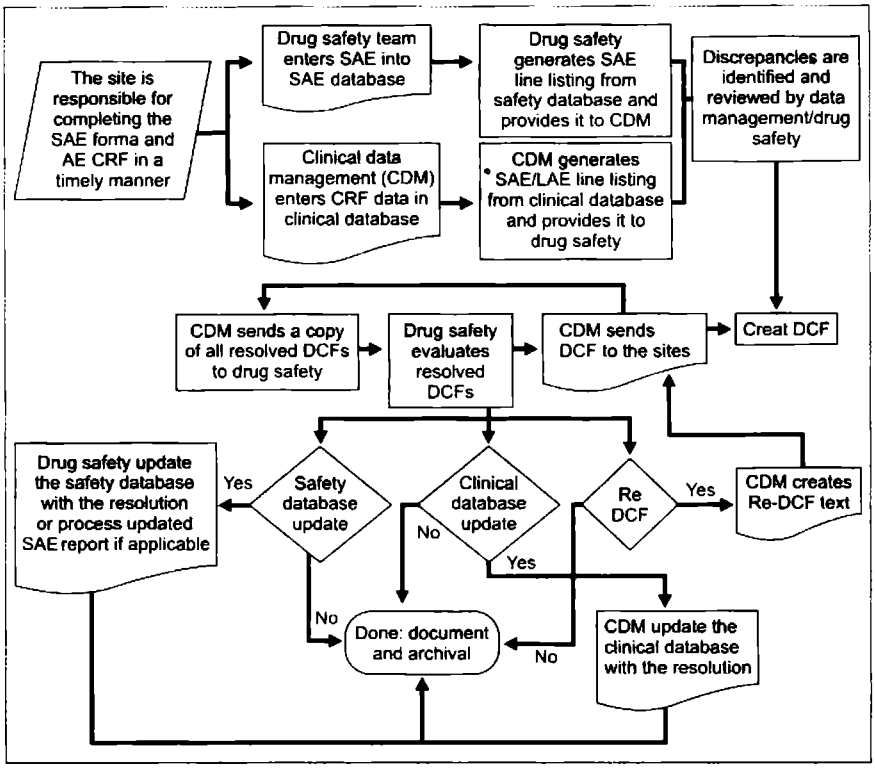
## SAE RECONCILIATION

The purpose of reconciling serious adverse events (SAE) in safety database with those recorded in clinical database is to ensure that SAEs are accurately and consistently captured in both the data bases. It is recommended that SAE reconciliation should be done automatically by the databases, in other words, the two databases should "talk" with each other and any discrepancies found should be verified from the investigative sites. Reconciliation of SAEs captured in clinical database during the conduct of clinical trial and SAEs recorded in the safety database is done as per project specific requirements or as and when required. The capture of SAEs in both clinical database and safety database is standardized and fields to be reconciled may include patient ID, date of birth, sex, study drug start date, SAE onset date, events (verbatim), MedDRA Preferred Term (PT) and system organ class (SOC), SAE criteria and SAE outcome. Changes to either database, as a result of reconciliation activities, is made in a timely manner to expedite clinical trial closure activities and/or safety reporting requirements. The other method apart from automated SAE reconciliation done by the system itself is the manual review of the line listings generated by the two databases. SAE reconciliation process can be initiated either by clinical data management or by drug safety department. Before initiating the reconciliation process, the designated drug safety and clinical data management personnel exchange the SAE line listings generated from their respective databases. It is the responsibility of clinical data management personnel to ensure that data included in the reconciliation cycle have been entered, that any data queries or clarifications have been returned and clinical database has been updated with the changes. During the process of reconciliation if any serious adverse event is found to be captured in clinical database, however not captured in the safety data base, the drug safety personnel should take it on a high priority and coordinate with the site to confirm whether the SAE has been actually missed by the site for reporting. In case it is confirmed that site has missed the SAE, it should be reported by the site as soon as possible and the reporting to the regulatory authorities should be done by the drug safety team as per the applicable regulations. A workflow showing the SAE reconciliation process is illustrated in Flow chart 10.1.

## ARCHIVAL

Safety department should archive a copy of all the source documents and final version of safety related documents in paper as well as electronically. These documents should be readily available for review whether by the company or during the audit. Standard operating procedures should be developed for archival of safety data. This may vary from organization to organization. These records should be kept in a secure and fire and water protected file room. Access to the file room should be limited, and files that

**Flow chart 10.1:** Workflow of SAE reconciliation process




leave the file room to be worked on by the staff or examined by someone else should be formally signed out and tracked. Old cases may be archived off-site, if need be, in a similarly protected environment but must be available for an audit within 1 working day. Hence the filing, indexing, and retrieval system must be very clearly worked out and efficient. Electronic records must also be kept and available for examination by an auditor. These documents, where appropriate, should be kept in the paper folders for each individual case safety report and easily retrievable during an inspection or audit by internal auditors.

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CHAPTER

# 11 TGN 1412: Lessons for Phase I Trials in India

*"This (TGN 1412) allegedly unprecedented event in clinical research represents a very human tragedy, one which will probably change forever the face of clinical drug development and testing, and one which gives us the opportunity to learn many valuable lessons."*

*Michael Goodyear Editorial B M J 2006* [1]

## INTRODUCTION

Over last 5 years, India has become a focus of off-shoring global clinical trials. Indian clinical trials arena has been moving, over last 12 years, through various stages. During late 90s, the country was facing the challenge of acceptance by international pharma sponsors. In the next 5 years, with the improvements in drug regulations and patent laws, the country has become attractive for global clinical trials.

The number of global trials in India, registered in clinicaltrials.gov, jumped from one between 1996-2000 to 149 between 2001 and 2005. Over the next 3 years, the number has quadrupled to 542 trials! Although the highest numbers of trials are in phase III, there is also an increase in early trials phase I and II.[2] As Indian clinical trial market grows, the Indian Contract Research Organizations (CROs) and pharma companies are considering India to be a destination for phase I studies. Although there are regulatory restrictions on phase I of drugs discovered outside India, the industry is hopeful that these restrictions will be removed in near future.

During this period, several clinical trial mishaps have occurred. One of the most tragic incidents was serious injuries to healthy volunteers in TGN 1412 phase I study.[1, 3, 5-7] This episode compelled the scientists, industries and regulators, to reassess the safety of phase I studies involving healthy volunteers. Several articles have discussed these issues and tried to draw lessons for planning and conduct of phase I studies.

## TGN 1412: THE SERIOUS ADVERSE EVENTS

On March 13, 2006, eight healthy male volunteers who were enrolled in a double-blind, randomized, placebo-controlled phase I study of the safety of TGN1412-a novel monoclonal antibody, suffered from serious adverse events (SAE).[3] TeGenero sponsored the trial of antibody TGN1412, which was

manufactured by Boehringer Ingelheim. The trial was conducted by Parexel International, a contract research organization at an independent clinical trials unit in Northwick Park and St. Mark's Hospital in London. On day 1 at 8 am, each volunteer received an intravenous infusion, 10 minutes apart, of either the study drug or placebo. The six volunteers in the treatment group were given TGN 1412 0.1 mg/kg body weight, infused at a rate of 2 mg per minute. The remaining two volunteers received a similar quantity of saline.

A series of adverse effects began to appear within 90 mins of TGN 1412 infusion. Five subjects complained of severe headache. This was accompanied by lumbar myalgia in all six subjects. Subsequently, they were restless and suffered from nausea, vomiting, bowel urgency, or diarrhea.[3] Five subjects developed amnestic episodes associated with severe pyrexia, restlessness, or both. All subjects had showed signs of a systemic inflammatory response that included erythema, and vasodilatation. Within four hours of infusion, all subjects developed hypotension (a reduction in systolic blood pressure of ≥ 20 mm Hg), accompanied by tachycardia, with maximal heart rates of 110 to 145 beats per minute. The temperatures recorded were 39.5 to 40.0°C. These adverse effects of early Phase were followed by serious complications in all subjects. Within 12 to 16 hours after infusion, all subjects became critical and showed signs of respiratory deterioration.[3] They developed pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Within 24 hours after infusion, severe depletion of lymphocytes and monocytes occurred.

All six subjects were transferred to an intensive care, where they received intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti–interleukin-2 receptor antagonist antibody.[3] All of them were given fresh frozen plasma and cryoprecipitate to correct coagulopathy. As the subjects had severe lymphopenia, they were treated with infusions of irradiated red cells and platelets, as required, to prevent possible graft-versus-host disease. Two subjects, who developed prolonged cardiovascular shock and acute respiratory distress syndrome, required intensive organ support for 8 and 16 days. Some problems persisted till 30 days after infusion. These were: generalized desquamation and muscle weakness in all; late myalgia, headache, difficulties with concentration, and short-term difficulties in finding words in five subjects; delayed hyperalgesia in three subjects; and, peripheral numbness in two subjects.

The clinical manifestations seemed to be a result of sudden and rapid release of proinflammatory cytokines produced by intravenous infusion of TGN 1412.[3] The course of illness resembled systemic inflammatory response syndrome (SIRS). The clinical progression showed four phases: (1) cytokine storm, involving the rapid induction of type 1 and type 2 cytokines and severe lymphopenia and monocytopenia; (2) reactive manifesting renal failure, disseminated intravascular coagulation, pulmonary infiltrates, and respiratory failure; (3) recovery of renal and pulmonary functions; (4) steady state characterized by normalization of the measured lab variables. Despite evidence of the multiple cytokine-release syndrome, all the six subjects survived.[3]

## TGN 1412: REGULATORY INSPECTION

Medicines and healthcare products regulatory agency (MHRA) and other European regulatory agencies conducted GCP, GLP, and GMP inspections from March 14 to 24, 2006.[4]

### MHRA GCP Inspection

The GCP inspection of TeGenero focused upon the preclinical work performed prior to the FIH study. MHRA did not find any irregularities in the preclinical work submitted. During the GCP inspection of Parexel, MHRA inspected clinical pharmacology research unit (CPRU) clinic, recruitment offices, reception, areas used to store the infusion pumps, office where blind break envelopes were stored, the sample laboratory and sample storage area. In addition, the Clinbase® electronic clinical trials database was viewed. The MHRA inspectors stated that there were no findings which could have contributed to the SAEs experienced by the trial subjects who received the study drug. However, they identified following discrepancies:

1. *Failure to adhere to documentation procedures*: Parexel failed to complete the full medical background of a trial subject in writing. One principal investigator did not update the medical history file in writing following a verbal consultation with one of the volunteers.
2. *Failure to document training and delegation for medical personnel:* The principal investigator failed to authorise, in the log, the full work remit for the bank screening physician at the start of their employment. MHRA inspectors were not satisfied about the adequacy of training of the bank screening physician for the assigned role.
3. *Failure to review insurance:* Parexel had not reviewed TeGenero's insurance policy to ensure that there were no exclusion categories within it that might impact upon their volunteers, in this study. However, the inspector did not find any exclusions which may have affected the volunteers' right for insurance cover.
4. *Failure to adhere to the unblinding procedure:* The two placebo volunteers were allowed to leave the trial before appropriate checks were undertaken to confirm that they were the ones to receive the placebo.
5. *Failure to have a contract:* There was no contract in place between TeGenero and Parexel, when the study started. The contract between Parexel and private laboratory was in the draft stage.
6. *Failure to provide medical cover:* There was no formal system in place to provide 24 hour medical cover for the volunteers.

### MHRA GMP Inspection

The GMP inspection included a review of the facilities, equipment, quality systems, documentation and records associated with the storage, preparation and release of TGN1412 and placebo at the unit. No deficiencies were found during the inspection.

The product batches used in the toxicology studies and the batch used for the subjects were tested to determine if the products met the batch release specification. All the results of product analysis confirmed that TGN1412, as administered to the trial volunteers, was fully compliant with the release specification. MHRA did not find any errors in the manufacture of TGN 1412.

### MHRA GLP Inspection

The purpose of the inspection was to assess whether the pivotal intravenous toxicity study in cynomolgus monkeys was conducted in accordance with the principles of GLP.

Additionally two validation studies and a dose-ranging study were also reviewed.

The inspector reported that the study was performed in accordance with the principles of GLP and that the results presented in the final report appeared to accurately reflect the raw data. No critical or major deficiencies were detected.

### MHRA Conclusion

The regulatory inspection suggested that the SAEs did not involve errors in the manufacture of TGN1412 or in its formulation, dilution or administration to trial participants. The MHRA, therefore, concluded that an unpredicted biological action of the drug in humans is the most likely cause of the adverse reactions in the trial subjects. TGN1412, a new class of monoclonal antibody has a stimulatory mode of action affecting certain types of cell in the immune system.

## TGN 1412: LESSONS

Post-TGN 1412, several articles have discussed the lessons from this tragedy.[5-7] The UK Government set-up an Expert Scientific Group (ESG) to review the lessons of from the TGN1412 trial, and to make recommendations to increase the safety of future FIH trials of the: (i) biological molecules with novel mechanisms of action; (ii) new agents with a highly species-specific action; and (iii) new drugs directed towards immune system targets.[8] The ESG reviewed diverse aspects of TGN1412 data and episode and made the following recommendations.

### Preclinical and Early Clinical Development

- Strategy for developing preclinical information relevant to safety of FIH trials science-based
- Regulatory process for FIH trials of higher risk agents and advanced medicinal products subject to regular review

- Need to expedite the collection of information from unpublished preclinical studies relevant to the safety of human exposure
- Expeditious sharing of safety information on FIH clinical trials between regulators.

### Preparation and Review of Clinical Trial Applications

- More communication between regulators and sponsors at an early stage
- Access for regulators to independent, specialist experts with research knowledge of their fields
- Flexibility in the time-scale of clinical trial appraisal in exceptional cases of unusual complexity.

### Design of the Phase I Trial

- Special consideration for new agents for which the primary pharmacological action for the proposed therapeutic effect cannot be demonstrated in an animal model
- Calculation of starting dose based on all relevant information; not just reliance on 'no observable effect level' (NOEL) or 'no observable adverse effect level' (NOAEL) in animal studies
- Selection of low starting dose, considering a margin of safety for FIH trials
- If preclinical information likely to be a poor guide to human responses *in vivo*, the calculation of starting doses to err on the side of caution
- Careful consideration to the route and the rate of administration of the first doses in FIH trials, with careful monitoring for an exaggerated response
- The trial design, including number of subjects, starting doses and the dose escalation regime, scientifically and statistically justifiable
- Sequential administration of new agents in FIH trials with an appropriate period of observation between dosing of individual subjects
- The decision whether to conduct a FIH trial in healthy volunteers or in patients carefully considered and fully justified.

### Clinical Environment

- Qualified principal investigators who are knowledgeable about the agent, its target and mechanism of action
- Development of a professional accreditation system for principal investigators conducting FIH clinical trials
- Treatment strategy for FIH studies where there is a predictable risk of certain types of severe adverse reaction to be planned beforehand
- Appropriate clinical environment supervised by staff with appropriate levels of training and expertise with immediate access to facilities for the treatment and stabilization of subjects in an acute emergency and with prearranged contingency availability of ITU facilities

- Adequate staffing and 24-hour cover when volunteers kept overnight
- All clinical sites for FIH trial to have standard operating procedures for emergency situations, and to ensure staff expertise in implementing these procedures through regular drills.

### Developing Expertise

- Need to increase availability of qualified and trained investigators
- Development and accreditation of specialist centers for phase I clinical trials of higher risk agents and advanced medicinal products.

## IMPACT ON PHARMACEUTICAL DEVELOPMENT

The TGN-1412 episode and ESG recommendations have influenced FIH trials of investigational medicinal products (IMP). In 2007, MHRA announced phase I accreditation scheme[9] and Association of the British Pharmaceutical Industry (ABPI) released new guidelines for phase I clinical trials.[10] Around the same time, European Medicines Agency's (*EMEA*) committee for medicinal products for human use (*CHMP*) prepared guidance on strategies for fir-in-human studies of IMP.[11] The British guidelines – MHRA and ABPI– reflect the ESG recommendations covering all IMPs – including high risk IMPs.

### Regulatory Guidelines

The MHRA reviews trials of higher-risk IMPs differently from trials of other IMPs. The MHRA regards certain IMPs as higher-risk.[10] Higher-risk IMPs:

- Act directly or indirectly on the immune system via a novel target or a novel mechanism of action
- Have the potential for a secondary effect on the immune system via a mechanism that is not well characterized
- May act via a species-specific mechanism or have activity that is unlikely to be predicted by animal studies.

The MHRA seeks the opinion of the clinical trials expert advisory group (CTEAG) of the commission on human medicines for those FIH studies with risk factors that would require review before a clinical trial may be authorized.[9,10] MHRA has also established a voluntary accreditation scheme for units conducting phase I trials in the UK, to create additional public confidence in the regulatory oversight of such trials.[10] The scheme defines a classification system based on facilities, training and experience of personnel and ability to manage trials with certain risk factors that would require review by the CTEAG.

### Standard Accreditation

Standard units are accredited to carry out all phase I trials other than FIH trials with risk factors that would require CTEAG review.

All units participating in the scheme are required to have the following:

1. The unit should have either an existing agreement with the hospital for supporting emergencies arising from their clinical trials or is able to demonstrate communication and notification of trial information (e.g. dosing times) with the hospitals, emergency teams. The hospital emergency response team and intensive therapy unit must be aware of the Research Unit, the nature of the research (e.g. FIH, biologicals, etc.), and that they could be referred patients from the unit at any time.
2. The unit must have robust (and tested) arrangements for immediate maintenance of life support (i.e. resuscitation and stabilization) and onward transfer of subjects to hospital, where necessary. Periodic all staff testing of emergency scenarios should occur within the unit and be documented.
3. There must be documentation that demonstrates that physicians are authorized to act as principal investigator in FIH studies—as described by their job description, and supported by a curriculum vitae and training record. It is expected that principal investigators have relevant clinical experience, plus a postgraduate qualification, such as a diploma in pharmaceutical medicine, diploma in human pharmacology, MSc in clinical pharmacology or equivalent.
4. The unit must have appropriate numbers of staff with adequate training to handle medical emergencies.
5. Contracts and agreements with sponsors (or internal memorandum of understanding for in-house units) must detail procedures and responsibilities for notifying the investigator immediately if/when new safety/toxicology data come to light.
6. There must be a procedure in place to address 'overvolunteering'.
7. There must be written standard operating procedures (SOPs) for every aspect of the study process. Specifically, these SOPs must include:
   a. Transfer of subjects to hospital; to include the provision of all relevant medical information regarding the trial and the subject(s) in question to the hospital.
   b. Medical emergencies to include stabilizing subjects in an acute emergency.
   c. Out-of-hours medical cover and contact with sponsor or IMP responsible person(s).
   d. Training and refresher training in emergency resuscitation procedures.
   e. Procedures for handling common medical emergencies, e.g. syncope, hypotension, anaphylaxis, cardiac arrest.
   f. Unblinding in an emergency.
   g. Dose escalation.
8. The unit must be able to demonstrate that there are sufficient number of trained staff employed by or contracted to the unit. There must be sufficient cover for dosing days and overnight stays. The unit must

have in place a policy or SOP that stipulates the minimum staffing levels during clinical conduct of the study.

9. Clinical staff must be appropriately and currently trained to initiate resuscitation, i.e. basic airway management and ventilation, IV cannulation and fluid therapy, giving adrenaline, CPR and use of an automated external defibrillator (AED). Annual updates are required. At a minimum clinical staff should receive immediate life-support training and annual updates.
10. An emergency trolley should be available that is easily and rapidly accessible. There should be a trolley in each main area that can be moved quickly to where it is needed. The emergency trolley should be stocked as per the current resuscitation council guidelines and should carry as a minimum:
    a. Oxygen and delivery apparatus.
    b. Equipment for procedures such as cannulation and suitable fluids for IV infusion.
    c. Laryngeal Mask Airways or other supraglottic airway devices.
    d. Self-inflating bag, or equivalent, for assisted ventilation.
    e. Suction equipment.
    f. Defibrillator—this should be an AED defibrillator with a manual override.
    g. Instruments for intubation and emergency cricothyroidotomy should be carried on the trolley for use by appropriately experienced personnel or a responding emergency team only.
11. Continuous monitoring equipment must be available to include ECG, pulse oximetry, vital signs such as blood pressure, heart rate and temperature.
12. The contents of the trolley should be checked weekly, and the checks documented. Expiry dates for medication on the trolley should be checked regularly and documented. If the trolley or the emergency drug box is sealed then the tamper proof seal should be checked weekly.
13. Subjects must be provided with 24-hour emergency contact numbers for while they are outside the unit. The unit must also hold the contact numbers for volunteers to ensure that they are able to be contacted outside the unit, should the need arise.
14. Beds (where used for dosing days) must be able to be tilted and adjusted for height.
15. There must be alarm points in areas where the subjects will be, e.g. showers, toilets, in the ward and recreational area. Staff must be able to open bathroom doors from the outside in an emergency.
16. There must be a robust procedure in place to accurately identify subjects, utilizing photographic identification, thereby ensuring that the person screened is the person dosed.

### Supplementary Accreditation

Phase 1 units who wish to be accredited to carry out clinical trials with compounds at all levels of risk, including higher risk IMPs can apply for supplementary accreditation. These units must demonstrate that appropriately trained and experienced staff is available on dosing days. If these units are not located within a hospital, they should be able to demonstrate that experienced personnel and facilities are immediately available to manage medical emergencies.

The following are additional to the requirements for standard accreditation:

1. It is essential that the unit demonstrates that appropriately trained and experienced staff is available on dosing days. Clinical research physicians in these units must be trained to advanced life support (ALS) standards and experienced in handling medical emergencies. In addition to theoretical knowledge, the clinical research physicians must have relevant and recent experience of handling medical emergencies. Units may approach this in a number of ways, for example:
   - Clinical research physicians may participate on an ongoing basis in periodic clinical attachments involving periodic participation in a hospital resuscitation team to ensure continued exposure to identifying and handling real medical emergencies and/or
   - Appropriately trained clinicians with up-to-date emergency medicine experience may be brought in to the unit on a contract basis during dosing days. These contract staff must also be trained in ALS, the study protocol, SOPs and GCP. The contractor would not be expected to take on the role of the principal investigator and must be appropriately supervised whilst in the unit. Indemnity arrangements made by the sponsor and/or unit must also apply to the contract *medic* and/or
   - Phase 1 units may be located within a hospital; with critical care facilities. The unit must have 24-hour access to the hospital emergency response team, who can arrive at the unit within minutes of an emergency.

   Research physicians employed by phase I units must be able to demonstrate appropriate training and experience in handling medical emergencies. A procedure must be in place to address the assessment of continuing competency in this area and may be achieved by peer review, audit or other means. This continuing assessment must be documented and countersigned by the assessors. A training record must be kept and a log maintained to document exposure to medical emergencies in order to demonstrate that they remain experienced and competent to handle such emergencies.
2. There must be a procedure in place for contingency planning. This must include consideration of availability of specific antidotes/emergency treatments and predictable reactions based on the pharmacology of the IMP.

3. It is a requirement that confirmation of subjects' past medical history for these trials is received via the subjects' GP, or other medic such as hospital consultant for patient studies, to provide assurance that inclusion and exclusion criteria are met.

The MHRA clinical trials unit can make a recommendation when issuing a clinical trial authorization that it is expected that the study should be carried out in a clinical trial unit with personnel and facilities appropriate to the perceived level of risk.

The accreditations are based on inspections. Standard accreditation inspections are as per MHRA's GCP inspections. Supplementary accreditation inspections are wider in scope and more detailed than the GCP inspections. The accreditation certificate will be valid for 2 years, and a re-inspection will be performed prior to renewal of the certificate. If there are any significant changes within this 2-year period, the units are required to inform the MHRA GCP Inspectorate. Inspection reports and accreditation certificates, noting the classification, are sent to ethics committees to assist them with their responsibility to carry out site-specific assessments of these units.

## ABPI PHASE I CLINICAL TRIALS GUIDELINE 2007

The ABPI guidelines cover MHRA recommendations regarding phase I unit location, infrastructure, equipment and staff training. In addition, it provides guidance on risk assessment and risk management of IMPs.[10]

### Risk Assessment

Phase 1 trials of an IMP do not benefit subjects. So the risk of harming the subjects must be minimal. The risk should be fully evaluated, especially during the transition from preclinical studies to the FIH trial. The preclinical data must be reviewed by scientific experts who have the appropriate technical, scientific and clinical expertise.[10] At least one of the reviewers should be independent of the project.

As compared with a new chemical entity (NCE), there is a paucity of data about overall safety of biological. Hence, the risk assessment of the higher-risk IMP needs greater care and expertise than is usual. If the risk of giving a biological IMP to healthy subjects is more than minimal, patients with the target disease should be selected for the study. For IMPs that affect the immune system, the screening should include tests to exclude active or recent infections, e.g. tuberculosis.

### Dose and Administration of IMP

The calculation of starting dose could be based on FDA guidance or ABPI taskforce recommendations. The FDA guidance is based on NOAEL, whilst the ABPI taskforce recommends calculation of the safe starting dose based

on minimal anticipated biological effect level (MABEL).[10] The MABEL approach uses all relevant information-novelty; potency; mechanism of action; degree of species specificity; dose-response data from human and animal cells *in vitro;* dose- and concentration-response data from animals *in vivo*; pharmacokinetic and pharmacodynamic modelling; calculated target occupancy versus concentration; and concentration of the target or target cells in humans *in vivo*. If different methods give different estimates, the lowest value should be taken and a margin of safety should be built into the actual starting dose.[10]

For phase I, increases in dose, and the amount, must be made only after a careful assessment of all the available data from previous doses. If there are any concerns about safety of the IMP or if there is a chance of exceeding the NOAEL, an intermediate dose should be given.[10] For higher-risk IMP, only one subject should be given an active. IMP at the very first administration. If the route of administration is intravenous, the dose should be given by slow infusion, unless there is a good reason to administer rapid infusion. In contrast, for low-risk IMP to be administered orally, cohorts of subjects can be dosed on the same occasion, and at short intervals.

## INDIAN SCENARIO FOR PHASE I AND FUTURE OPTIONS

Schedule Y 2005 recommends following for phase I studies:

- For new drug substances discovered in India, clinical trials are required to be carried out in India right from phase I
- For new drug substances discovered in countries other than India, phase I data are to be submitted along with the application. After submission of phase I data generated outside India to the licensing authority, permission may be granted to repeat phase I trials and/or to conduct phase II trials. This means that FIH for drugs discovered outside India are not permitted in India.

As India has become an attractive clinical trial destination and has been a location of bioequivalence (BE) studies to support generic export submissions, there has been a demand from foreign multinationals and Indian CROs conducting BE studies to remove the restrictions on FIH/phase I studies for drugs discovered outside India. However, the current experience of conducting phase I in India is very limited. A Pubmed search of last 5 years showed only 5 phase I studies from India. During this period, the US registry clinicaltrials.gov had only 7 registered phase I trials in healthy volunteers. The CTRI shows only one phase I study in healthy volunteers. These studies are conducted on new chemical entities (NCEs). Some Indian CROs, who provide phase I services, have conducted phase I for Indian pharma companies. Their websites describe the location, facility and services but do not provide any details of staff experience and training and process for managing acute medical emergencies. During this period, there have been two reported cases of death in BE studies. This scenario does not give confidence that the country is ready for phase I studies.

The development and growth of phase I sector in India requires implementation of regulatory recommendations and industrial actions consensus brought about in UK—a country which has long experience of conducting phase I studies. These would include:

- Developing regulatory expertise for review of preclinical information of NCE and high-risk IMPs
- Availability of independent experts to support regulatory agency and the pharma company in reviewing the preclinical data and planning of FIH studies
- Training and development of clinical pharmacologists and medical experts in understanding and managing the scientific and human protection aspects of FIH studies
- Training of phase I unit staff in resuscitation procedures
- Appropriate infrastructure/equipment in phase I unit which can take care of the scientific aspects of the study and which caters to protecting safety of volunteers
- Establishment of phase I units in or near hospital settings where the volunteer can receive emergency medical care promptly
- Regulatory system for inspection and accreditation of phase I units along the lines of MHRA scheme.

## CONCLUSION

The serious adverse events of TGN 1412 have shocked the pharmaceutical companies, scientific experts and the regulators to develop guidelines to prevent such a situation in future. The guidance lays stress on careful expert assessment of risk for essentially non-therapeutic studies—FIH and phase I—in healthy volunteers, development of appropriate infrastructure and strategy in phase I units to manage medical emergency and training of phase I unit manpower—clinical pharmacologists, physicians, and staff—to become competent in managing scientific aspects and to managing volunteer safety issues. The regulatory guidance will provide much needed public assurance in safety of FIH and phase I studies. These lessons are important for Indian industry and regulators to create a pragmatic phase I study set-up balancing the science and the ethics.

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# CHAPTER 12 Safety and Medical Monitoring in Clinical Trials: An Overview

## INTRODUCTION

The drug development process is long-drawn, with high investments and risks taken to yield new molecules and improve healthcare management.[1] In the clinical phase of development, demonstration of safety and efficacy in the intended patient population is a critical objective. The three basic ethical principles (respect for persons, beneficence, justice) outlined in the Belmont Report,[2] relate to research involving human subjects, and serve as a guide to all stakeholders in clinical research. This report is a tenet for ensuring adequate protection measures for all trial participants. This report also clearly highlights the requirement that research be justified on the basis of a favorable risk/benefit assessment.

Over the last several years, clinical research has witnessed a remarkable growth. Trials that were hitherto conducted on a relatively small-scale have been transformed into larger, multicentric, international trials. With this scale-up, research protocols have become more complicated and the level of risk to patients has also increased.[3,4] Safety of human subjects who are trial participants still remains of prime importance and concern. Research plans, therefore, need to make more robust provisions for monitoring the data collected to ensure the safety of participants. There is a continuous need to improvise existing systems of oversight in clinical research—particularly those related to assessing risks and minimizing harm to trial participants, and ensuring integrity of clinical research.[5] It is the responsibility of all stakeholders: the sponsors, research ethics committees, investigators, data monitoring committees (DMCs) and associated staff to ensure that all risks of trial participation are adequately assessed, while ensuring that appropriate measures have been well defined to minimize risk to all trial participants. Needless to say, this necessitates regular, effective communication and smooth coordination between these stakeholders.

## MONITORING IN CLINICAL TRIALS

Randomized clinical trials (RCTs) must be monitored for patient recruitment, quality of data, early evidence of benefits/risks, adherence to patient care, and appropriateness of preventive measures.[6] It is, therefore, essential that

all monitoring schemes be decided during the planning stages of a trial. Below is a description of data and safety monitoring and medical monitoring.

### Data and Safety Monitoring

Data and safety monitoring in clinical trials entails an ongoing review of data collected during the study with the basic intent of protecting the safety of trial participants, the credibility of the trial and the validity of trial results.[7] The level of monitoring is based on the regulatory and study requirements: trials usually have local safety monitoring as well as external and independent monitoring.[8] The external monitoring is usually conducted by a group of experts who constitute the Data Safety Monitoring Board (DSMB), also known as the Data Monitoring Committee (DMC).

**Data and safety monitoring is a process for reviewing accumulated outcome data from an ongoing clinical study with the purpose to ensure:**

i. **continuing safety of participants currently in the study as well as those yet to be recruited**
ii. **continuing validity and scientific merit of the study**

### Medical Monitoring

Medical monitoring has gained a lot of importance in recent years. This is due to the increase in the number and scope of trials, large volumes of data generated, more reporting requirements for the regulatory bodies, and specific trial requirements, e.g. trials involving cancer patients require intense monitoring—the end-point often being survival. Medical monitoring should be done by a licensed physician having experience in clinical development and capable of reviewing adverse events (AEs) and serious adverse events (SAEs). A medical monitor should, therefore, ideally be a person having clinical as well as research experience—preferably from protocol development to SAE reporting.

**Medical monitoring by a licensed physician is an essential function to ensure the safety of trial participants as well as the clinical integrity of the trial**

Various aspects of safety management are highlighted in this chapter, with a special reference to the growing significance of medical monitoring in clinical trial conduct.

## ROLE AND RESPONSIBILITIES OF A MEDICAL MONITOR IN CLINICAL TRIALS

A medical monitor is responsible for identifying safety signals and trends and analyzing data that could impact medical outcomes. Close consultation with the investigator/study team throughout the conduct of a clinical trial will considerably help in this process. Having identified any such trends, a medical monitor should send an alert to the relevant personnel and the

DSMB/DMC, making visible any potential issue/concern, which could then be further evaluated. In addition to tracking patient safety throughout the trial, a medical monitor evaluates study protocols, assesses subject eligibility, conducts a medical review of study documents, ensures the integrity of the trial results and overall provides medical oversight of the study on an ongoing basis. A medical monitor should be a strong internal consultant to the clinical research team.

### Importance of Training for and by a Medical Monitor

Given the critical nature of the responsibilities of the medical monitor, it is extremely crucial that timely, adequate and appropriate training be imparted to potential candidates for this role. The medical monitor should embark in this role only on completion of the requisite training. In turn, he/she should proactively train the study team on relevant disease states, treatments available, various aspects of protocol compliance, and provide detailed explanation and interpretation of the inclusion/exclusion criteria, all the medical procedures described in the study as well as the different assessments/investigations that are to be carried out in the study (Fig. 12.1).

### Interface of The Medical Monitor With DSMB/DMC

It is the responsibility of the medical monitor to periodically review or analyze accumulating data with an emphasis on SAEs and be in regular contact and communication with the Clinical Safety Officer while SAEs are reported to the DSMB. The sponsor appoints a DSMB, which comprises of a group of experts who are independent from itself and the investigator(s).[9] This includes clinicians, statisticians and other professionals having expertise in the design and conduct of clinical trials and having no financial or other conflicting interests with the study investigators. The committee meets at regular intervals to evaluate individual and aggregate safety data. The key

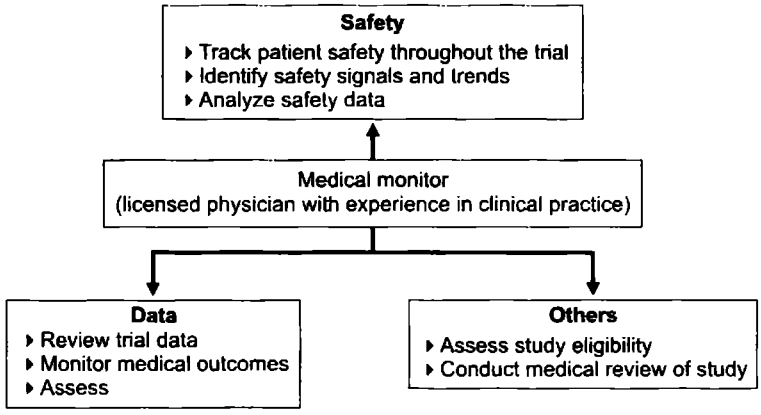


**Fig. 12.1:** The key responsibilities of a medical monitor

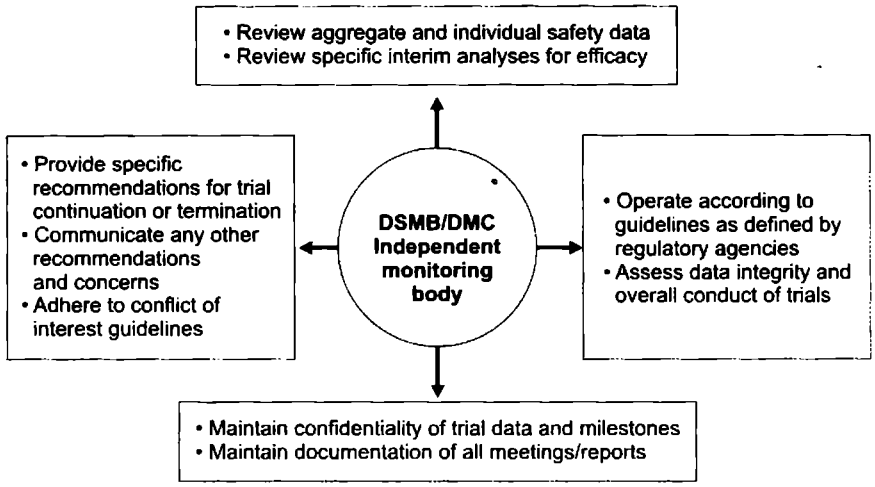


**Fig. 12.2:** Key responsibilities of the DSMB/DMC
Abbr: DSMB: Data safety monitoring board; DMC: Data monitoring committee

responsibilities of the DSMB are outlined in (Fig. 12.2). The DSMB is well-acquainted with or well informed about the interventions used. In the event of a serious or unanticipated adverse experience occurring, the DSMB is immediately notified and depending on the data available, the committee makes recommendations regarding the trial.[8] If the DSMB decides that there are no safety-concerns, the clinical trial can proceed as planned. However, during an interim review, if they decide any trend requires further assessment, the data is reviewed more stringently. In such instances, the DSMB can request for further review of data, and can even call a halt to the study pending the further review of this data. These recommendations are shared with the sponsor, local investigators, respective ethics committees and the relevant regulatory bodies.

**DSMB advises the sponsors on the continuing safety of trial participants, continuing validity of data and the scientific justification of the trial**

### *Recommendations made by the DSMB*

Based on the evaluation of data available, the DSMB can make the following recommendations:

a. The trial be continued as planned
b. The trial be modified
c. The trial be terminated.

A trial can be terminated either because one drug works far better than the other, or because one drug has too many side effects or the question 'which drug works better' cannot be answered.

The functioning of the DSMB is regulated by governing bodies, such as the US Food and Drug Administration (FDA), National Institutes of Health (NIH), the US Department of Veterans Affairs (VA) and the International Conference on Harmonization (ICH). These agencies formulate guidelines for the proper functioning of the DSMB.[10] The guidelines also include criteria for deciding which trials require DSMB. Generally, all confirmatory (Phase III) trials have independent review, such as a formal DSMB. These trials are usually multicentric, with important efficacy and safety end-points to evaluate treatments that prolong life or reduce risk of major health outcomes, e.g. cardiovascular disease, cancer. The smaller exploratory (Phase I, II) trials do not necessarily have a formal DSMB; these have other models to meet requirements though at present, there is a growing demand for formal data monitoring plans for all trials, both exploratory and confirmatory, especially in the US.[11] This is because exploratory trials are common in oncology and a large number of clinical trials in every phase are conducted at several National Cancer Institute (NCI)—designated centers in the US. This has resulted in the formulation of guidelines for exploratory trials that do not necessarily require the conventional DSMBs.[12]

## Key Challenges Faced by Different Stakeholders in Conducting Safety and Medical Monitoring

Any data safety monitoring plan for a clinical trial is based on the medical- or health-related context of that study, and the degree of risk to which trial participants are exposed. However, all stakeholders in a clinical trial face certain challenges that sometimes necessitate greater efforts at ensuring appropriate safety management—especially in certain clinical situations. These are described as fillows:

### *Sponsors*

Sponsors may be over reliant on data audits alone. Furthermore, there may be a tendency to communicate critical recommendations related to safety management along with other audit recommendations, rather than disseminate such critical data on a priority basis. Corrective measures for safety-related findings should similarly be implemented on priority. In addition, the clinical research staff may not be fully trained and/or experienced to response to safety alerts with a sense of urgency.

### *Ethics Committees*

Ethics Committees are often overwhelmed by the large volumes of data submitted to them for review. Therefore, the review process becomes time consuming. This is further compounded by too many and/or very frequent protocol amendments.

### *Regulators*

Regulators have not harmonized their policies related to safety monitoring and reporting.

### Study Team at Sites

The investigator(s) and study team at sites may be unable to devote adequate time to regularly review safety data of trial participants; analyze in some detail each and every AE/SAE in relation to the patient's general condition, disease state and nature of treatment being provided. In turn, it becomes quite difficult for clinicians in charge of the study to ensure continuous medical monitoring of trial participants, which is actually of crucial importance in contributing significantly to the overall safety management of trial subjects.

## Intensive Safety and Medical Monitoring in Special Conditions

### Oncology Trials

Patients who participate in oncology trials pose certain special safety and ethical concerns. Not only are there issues and concerns related to their disease but also concerns regarding their consent to try out a new drug for any possible benefit—sometimes without much regard to its safety profile. Disease progression in these patients also poses special concerns, such as an increased incidence, severity of symptoms or AEs that may not be related to the drug. Medical records that need to be reviewed for these patients are quite extensive and this too is a contributory factor for intensive monitoring in oncology trials.

### Neurology Trials

Trials testing interventions in patients with neurological diseases who have impaired cognition or consciousness also pose a different challenge in safety management. In such studies, patients may be enrolled through surrogate consent obtained from an authorized representative.

### Trials Enrolling Subjects at Extremes of Age

In trials enrolling pediatric or geriatric population, intensive monitoring measures must be outlined in a detailed plan to assure subject safety.

## Medical Management Decisions and the Effect on Outcomes

Medical care is affected by various factors including the existing healthcare infrastructure/system of care (e.g. whether in independent practice or large, hospital-based setting and which could be either a private or government hospital), clinician specialty/expertise, severity of the illness, diagnostic methods, local medical practices followed, physicians' decision-making ability and patient-specific features (e.g. age and general condition of patients) (Fig. 12.3).

# GOOD SAFETY AND MEDICAL MONITORING PRACTICES

Overall, a data and safety monitoring plan (DSMP) is an integral part of any clinical trial.[13] National Institutes of Health (NIH) guidelines[14], the

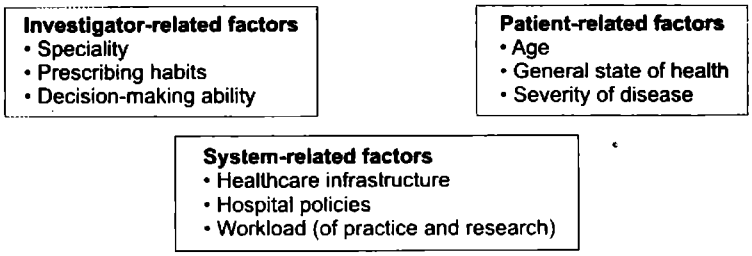


**Fig. 12.3:** Schematic representation of factors affecting medical care and outcomes

Code of federal regulations (CFR)[15] and Good clinical practice (GCP)[16] guidelines highlight the purpose of DSMPs—to ensure subject safety and data validity. It is critical to ensure that DSMPs are well designed and incorporate all the essential elements that are required with a system of oversight clearly defined.

Table 12.1 gives a brief outline of some good safety and medical monitoring practices that can be employed by the investigator(s) and study team, the sponsor and the Ethics Committee in a clinical trial.

## FUTURE TRENDS

### Optimizing use of Electronic Data Capture (EDC)

Electronic data capture has facilitated monitoring of trial data.[17] Safety management has also been facilitated with the paradigm shift in data monitoring and cleaning that EDC has provided. It is possible to accomplish query resolution within minutes instead of weeks with appropriate site team support. In trials facilitated with EDC, monitors can and should take time to review the data of trial subjects prior to their monitoring visit, paying close attention to safety data. Thus, they will have much more information about trial patients at their site, which will be of immense help during their site visit.

### Risk Evaluation Mitigation Strategies (REMS)

The US FDA is now increasingly requiring companies to have risk evaluation mitigation strategies (REMS) in place.[18] After a drug completes Phase II studies, the clinical trial team should be aware of any potential risks that the drug would elicit when used in a larger population. Once this critical information is known, a decision can be taken to begin the REMS process early and thus avoid a sudden REMS requirement near the completion phase of the trial.

**Table 12.1:** Good safety and medical monitoring practices

| *Stakeholder* | *Good practices recommended* |
|---|---|
| Investigator(s)/study team | • Prepare and maintain accurate records of all observations and other data relevant to the medical management of the patient<br>• Maintain primary source documents (this includes all tests/evaluations done and medical notes) supporting the data entered in the case record forms<br>• Ascertain easy availability of source documentation during monitoring visits and audits<br>• Ensure training of study team on ongoing basis and especially, if change in study team composition<br>• Make time to evaluate patient's complaints and ascertain whether due to disease or drug |
| Sponsor | • Increase monitoring frequency if patient recruitment is very quick<br>• Ensure compliance of any third party to safety management and medical monitoring<br>• Maintain continuity in site monitoring if any change in study team composition<br>• Pay more attention to monitoring adverse events and not just to reporting them<br>• Train entire team on an ongoing basis in safety and medical monitoring<br>• Have dedicated medical monitors apart from safety officers |
| Ethics committee | • Ensure all safety reports received adhere to required standards; these have to be complete and as per the context requirements<br>• Highlight all safety related processes to be followed in the SOPs<br>• Review safety data periodically throughout study conduct<br>• Maintain response timelines (on high priority) for safety related issues. |

## Moving Towards Telehealth Technology

The use of telehealth technology in clinical trials can greatly facilitate the improvement of efficiency, quality and overall management of trials.[19] Some of the benefits include very close monitoring of side effects, collection of pharmacokinetic and pharmacodynamic data at various intervals in the day, thus providing information on drug uptake and any effect on drug

interactions. Trends in technology have ensured the availability of several devices that could assist in medical monitoring.

### Establishing Formal Multidisciplinary Safety Management Teams (SMTs)

Establishing multidisciplinary SMTs for more robust safety and medical monitoring, as an integral component of a data and safety monitoring plan can help ensure that various aspects of medical care are attended to in a timely manner and on priority. In addition, this will assure that the other important aspects of ethical, regulatory, and study protocol—and GCP-related requirements are also given due attention.

## CONCLUSION

Drug development is undergoing many changes in its expansion, worldwide. Both patients and prescribing doctors have the expectation that new drugs that reach the market are safe and effective. Vigilant oversight by all the stakeholders in clinical trials helps to meet this expectation. The development of more practical and user-friendly monitoring aids/tools to monitor patients, both in practice and research will go a long way in boosting safety management and medical monitoring. In turn, regular, routine and consistent monitoring further assists in:

i. understanding and detection of changes in the course of a disease.
ii. choosing amongst various therapeutic options while keeping in mind the patient's overall state of health.
iii. predicting more accurately the course of disease.

There is a growing need to intensify efforts and strategies to provide closer and more regular safety and medical monitoring in today's dynamic clinical research environment, where both researchers and monitors are struggling to cope with complex and challenging protocols. Each investigator and monitor should do his/her bit to proactively contribute more effectively to safety and medical monitoring of trial subjects. It is important to regularly monitor not just the patient alone—but also the medical care provided and its results on the patient, in consultation with the investigator at each and every clinical site where the study is being conducted. This will greatly facilitate an overall assessment of medical practices and medical care provided across different sites in a single study, and as a result, an assessment of the medical outcomes.

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# CHAPTER 13 Clinical Trials in Asia-Pacific—New Challenges and Opportunities

## INTRODUCTION

In an effort to get drugs registered and marketed quickly as possible, pharmaceutical and biopharmaceutical companies are being increasingly drawn to the Asia-Pacific region. The contribution of USA and Europe to global pharmaceutical market is expected to decline by 2010. Market saturation, declining population size and increasing cost of drug development and manufacturing have been some of the given explanations (Fig. 13.1). It is also expected that pharmaceutical R & D expenditure in Asia is growing faster than in US and Europe. In 2004, the global contract research market was estimated at $10 billion. It was projected that 40 to 50 percent of global clinical trials market will be outsourced to developing countries by 2010.

## OPPORTUNITIES AND CHALLENGES

Access to large Asia-Pacific population of 3.9 billion in this region, estimated lower costs of drug introductions, significant time-savings, as well as the opportunity to market drugs in the region, are the main drivers for the rapid considerations and the potential growth of clinical research in this region. The protection of intellectual property rights in India which was one of the biggest concerns of global pharmaceutical companies seeking to enter India in the past has changes rapidly to adapt to a post-TRIPS and WTO scenario and there are well-established

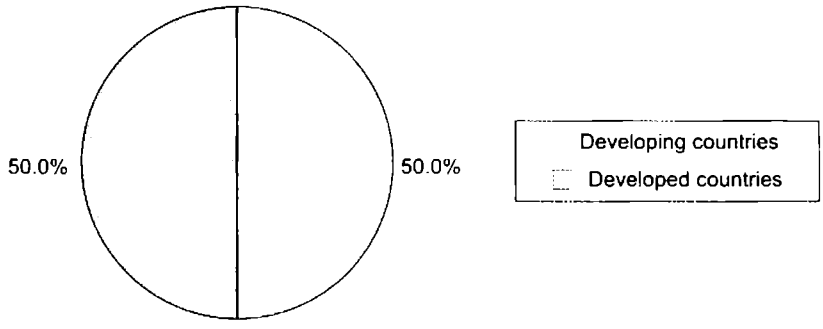


**Fig. 13.1:** Profile of outsource

statutory, administrative and judicial frameworks, to safeguard intellectual property rights in India.

Despite some of these convincing regional opportunities and benefits, just as many challenges exist, among them: Intellectual Property (IP), a mire of regulatory hassles, and obtaining/retaining skilled staff. In addition, enlisted below have been some of the difficulties practically encountered in these markets:

- Regulation and adherence to good clinical practice (GCP) vary among countries in Asia-Pacific
- Increased competition for GCP-trained investigators
- Importing drug samples and clinical supplies
- Infrastructure for electronic data capture (EDC) varies by country
- Low literacy rates in patients complicated obtaining Informed Consent.

Clinical Research Organizations (CROs) continue to develop operations in the region in pursuit of sponsor trials, taking on the myriad opportunities and challenges of this still emerging market. The constraints of outsourcing to Asia are regulatory hurdles and red tapism, competition for trained clinical research associates (CRAs), lack of uniform clinical practice protocols and low entry barriers resulting in mushrooming of small CROs and subsequent price war. The key drivers are large patient pools, high-disease incidence, higher-life expectancy, data approval by international regulatory authorities and fast growing pharma markets.

From the pharmaceutical industry perspective, there are many reasons for the explosive growth in the Asia-Pacific region. First, this region represents a huge market, billions of potential consumers, many of whom are quickly becoming more affluent and health conscious, educated and interested in gaining access to advanced medical treatments. Second, given the pace of growth in India and China, many analysts today see both of these nations completing the transition from 'developing' to 'developed' in the next decade.

A recent PricewaterhouseCoopers (PwC) survey of 185 senior pharmaceutical company executives from the Asia-Pacific region found that 58 percent believe "the center of gravity" of the global pharmaceutical market will be in Asia rather than North America and Europe in the near future. Their belief is reinforced by the fact that almost 27 percent of total market growth in the pharmaceutical industry is now coming from countries with a per capita gross national income of under $20,000 per year. As recently as 2001, these same countries contributed just 13 percent of growth.

Since more than 50 percent of clinical trials are currently being outsourced to the CRO industry, and because the biopharmaceutical industry is being driven towards the Asia-Pacific region, it is only natural that the CRO industry is leading the change and CROs are always looking for a competitive advantage.

## RISK/BENEFIT PROFILE

Put together, a combined population of more than 2.5 billion people, India and China can offer good benefit profile in view of its advantages, viz.

westernized disease patterns, the opportunity to work with treatment-naïve patients, and the commercial and clinical research potential. Access to large patient populations of a variety of therapeutic areas speeds up enrollment in clinical trials and trials can often be completed quicker as a result. This in turn could potentially contribute to the overall speed of drug development.

Patient access, quality of data, and timelines have trumped cost-savings as driver for recent CRO expansion into the Asia-Pacific region. Costs to conduct studies in some countries in the Asia-Pacific region can be approximately 30 to 60 percent less than in the US. Although, lower costs have attracted sponsors and CROs alike, this is becoming less of a consideration in the wake of the region's opportunities.

Another advantage is that, although investigator fees tend to be lower as compared to the Western world, the quality data that is obtained in the Asia-Pacific region increases the ability to get drugs registered around the world at approximately the same time, maximizing the revenue uptake curve (Fig. 13.2).

In January 2005, the Government of India enacted a new rule that allows foreign pharmaceutical companies and other interested parties to conduct trials of new drugs in India at the same time that trials of the same phase are being conducted in other countries. This new rule supersedes a directive of India's Drugs and Cosmetics Rules that required a "phase lag" between India and the rest of the world. According to the old rule, if a phase III study had been completed elsewhere, only a phase II study was permitted in India. Even under the new rule, phase I trials will not normally be permitted in India. The old rule was designed to protect Indians from being used as Guinea pigs in the testing of unproved drugs of foreign origin; trials of domestically discovered drugs were not subject to this provision. The change was made in response to vociferous demands from multinational drug companies and private organizations that conduct clinical research for a relaxation of the rules for drug trials —those necessary hurdles whose price tags can run to 40 percent of the cost of drug

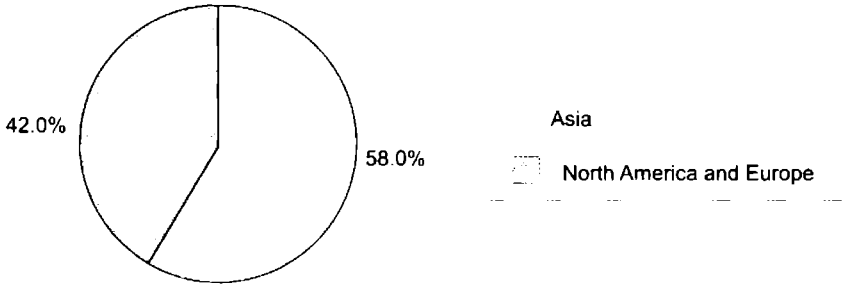


**Fig. 13.2:** Profile of center of gravity of the global pharmaceutical market

development. It has become increasingly difficult to test drugs in western countries, with their strict regulations, elaborate safety and compensation requirements, and small populations, all of which make the recruitment of research subjects slow and expensive. Consequently, many research-based companies are now outsourcing some of their trials to Third World countries such as China, Indonesia, Thailand and India.

India is a particularly attractive site for such trials because of its genetically diverse population of more than 1 billion people who have not been exposed to many medications but have myriad diseases, ranging from tropical infections to degenerative disorders. Virtually all Indian doctors speak English, and many have acquired postgraduate qualifications abroad, primarily in UK or the United States. Added to these attractions are cheap labor and low infrastructure costs, which can reduce expenditures for clinical trials by as much as 60 percent. However, even from the viewpoint of foreign drug companies, there are some drawbacks to working in India. Sponsors do not have exclusive rights to the clinical data they generate—because trial reports are in the public domain, manufacturers of generic drugs can use the data to obtain regulatory approval of their own versions of a drug.

India presently occupies a very small pie of the global opportunity. The total number of clinical trials in India stood at 221 in 2007, which equates to less than 2 percent of the global clinical trials. With all major pharmaceutical/biotech companies and CROs establishing their presence in India, the number of clinical trials in the country is expected to grow several folds in the next five years. The country is projected to conduct nearly 5 percent of the global clinical trials by 2012. However, to achieve its goal of becoming a global hub of clinical trials, the country has to overcome challenges like unethical trials, delay in trial approval, appropriate protection of clinical data, and lack of GCP certified sites and investigators.

Being the world's third largest producer of drugs by volume and the third largest drug research and development workforce, India is fast becoming the most preferred destination for contract research and clinical trials. A joint study by the Federation of Indian Chamber of Commerce and Industry (FICCI) and Ernst and Young found clinical trials in India cost 50 to 60 percent cheaper than in the developed markets. The country has a booming domestic pharma market that is growing at a rate of 12 to 14 percent annually. The number of investigators in India has also grown the fastest among Asian, Latin American and Eastern European countries with a 42 percent compound annual growth rate (CAGR) during 2002 to 2008, the study added. Additionally, the fact that India has 840,000 hospital beds in urban areas, over 600,000 English speaking physicians and nearly 100,000 specialists, with many of them having been trained in the best global institutes, also adds to India's competitiveness. The study said this was also a prime reason that nine of the top 15 global pharmaceutical and biotech companies have set-up captive clinical research centers in the country. India constitutes 16 percent of the global population with 20 percent of the global disease burden.

Despite accounting for only 2 percent of the global clinical trials pie in terms of volumes, India has emerged as the third most attractive destination

for clinical trials in the AT Kearney global survey and the twelfth most active country in terms of industry-sponsored phase II and III sites.

The number of industry-sponsored phase II to III sites in India has grown by 116 percent over the last 15 months and India has moved from rank 18 to 12 among the 60 most active countries. India ranks second in Asia after Japan in the number of industry-sponsored phase II to III clinical trial study sites and accounts for nearly 20 percent of all Asian study sites, a FICCI-E and Y paper notes.

Indian clinical trials market has a growth rate of two and a half times the overall market growth, albeit at a lower base. India participates in 7 percent of global phase III and 3.2 percent of phase II trials with industry-sponsored trials having grown at 39 percent CAGR between 2004-2008. The number of clinical trials investigators in India has also grown the fastest among Asian, Latin American and Eastern European countries with a 42 percent CAGR between 2002-2008. There are 1500 investigators currently and the government is laying emphasis on training and capacity building in the area with the department of biotechnology setting-up six clinical research training centres to provide specialized training to clinical investigators.

India has one of the fastest clinical trial subject recruitment rates globally and dropout rates of subjects are lower by nearly 40 to 50 percent, as compared to global averages. As a result, India contributes 15 to 30 percent of global enrolment in multicentric studies in which it participates. In addition, clinical trial conduct in India comes at 50 to 60 percent of the cost as compared to developed markets.

The study concluded that India's strength also lies in encashing on the clinical trials associated subsectors. Additionally, India's value proposition extends beyond phase I to IV trials with other allied services such as data management, medical writing, pharmacovigilance and biostatistics services gaining the attention of sponsors and CROs. Delivery of allied services requires an appropriate blend of system and domain skills, and India's proven track record has made it a destination of choice for these services.

In terms of economic growth, China is projected to be the fifth largest pharmaceutical market in 2010 and the third largest in 2020, with 28 percent annual growth. It is also noteworthy that China is making very significant technology and infrastructure investments.

The number of well-trained investigators in Asia-Pacific region from US and UK, who are very enthusiastic about conducting clinical trials are increasing. Patients are highly-motivated to participate in trials, and overall compliance is quite good. Data generated in the region is generally of good quality and has been used for both FDA and EMEA submissions.

The one great positive aspect of this region can be attributed to the "attitude" of the patients and the investigators. Most of the time, both have a 'can-do,' enthusiastic attitude, which is why such good metrics come out of the region.

However, all of these benefits don't necessarily come easy. There's a tremendous amount of knowledge needed to develop successful operations

in this region, specifically in China, with regards to local regulatory authorities, culture/language and the talent tug-of-war. Access to and retaining of skilled clinical research staff is becoming an issue as trial activity explodes in the Asia-Pacific region. Also, IP is still considered to be a pitfall in China and, unlike India, which is for the most part an English speaking country, language and cultural barriers exist in China.

With demand comes shortage and then comes competition. Such is the case with obtaining/retaining experienced clinical staff such as coordinators, monitors, and other research staff. To differentiate itself, a CRO must offer industry-experienced staff with expertise in managing global megatrials and navigating the regulatory landscape for their customers.

One of the main regulatory obstacles for CROs in China is obtaining the necessary permits to conduct clinical trials. The SFDA requires inspection of sites and approval to conduct trials and gaining these regulatory approvals can be very complicated and time consuming. However, the regulatory authority in China is trying to speed up its regulatory process.

## ASIA-PACIFIC MARKET DEMANDS

Regardless, of its benefit/risk profile, there is considerable market demand to conduct clinical trials in the Asia-Pacific region. To support this growing demand, CROs are flocking to the region, setting-up and strengthening operations. Demand in the region includes all phases of drug development, although multinational companies are still not allowed to conduct first-in-human phase I studies in India and China. For the most part, these CROs are working with western pharma/biopharma companies and for registration studies, in both local and global markets.

Traditionally, late-stage development has played a dominant role in the Asian market with the focus being on clinical research in registration studies. As the capabilities of countries increase and as sponsors increasingly use Asian countries, there will be a spike in the numbers of phase II and even phase I studies as well.

While in the past the CROs were mainly working with multinational pharma companies, today the scenario has changed wherein they are partnering with more of the local Pharma businesses also. The profile is also shifting to include a diverse blend of sectors beyond just Big Pharma. Biopharma, small-to-mid-tier pharma, specialty pharma, and nutraceuticals are all taking center stage today. Another key factor for trial demand in the region is related to desired disease indications.

Historically, companies expanded their trial to Asia-Pacific for 'Asian indications'—mainly infectious diseases. Today, the trend has changed significantly as the region assumes a more western disease profile with lots of studies in oncology, CNS, cardiovascular and endocrinology.

Thus, a real transformation to Asia is set to becoming an integral part of global drug development.

### Regulations, IP

Regulatory and IP concerns have long been cited as significant challenges associated with drug development in the Asia-Pacific region, and some critical issues remain. However, adoption of international standards and the passing of patent protection laws have improved in the last few years, particularly in India, China and Japan, because of industry-wide efforts.

Regulatory agencies in the region are adopting more global standards, rather than trying to maintain their own individual standards. The most significant is the International Conference on Harmonization (ICH) Guidance document on GCP, which provides a unified standard for the European Union (EU), Japan, and the US to facilitate the mutual acceptance of clinical data by regulatory authorities. ICH GCP was implemented nearly 10 years ago in much of the Asia-Pacific region. As countries follow ICH GCP and companies establish the appropriate SOPs, the issues are fast becoming minimal. Leading CROs are fostering a movement by local and global CROs toward working on global industry standards (GCPs) and standardization (such as CDISC) and SOPs. CROs bring value to new clinical trial environments by helping bring the clinical and regulatory infrastructure and practices in these regions in line with 'recognized' ICH GCP standards.

Asia does not have a long history of conducting global studies. This lack of history means that we often find immature infrastructures and facilities, and unclear regulatory guidelines and ethics committees in hospitals who are not fully informed about GCP guidelines. However, sponsors, CROs and regulatory agencies are putting forth a great effort to increase GCP training and bring more scrutiny and adherence to GCP standards in this region.

China also follows the ICH GCP guidance but some industry sources say the requirements in China are not as specific as the FDA's, leaving them open to interpretation. One area that lacks specificity has to do with where trial responsibility lies. There may be some differences in specific requirements such as procedures.

IP concerns are also being addressed. The Asia-Pacific region has come a long way in the last few years. China becoming a member of the WTO in 2001 prompted the country to tighten IP rights. At that time, the Chinese government also committed to upholding the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Accord, which recognizes 20 years of patent protection for new drugs. More significantly, China formed the State Food and Drug Administration (SFDA), which is modelled after the US FDA, and whose mission is to offer better protections and more transparency in the drug development process in China. Also, the Patent Protection Association of China (PPAC) was founded in 2003. In January 2005, India also became TRIPS compliant and is making efforts to better protect international patents.

Despite patent protection efforts, there still exists a threat to IP, particularly in China. What differentiates China from essentially every other country in the world is that its SFDA drug applications require extensive amounts of information in terms of the level of detail and the kind of

information required. Specifically, in the chemistry, manufacturing and controls (CMC) section, this is frequently more than a company is willing to disclose. In addition to information about the chemical entity itself, both from a chemical synthesis perspective with the bulk formulation, as well as the finished product formulation, the manufacturing process is required to be submitted. Providing information of such extensive nature to a regulatory agency is a concern, to say the least, for pharma/biopharma companies. Although, many global pharmaceutical companies have already set-up R and D centers in China, lengthy regulatory approval timelines prevents China from attracting more global studies.

With the passing of patent legislation and adoption of ICH GCP guidelines in countries such as India, China and Japan, it is expected that these regions will see even further growth in the clinical trials and drug development arena but that is not withstanding revisions to the regulatory process and strengthening of IP rights.

## KEY FACTORS FOR SUCCESSFUL OPERATIONS

Having taken into account the many challenges in the region, CROs must address the key factors for setting-up successful operations. CRO "must haves" include: local knowledge and expertise : both regulatory and culturally, industry-experienced staff, extensive SOP training programs to ensure GCP standards, and perhaps above all, a commitment to the region and strong government relations.

Asia in particular, places a high value on culture and tradition, so on-the-ground experience and local expertise is critical. Therefore, companies showing respect for the local environment and a commitment to developing local expertise are likely to see continued growth. Although most countries in the Asia-Pacific region, including China, have adopted ICH guidelines, CROs must have local knowledge of regulatory requirements and processes and an understanding of how to apply international standards to the local clinical research environments. Recruiting and training talent in global SOPs is essential and understanding GCP guidelines is relatively new for many sites. Beyond patient consent and care, it is very critical to build a skilled core team to conduct trials and to invest in the right kind of training to ensure that GCP and regulatory guidelines are understood and followed. Many commercial institutions are being set-up in Asia to provide training and certification. Local educational institutions are also working in collaboration with western universities to provide certified courses. The SFDA of China has GCP approved sites in Singapore and key site personnel (especially the principal investigator) are required to be GCP certified.

Despite intense scrutiny around concerns and challenges in the Asia-Pacific region, particularly China, the industry's enthusiasm for the drug development opportunities is unquestionable. Progress has been

exponential, from addressing regulatory and IP concerns to the first drug submissions. Regulatory and IP concerns have abated to some extent, and as capabilities and sponsor demand to conduct clinical trials in the region increases, further expansion as well as more comprehensive drug development, is imminent.

## CONCLUSION

As pharmaceutical and biotechnology companies continue to explore new geographic opportunities to expand their pipelines of products and create business efficiencies, the importance of Asia-Pacific market is growing.

Asia-Pacific region does offer some of the convincing regional opportunities and benefits, while just as many challenges exist, which need to be overcome for the successful execution of clnical research in these regions.

In view of more stringent regulations, higher safety and compensation requirements, and small sized populations, it is increasingly difficult to test drugs in western countries, as all these factors in turn result in slower and expensive recruitment of research subjects. Consequently, many research-based companies are now outsourcing some of their trials to Asia-Pacific region. Being the world's third largest producer of drugs by volume and the third largest drug research and development workforce, India is fast becoming the most preferred destination for contract research and clinical trials. The number of investigators in India has also grown the fastest among Asian, Latin American and Eastern European countries.

There is increasing market demand to conduct clinical trials in the Asia-Pacific region, irrespective of the benefit/risk profile. To support this growing demand, CROs are flocking to the region, setting-up and strengthening operations. As the capabilities of countries in these regions increase and as sponsors increasingly use Asian countries, the number of phase II and even phase I studies, will be on the rise.

The present scenario has changed wherein CROs are now working with not only multinational Pharma companies, but showing increased partnering with more of the local Pharma businesses also. Another key factor for trial demand in the region is related to desired disease indications.

Historically companies expanded their trial to Asia-Pacific for 'Asian indications', mainly infectious diseases. Today, the trend has changed significantly as the region assumes a more western disease profile with lots of studies in oncology, CNS, cardiovascular and endocrinology.

With the passing of patent legislation and adoption of ICH GCP guidelines in countries such as India, China and Japan, it is expected that these regions will see even further growth in the clinical trials and drug

development arena but that is not withstanding revisions to the regulatory process and strengthening of IP rights.

Thus, in all respects, a real transformation in the clinical research scenario in the Asia-Pacific is set to becoming an integral part of global drug development.

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# CHAPTER 14

# Principles of Patient Recruitment

## INTRODUCTION

With the advent of new drug discovery technologies such as genomics-based medicine and the implementation of time saving technologies such as electronic data capture (EDC) and web-based clinical trials, companies have more new compounds/projects entering the pipeline than ever before. Even with the introduction of new and sophisticated technologies, an influx of new research techniques and processes, it is taking longer than ever to move a drug from the bench to bedside. Another innovation is the acceptance of 'adaptive' design of clinical trials by the regulatory agencies in therapeutic areas of oncology and, Alzheimer's and HIV. Mean clinical times and mean approval times are both up from low points seen during the 1980s. Under heavy scrutiny in the wake of the Vioxx debacle, the FDA has imposed tougher guidelines for the review and approval of new therapies. In other countries such as Japan and Germany, approval of drugs takes far less time. In fact, as of 1993, Japan had its average approval time down to less than a year. But it is also taking us much longer to move a drug through the clinical phase of research. There are a number of factors that are influencing these delays, but perhaps the most well-known and accepted by industry professionals as the biggest challenge is patient recruitment.

The reason is simple, the longer it takes to enroll patients in a trial, the more direct out-of-pocket expense incurred, the greater the opportunity lost. The day-to- day cost of running a clinical trial in 2007 was more than sixty-thousand dollars, today it is probably a good 10 to 15 percent higher, while the opportunity cost can be much higher to in the range of 1-3 M USD per day. Now, consider that with a fact which is now common knowledge across the industry—90 percent of clinical trials are delayed by at least one month—and you can understand why industry is constantly grappling with the question of how to speed up trials, primarily through faster enrollment (Fig. 14.1).

For many years, the industry answered the call in a similar way to which it tries to solve many problems, through spending more. Using historical data and information from interviews of industry experts and analyzing growth rates, the author estimates that spending on patient recruitment, primarily in the form of print and radio advertising, grew from some $250 M in 2002 to $600 M in 2007 and more than $800 M today. However, there are several factors that appear to be slowing the growth rate of spending on patient recruitment.

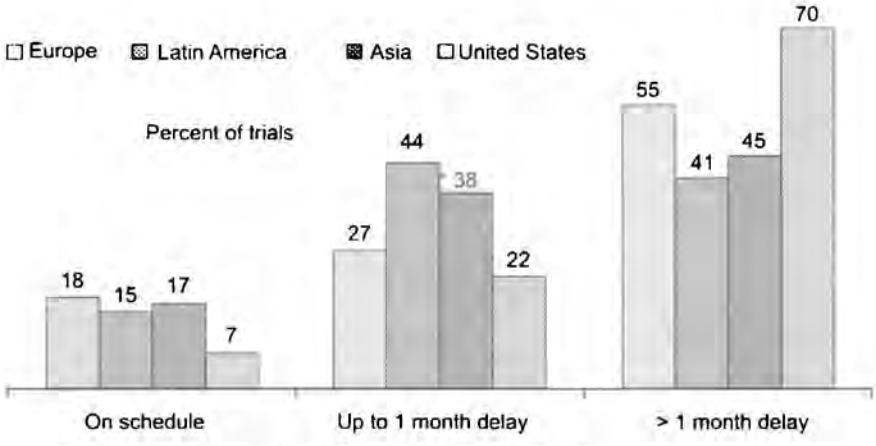


**Fig. 14.1:** Study delays by region
(*Source:* CenterWatch Survey of investigative sites US, Latin America, Asia pacific, European, 2004-2007)

### Knowledge Through Experience

Companies have a better understanding of the patients' perspective and the need to customize recruitment programs around patient needs and perceptions. Several market research firms, patient recruitment companies and other industry stakeholders like Harris Interactive, D Anderson and Company, BBK Worldwide, Tufts Center for the Study of Drug Development and CenterWatch have all published ground-breaking reports on studies analyzing the needs and perceptions of this critical partner in the clinical trials process.

### Innovation/New Technologies

The use of web-based mediums such as trial listing services, clinical trials registries, social-networking sites and targeted search engine advertising have undercut the value of print advertising while often providing advertisers with more targeted messaging and better performance metrics.

### Globalization

In an effort to speed the drug development process, reduce costs and open the door to new markets for commercialization, the industry has undergone a rapid globalization process. The entrance of emerging markets in Eastern Europe, Brazil, Russia, India and China is having a dramatic impact on enrollment rates for global studies, while simultaneously decreasing the direct and opportunity costs associated with development of a compound.

The methods for successfully recruiting patients for clinical trials has evolved signficantly over a short time period, some 20 years from 1990 to 2010. Though it is interesting to note that, for the most part, older strategies have not been

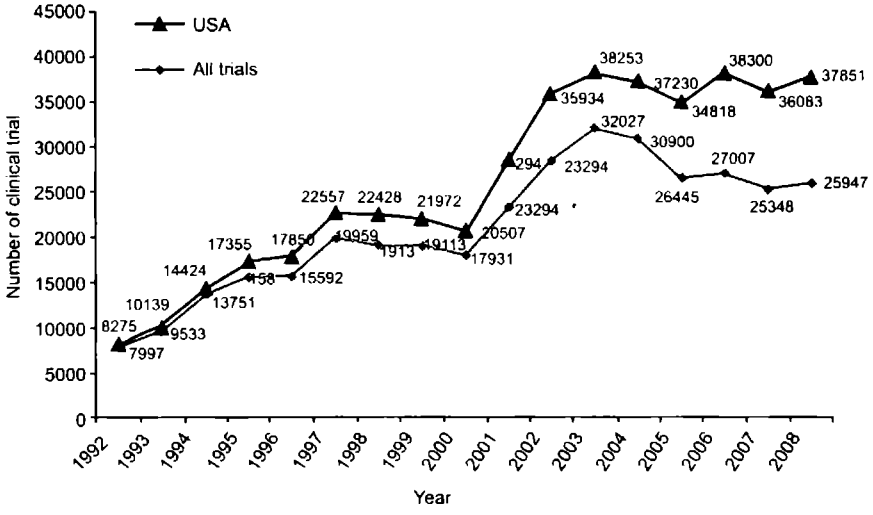


**Fig. 14.2:** Global increase in clinical trials

**Nearly half of all studies taking place in 2007 involved multiple countries outside the United States—increasing the importance of proactive planning and early submission of R&R support materials to translation companies and Ethics Committees**

entirely replaced by newer ones, but instead new strategies are being used in a complimentary fashion to fill in the gaps. This chapter will explore the evolution of the patient recruitment function within clinical research, where it has gone and where it is going. Specifically the following key elements will be covered (Fig. 14.2):

- Background and industry trends
- Understanding the patient—perceptions, participation rates and experiences
- Portfolio of strategies for effective patient recruitment
- Case studies and takeaways.

## BACKGROUND AND INDUSTRY TRENDS

Patient recruitment has always been a function of clinical research trials, though the methods involved in recruiting patients has evolved considerably, from a low sophistication doctor-patient relationship driven method to a technology driven highly targeted one. Before the early 90's the vast majority of patients who participated in clinical research—some 70% were referred into the study through their primary care physician or nurse. Clinical research participation was an unknown entity in the public domain and advertising of trials was reserved to small displays on subway cars and even smaller print advertisements in the classified section of major metropolitan daily newspapers and at colleges. While the methods used

for patient recruitment remained stagnant and traditional, the number of new compounds in the pipeline was growing rapidly with the advancement of science and new discovery techniques. From 1993 to 1999 the number of new projects in the pipeline globally grew by more than 73 percent. Mirroring this growth was a growth in spending on research and development across pharma, but declining productivity. From 1999 to 2000 spending on R & D grew more than 61 percent, while productivity—the amount of drugs research the market was more than halved (53 to 27%) during the same time period. This created a startling dilemma for the industry— how would the industry supply enough patients for valid completion of the studies and advancement of the compound? From this dilemma came the rapid formulation of patient recruitment as a key function area within the industry.

Specifically, there were three developments which crystallized the emergence of patient recruitment as a critical area of focus for the biopharmaceutical industry going forward:

### Patient Recruitment Conferences

The launch of the first patient recruitment conference in 1999 by Barnett International, followed by DIA, Marcus Evans and others. Many of these events have been held annually for the past decade and have been attended by thousands of industry professionals.

**In 2001, 60% of recruitment programs involved a study that was already underway. In 2007, 55% of recruitment and retention programs were proactively planned in advance of the study start date.**

### Major Pharma Centralizes Recruitment Function

The creation of centralized patient recruitment functions within major biopharmaceutical companies. Starting in the late 90s and continuing into the new millennium, J and J, Eli Lilly, Novartis, Pfizer, GSK and several other global companies had developed such departments with a specific charge of supporting clinical operations with recruitment strategies, enrollment performance measurement and outsourcing to patient recruitment providers as needed. Patient recruitment was now being considered much earlier on in the clinical trials planning process and the impacts of protocol design and site selection were being tied to recruitment outcome prediction modeling. At least 3 out of the top 5 biotechnology companies and 6 out of the top 10 pharmaceutical companies have developed patient recruitment departments or sophisticated planning and execution of SOPs related to patient recruitment.

### Launch of Specialized Patient Recruitment Firms

Within a few years, several specialized firms focused solely on patient recruitment and retention sprouted up in the United States. The trend started in 1983 with the launch of recruitment pioneers BBK Patient Recruitment

of Newton, MA USA and continued into the early 90's with the launch of global patient recruitment houses, MediciGlobal, Matthews Media Group (MMG) and D. Anderson and Company. Later, the number of specialized firms would grow to as many as 15 globally. While some were more marketing agency and media buyers than strategists, several have evolved with time and have gone on to become global players creating innovative and highly customized recruitment plans for some of the world's leading clinical trial sponsors. Today most major CROs offer specialized recruitment departments supported by big budgets and cutting edge technologies.

## INVESTIGATIVE SITES

Investigative sites are on the frontlines of patient recruitment, often required to do the most to find and retain patients and often receiving the lion's share of the blame when things do not go as expected. Sites too have evolved significantly over the years as the industry struggles to meet the challenge of more patients in less time at less cost. Often selected as much for their status as thought leaders, or because of their willingness to accept a sponsor's contract terms, as they are because of their access to patients and past experience, many sites started a trial and the enrollment process from a position of weakness rather than strength.

Within the sites, it has long been clinical research coordinators who not only act as in house project manager, but also patient recruitment specialist and nurse. Historical sites would receive a study budget that may have some dollars included for patient recruitment and would leave it up to the CRC to run ads, create flyers and find other ways to market the study to patients, With some CRCs having upwards of 200 daily responsibilities, and most not having a background in marketing or design, results were often predictable. Not to mention that in mature markets such as the US, Canada and Western Europe, many coordinators are responsible for several studies. Given these factors, it should not be surprising to learn the following:

- Approximately 50% of Investigators in the United States recruit <5% of evaluable patients
- 20% recruit approximately 20% of patients
- 30% recruit 50% of patients
- Estimated 23% of sites note patient recruitment as their number one challenge, second only to finding and competing for new studies.

Today sites are becoming increasingly savvy about the way they run their business. One of the things that sites are realizing is that successful patient recruitment requires a specialized skill set. Today, upwards of 55% of part time and full time sites are employing a patient recruitment specialist on staff, while 48% of Academic/Major Medical Centers are doing so. In order for sites to be more successful they will also need help from sponsor companies. In a 2006 CenterWatch survey of Investigative sites, 37% of

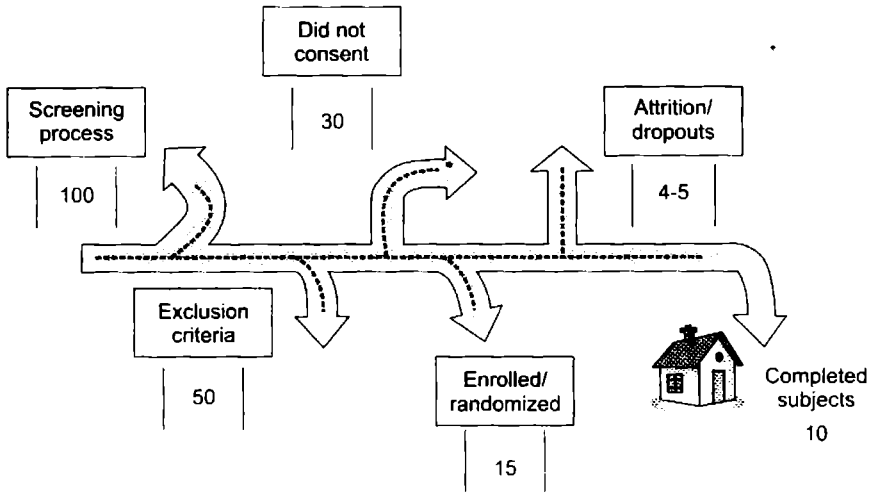


**Fig. 14.3:** Mature market enrollment scenario

sites in the US and 40% of sites in Europe rated patient recruitment support as the number one activity that sponsors could assist to "best prevent future delays" (Fig. 14.3).

## THE PATIENT—OUR PARTNER IN THE CLINICAL RESEARCH PROCESS

We need to be considering patients as a partner in the clinical trials process, because that is really what they are. Without them, we do not have the ability to conduct proper testing of new compounds and fuel the unending need to fight and eradicate disease around the world. Unfortunately, patients are still too often viewed as a means to an end and while the situation is improving, industry has historically done very little to make them feel otherwise or to educate the public about the importance of volunteering for clinical research and the positive impact volunteers have on public health. Until recently, there were very few organizations promoting awareness about clinical trials to the public, media and politicians in the United States, a market that has suffered for a long time under the spotlight of negative media coverage and public misconception about the importance of clinical research. As part of our awareness building efforts across the world, we need to share the experiences of individuals who participate in research with the general public and start telling some of the good stories coming out of clinical research to match the negative offensive pushed through the media.

Like any business partner, you need to be cognizant of your relationship with that partner at all times, how you respond to them, address their concerns and find mutually beneficial end-points. Your relationship with the patient is very similar. The patient has needs, some physical, some

emotional, etc. By treating a patient well and addressing these needs in an ethical way of course, you have taken a very important step in the building of a strong relationship and will have laid the ground work for success.

Here are some statistics regarding patient participation in research:

- Only 12% or 6,000,000 of the 50 million eligible study volunteers participate annually; 25% dropout (average) - <2% UK patients; <1% Japan
- Forty-one percent of physicians lack information on treatments, new investigational drugs or trials to feel confident referring patients into clinical trials
- Thirteen percent of physicians do not have enough time to do research and consult patients on potential trials
- Positively, in the United States 82% of clinical trial participants were aware of clinical research before learning about the study they participated in, representing a knowledgeable and active group
- Retention rates in North America average 70 to 75%.

For comparison purposes, here are some statistics from India, an ascending market and fairly new player in the global clinical trials space:

- Clinical research is largely unknown across India
- Estimated 30 K of India's 1.2 billion patients have participated in clinical trials
- Nearly 60% of clinical trial participants were completely unaware of clinical research before participating in the study, while 38% classified themselves as aware of clinical research
- Retention rates in India average above 90%. Patients who decide to participate usually stay in the study.

As clinical research continues to accelerate into a global enterprise, our understanding about patients and their needs and motivations have to evolve as well. In 2009, Excel Life Sciences a US-based globally focused Trial management organization conducted a survey of clinical trial volunteers in India. The survey examined the experiences of clinical trial volunteers who had completed the informed consent process and were randomized into a trial. Part of the analysis compared findings with an earlier 2006 survey conducted by industry publisher CenterWatch, which looked at the experiences of clinical trial volunteers in the North America. The findings from these surveys act as a valuable guide into understanding patients' needs when building a recruitment plan for clinical research. Table 14.1 presents some of the findings from that research.

### Additional Findings from North American Survey

- Patients are well satisfied with their overall quality of care in clinical trials (92% rating good or excellent)
- Ninety-one percent of study participants would volunteer for another study

**Table 14.1:** Findings from the Global Surveys

| *Question* | *North America* | *India* | *Takeaways* |
|---|---|---|---|
| How did volunteer first learned about the trial? | 23% through physician and others through media (Internet, radio, television) | 97% through physician | The majority of patients in NA are going outside their managed care organization and self referring into clinical trials. Therefore, a variety of mediums must be used to raise awareness about a study. In emerging markets such as India and Eastern Europe, a more traditional physician-patient relationship exists and patients still rely heavily on the advise of their physician, therefore a strong study feasibility process and selection of the right investigators is critical to success, as is use of physician referral programs. |
| What were the top three reasons for participating in a clinical trial? | 1. To help myself and others/to advance science<br>2 To find a better treatment<br>3. To receive high quality medical care | 1. To receive high quality medical care<br>2. To find a better treatment<br>3. To find a cure | While certainly promoting clinical trials as a means to better treatment or a cure would be a major ethical violation, it is important to understand and appreciate the motivations patients have for participating. For example, there have been several studies of clinical trial volunteers, including this one, which show that volunteers report receiving more attention and higher quality care while in the clinical trial than what they receive from their own physician. Likewise, patients almost always receive free medical care while in the trial, something that many patients appreciate. Lastly, it is perfectly fair to communicate the importance of clinical research to the improvement of health care and |

*Contd...*

*Contd...*

| *Question* | *North America* | *India* | *Takeaways* |
|---|---|---|---|
| What concerns did the patients have regarding participation? | Top three concerns:<br>1. Flexible hours<br>2. Easy to get to by public transportation<br>3. Study only required a few visits | Top three concerns:<br>1. Visits required<br>2. Site hours of operation<br>3. Accessibility of site<br><br>**A separate CenterWatch analysis of more than 1,700 prequalified study volunteers found that 13% never enrolled because there was no conveniently located investigative site** | to thank the patients for volunteering themselves to advance science. While some of this can be used in advertising and public awareness building campaigns, it is also effective in a personal setting when patients first meet with a study coordinator or clinical investigator.<br>What has come up in both the North American and the India surveys is that convenience is a major factor in a patient's decision to participate. Things like flexible hours, accessibility by public transportation and the number of required visits are big concerns. Therefore, you must account for these concerns when identifying which sites you will use (is it easily accessible by public transportation and major routes); ensuring that sites selected have extended hours of operations (choose sites that can be open some week nights and at least one day on the weekend); understand the home and work obligations and schedule of patients so that visits can be scheduled at a time convenient to them; be clear about the number of visits upfront and keep lines of communication open with the patient so they are fully aware of upcoming visits. Sending text messages and making follow-up phone calls to patients will ensure that they are aware of upcoming visits |

*Contd...*

*Contd...*

| *Question* | *North America* | *India* | *Takeaways* |
|---|---|---|---|
| Who assisted the patient with the decision to participate? | Alone: 65%<br>Family member: 24%<br>Family doctor: 13%<br>Specialist doctor: 12%<br>A friend: 9%<br>A patient group: 5%<br>Internet: 1% | Spouse: 31%<br>Primary care provider: 26%<br>Parents: 21%<br>Other: 9%<br>Nobody: 8%<br>Siblings: 5% | One of the more interesting data points came from a question about who assisted patients with their decision to participate. Understanding who is involved in the decision is an important part of any recruitment plan. In North America, the majority of patients, some 65% made the decision to participate on their own. Whereas in India, only 8% made the decision on their own, with most patients turning to their spouse or primary care physician for advise. In an ascending market like India, where culturally there are usually several family members involved in making health care decisions you can understand the importance of providing not only the patient with educational information and materials about the study but also the caregivers. Whereas in North America, patients are making the decision on their own and also more apt to turn to resources like the internet and media to learn about the study, so a heavier focus on these mediums may need to be considered. |
| Patients understood the number of times they would have to visit the study doctor | 95% agree<br>5% disagree | 98% agree<br>2% disagree | One of the most interesting findings from the surveys of study volunteers conducted in India and the North America was the similarities between the two areas with regards to the patients' level of understanding. Despite the longer age of the industry, availability of information about clinical research and media exposure in North America, |

*Contd...*

*Contd...*

| *Question* | *North America* | *India* | *Takeaways* |
|---|---|---|---|
| Patients understood that they could quit the study at anytime | 96% agree<br>4% no/unsure | 86% agree<br>14% no/unsure | there was hardly a difference between the regions and in some cases Indian patients projected a higher level of understanding or comfort with elements of the study when compared to their North American peers. Several experts consulted about the findings of the survey believed that patients in India are understanding better because of the cultural support system in place which we previously touched on, where family members are present at visits and help with health care related decisions, and because of the higher level of attention patients received from study staff as part of the informed consent and study participation process. In this case, many of the research centers were supported by a full time clinical research coordinator (CRC) who was not employed by the research site, but instead was supplied by an outside contract research organization and dedicated only to that study. Compare this to the model in North America, which often has a single CRC spread out across multiple studies and sometimes even multiple sites. "High touch" studies requiring frequent visits and lots of patient interaction and follow-up with patients could enroll and retain patients better is day-to-day study conduct support at the study site can be increased and ideally, subsidized. |
| Patients understood that the study would carry additional risks and discomforts | 81% agree<br>19%no/unsure | 93% agree<br>7% no/unsure | |
| Patients understood that they might receive a placebo or sugar pill | 77% agree<br>18% disagree<br>5% unsure | 88% agree<br>10% disagree<br>2% unsure | |
| Patients' understanding of the informed consent form | 87% very well<br>11% well<br>2% not at all | 70% very well<br>27% well<br>3% not at all | |

- Across a range of responses, patients showed a very good understanding of what to expect in the clinical trials process
- Patients would feel safe recommending a friend or family member to a clinical study (87%).

### Other Findings

A patient interested in clinical research is—at the start—often a motivated and enthusiastic partner. Looking at the responsiveness of investigative sites in North America, the survey found that a strong majority of patients heard back from the site within 2 to 3 days after an initial inquiry into study participation (Fig. 14.4). That is very good news, though responsiveness seems to be lagging a bit from where it was during early surveys. Luckily, eighty percent of study volunteers who responded to the 2006 Center Watch survey noted that they had followed-up with the trial site more than once before hearing back from the center. Ultimately though, poor follow-up can be catastrophic to the enrollment process. The survey data communicates that poor customer service significantly harms patient recruitment and retention effectiveness. Nearly 40% of all prequalified volunteers fail to enroll due to inconvenience and lack of responsiveness from investigative site personnel. In North America, the majority of study subjects first contacted the study center by phone, but it is interesting to note that in 1999 about 10% of patients first contacted the study center by email, today nearly 30% do. Follow-up rates increase dramatically when an email address is included with an online trial listing or printed advertisement. It not only allows patients to send a descriptive explanation of their situation, but also takes the burden off study staff to respond immediately. In the India survey, the majority of patients followed a more traditional route to the study, identified during a visit to the study site.

***Rapid Follow-up with Study Volunteers is Critical:***
***A whopping 23% of prequalified volunteers were never randomized because no one contacted them after the initial phone screen.***

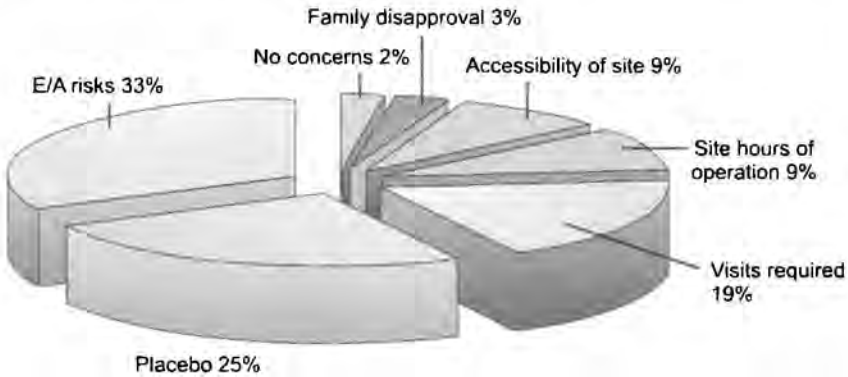


**Fig. 14.4:** Concerns regarding participation

## STRATEGIES FOR SUCCESSFUL RECRUITMENT

Finding patients to participate in clinical research trials, has become an advanced function within drug development and is now supported by the years of experience accumulated by patient recruitment providers, contract research companies, trial sponsors and investigative sites. There are an ever growing number of recruitment strategies and techniques being used across the world to identify, recruit and randomize patients into clinical trials. This section of the chapter includes information about fundamental considerations for enrolling patients, a description of some of the strategies being deployed across the world today and provides suggestions on appropriate times to consider certain strategies.

When you think about it, it becomes quite clear that there are really only four primary sources of patients from which to recruit and enroll into a clinical trial. Specifically, they include the General public, the Medical community, the Study/Investigative sites and nongovernmental organizations like Health Associations and patient advocacy groups (Fig. 14.5).

There are a number of effective ways to reach these different groups depending on the needs of your study. For example, a study for a disease with a high level of prevalence and awareness in the general public (i.e. male pattern baldness, irritable bowel syndrome, acne, diabetes), may provide an opportunity to use mass media (newspapers, magazines, radio and television) to raise awareness about the study and drive referrals. Studies for other conditions including those which are hard to diagnose, those which require patients to have completed a certain level of care, or those requiring frequent visits and treatment at a medical center, would be


**Fig. 14.5:** Four sources for finding study subjects *(For color version, see Plate 4)*

better suited for strategies which speak directly to the medical community. For example, physician referral programs, which we will address a little later in the chapter.

Outlined below are some of the potential strategies, which could be used depending on the type of study, study budget, local regulations and customs. While some guidance is provided on the appropriate times and places to use these strategies, you should check with local regulatory bodies (government and IRB/EC) and discuss with your sites before making a commitment to deploy such strategies.

## GENERAL RECRUITMENT PLANNING AND SITE BASED STRATEGIES

### Study Feasibility Analysis

Successful conduct of any study requires planning and execution of a comprehensive study feasibility analysis. This process helps determine the likelihood of successful enrollment and considers many different factors so that clinical operation teams can put together a realistic enrollment plan. The feasibility process can also reveal potential challenges, which will need to be addressed in the overall study planning process. Historically, study feasibility included completion of a questionnaire style survey with investigators from various potential research sites. Sites would be open to completing the questionnaire because it was an indicator that the site was being considered for award of the study. This was an onsite interview, which took place between a member of the sponsor or contract research organizations clinical operations team and the principal investigator and/or study team from the site. This process still exists today in newer ascending/emerging markets involved in clinical research, e.g. India, China, parts of Latin America and Eastern Europe.

Today, there is a hybrid feasibility process that is most often used in more mature clinical research markets such as those in North America and Western Europe. These involve paper-based questionnaires with occasional onsite interviews, combined with the use of technology to capture this information. For example, the most rudimentary being the use of a fax machine to simply fax the form to study sites, which complete it and fax it back to the sponsors. More sophisticated approaches now involve the use of confidential web-based forms, which allow sponsors to create a deadline for responses, force consistency in the data entry with the use of mandatory fields and more easily aggregate and analyze the data entered by respondents. The most sophisticated approaches now involved the use of data driven technologies, which provide sponsors with a highly targeted method for identifying patients. This will be covered later in the chapter.

To be successful conducting a clinical trial in any market, there are critical fundamentals, which must be applied during the planning and study feasibility process. These include understanding and applying epidemiologic data, determining which sites to include, developing the

questionnaire, identifying patient pools, projecting enrollment rates and more-identifying and selecting sites with the infrastructure, personnel, expertise and patient pool to be successful on your study while retaining a good mix of sites which are well-known and effective, not well-known and effective and not well-known and potentially effective-understanding patient dynamics related to culture, location and language and how these elements impact the screening, informed consent, enrollment and retention process—knowing how and where to find patients and using intersite and external strategies to draw potential patients to the study.

### Critical Elements for Consideration

- True "on the ground" local expertise is essential in all markets, but absolutely required in ascending markets such as Eastern Europe, India and China
- Ideally includes an onsite visit by highly trained project personnel who can visibly confirm much of the data provided by site staff
- Most feasibility questionnaires include, but are not limited to the following data points:
  - Number of patients
  - Standard of care
  - Ongoing competitive trials (OCT) at the site, local region and countrywide)
  - Investigator's experience in clinical research
  - Laboratory facilities
  - EC/IRB details (make-up, meeting dates, submission requirements)
  - Geographic location of site
  - Transportation routes and access points
  - Languages spoken
  - Religious and cultural considerations (holidays, view on medicine, etc.)
  - Familiarity with hospital and PI experience and reputation
  - Willingness of PIs to refer patients
  - A visual inspection of the facility is possible
  - F2F interviews with key clinical trial personnel can occur
  - Feasibility analyst will often need to hunt down answers to various questions which can only be done in person.

## FEASIBILITY ANALYSIS CASE STUDY

### India

Below are some examples of country-specific study feasibility considerations for India which may not commonly be considered, but can help determine success or failure for certain studies:

- *Religion*: For example, some Indian women fast as part of their religion. These patients may not have anything to eat all day, but per protocol they must have two shots of insulin in the evening and all of a sudden you have a problem.
- *Language*: Although English is the official language of India, according to the 2001 Census of India, 29 languages are spoken by more than a million native speakers. For a typical trial, you will need to have the informed consent document and any other patient-facing documents translated into at least 3 to 5 local languages and hire study staff that are multilingual.
- *Transportation*: Most patients will need to take public transportation or be driven to their study visits. Nearly three-quarters of the population still live in rural areas, and an estimated 27.5% of Indians are living below the national poverty line. Therefore, it is normal for people to travel for several hours to receive care. Literally, trying to get across Mumbai at the wrong time of day can take 2 hours on its own.

Obviously, every country that you might enter presents new and unique challenges, so the importance of prior planning is absolutely critical and having or working with organizations with true local and to some extent grassroots knowledge of day-to-day conditions, life and healthcare in that country.

## MEDICAL COMMUNITY OUTREACH

### Physician Referral Programs

It is often not feasible to expect all patients needed for a clinical trial to come directly from the patient pool at the investigative sites. Today, a core strategy for recruitment, which should be considered for nearly every trial is a physician referral program. While ideal for trials in conditions which require previous diagnosis, or use of certain measurements which can only be conducted by physicians, this strategy can also be used for any number of conditions and according to recent surveys conducted by CenterWatch and Excel Life Sciences, it has become more accepted and increasingly common for physicians to refer patients to another site to participate in a clinical trial. In fact, the 2006 CenterWatch physician survey found that 73% of physicians with previous experience conducting clinical trials have referred patients to another physician to learn more about a trial. Overall, greater than 60% of physicians had referred a patient to another practice to learn more about a trial.

Execution of a physician referral program will often include the following steps and materials:

- *Identification of potential referrers:* Sources might include:
  - Asking the principal investigator for a list of trusted colleagues who see appropriate patients and might be willing to refer

  - Purchasing a list from a data aggregator or mailing list company
  - Visiting medical institutions in the local community and speaking with applicable physicians
  - Contacting physician groups and medical associations
- *Development of physician referral materials:* These will need to be created in concert with the study sponsor. In most countries, any material which will be created and distributed to raise awareness about the study will have to be approved by an Institutional Review Board (IRB) or local Ethics Committee (EC). Often, a physician referral packet is created consisting of the following items:
  - Template letter
  - Inclusion/exclusion criteria checklist
  - Pocket cards
  - Chart review stickers
  - Referral instructions.

**In a 2006 CenterWatch Survey of Physician/Investigators more than 40% had never referred a patient into a clinical trial due to a lack of information about clinical trials in their geographic area.**

## GENERAL PUBLIC-PATIENT-FACING STRATEGIES

### Patient Awareness Packets

An additional and fairly simple to create standard recruitment strategy which can be considered for most clinical trials are patient awareness building packets. These packets are used to create awareness about the study in and around the study site and include a variety of educational and promotional materials. Packets can be distributed to potential patients by study coordinators and clinical investigators within the study site and materials can be displayed in public areas and be shared with other medical centers and community groups in the area.

**Any material, which will be shared with the patient about the trial will need prior approval from the study sponsor and the IRB/EC with responsibility for that investigative site.**

Common items for inclusion in patient awareness packets include:

- Study flyers
- Study brochures
- Patient letter
- Wallet appointment reminder cards
- Anniversary/birthday cards
- Study branded pens and sticky notes.

### Mass Media

The use of mass media to recruit patients for clinical trials is increasingly being questioned by sponsor companies given its relatively high cost and

questionable effectiveness for many conditions. While, as previously noted in this chapter, most patients in the US go outside of their managed care organization and self refer to a study site, the vast majority of patients around the world follow the traditional route into the study via their primary care physician, clinical investigator or study coordinator. Examples of mass media commonly used for clinical trials include:

- Distribution of study flyers
- Newspaper advertisements (most common)
- Display advertising (e.g. inside subway/train stations and railcars)
- Radio advertising
- Television advertising.

Mass media is most often used for conditions with higher rates of prevalence and for conditions which are commonly known in the general public. This is why you can probably recall hearing radio advertisement's about clinical trials for depression, male pattern baldness, erectile dysfunction, acid reflux, acne and diabetes. It is commonly considered for studies, which require a large number of patients to be enrolled and/or have an aggressive enrollment deadline. In addition, mass media is sometimes used in "rescue" situations where a study is enrolling behind schedule and patients need to be found quickly. Besides often being expensive, one of the additional downsides to mass media advertising is a high screen failure rate.

More than other recruitment strategies, effective use of mass media requires previous experience, good planning and an understanding of media buying and related negotiating tactics. In most cases, study sponsors and CROs will outsource this function to a media buying agency, marketing firm or patient recruitment company. Only a small amount of sophisticated and well-funded investigative sites typically engage in media planning, buying and distribution without outside support.

## COMMUNITY OUTREACH AND HEALTH ASSOCIATIONS

### Community Outreach Programs

One of the lower cost activities, which can often be done to raise awareness about a trial and increase referral of potential study subjects are community outreach programs. These programs involve reaching out to local community groups who have frequent contact with individuals who fit the general profile of the patient you may need for your clinical trial. For example, clinical trials for conditions, requiring patients who are elderly and suffering from conditions which often impact that age group, might benefit from a community outreach program to local nursing homes, senior centers and social volunteer organizations like the Red Hat Society or VFW. In countries such as India, neighborhood associations, social organizations like Rotary, Lions, Inner Wheel, etc. could be effectively used to spread awareness of medical research in general and clinical research in particular, and encourage community participation.

*Key Considerations for Conduct of Community Outreach Programs*

- Develop a list of applicable organizations and groups within reasonable commuting distance from the study site
- Set-up appointments with group administrators to introduce the clinical trial, discuss the importance of raising awareness and provide some background information about clinical research and the important role it plays in the development of new medicine
- With permission from administrators, setup times to meet with members of the organization or group, present information about the study and hand out materials which explain the study in more details and provide instructions for following up with the study site, e.g. a screening camp, where community members can come to learn more about a disease and receive free information and a screening. Use of materials within the patient awareness packets is perfect for this activity.

## HEALTH ASSOCIATIONS

Health associations, foundations and patient advocacy groups represent some of the most active and well connected organizations for reaching and educating patients about clinical research. Many of these organizations actively fund research of new treatments and have developed a strong communication network with members and a high level of credibility and trust with members and within the communities from which they operate. Therefore, these organizations can be used as a catalyst to raise awareness about clinical research trials currently seeking patients. Similar to the community outreach programs previously described in this chapter, working with health associations requires that you establish a relationship with association administrators, educate them about the study and your goals and that you are in concert with them about how you can approach their members.

*Key Considerations for Working with Health Associations*

- Develop a list of potential associations for collaboration. The internet is a usual tool for finding health associations, which given their connections with the general public, typically have well-designed, informative and easy to find websites
- Approach association administrators and receive permission to reach out to their membership
- Typical distribution channels available include:
  - Associations newsletter
  - Associations website
  - Member mailing list
  - Hosting a gathering or other type of event
  - Staffing a table at one of the organizations events, i.e. a race/walk event.

*Tip*: There are often several health associations and patient advocacy groups for any one condition. While you will certainly want to approach the larger associations due to their expanded reach, the smaller associations are often hungrier for new information to provide their members and often have very active and passionate members who may prove to be more responsive to the information provided about your clinical trial.

## OTHER EMERGING STRATEGIES FOR RECRUITMENT

The explosion of the internet across the globe and the use of cell phones, text messaging and social networks have created a variety of new and interesting ways to raise awareness about clinical trials, engage potential study subjects and even retain study subjects who are already participating. Here we include a few examples of some of the technologies being used and which might be appropriate for your study.

### Data Driven Site Selection and Patient Targeting

We know the top site selection criteria for sponsors, but that does not necessarily mean that sponsors are using the most effective methods. A number of emerging data driven technology solutions are allowing sponsors to systematically target sites by where they are in relation to areas of highest prevalence for a disease. Using insurance claims data and other survey data, a number of services providers are helping sponsors zero in on specific physicians and investigators that operate a practice in an area where there are the highest numbers of patients suffering from a particular disease. Essentially, drilling where there is oil.

Many of these systems are sophisticated enough to identify physicians by name in a specific designated market area and/or zip code. They allow sponsors to understand where patients live who have higher prevalence of a disease, where they are treated, their diagnoses and even their treatment regimen. These health and lifestyle databases, such as those which capture insurance claims data, epidemiologic data, investigative site profile data, can create a map for sponsors to more accurately target those sites with the highest probability of successfully recruiting patients. Unfortunately, these types of systems are not available in all countries and outside the US and some European countries, this technology has not been widely used due to a lack of available data, privacy regulations or it is simply not needed due to the effectiveness of more traditional strategies.

### The Internet

Since 1994, the internet has been increasingly used as a vehicle for reaching patients with information about clinical trials. From the launch of CenterWatch.com, the first online clinical trials listing service for patients

to the launch of ClinicalTrials.gov in 2000 to the use of large health portals, keyword searches and now social networks, the Internet has grown in importance as a vehicle for not only distributing information and raising awareness, but also actively engaging potential study subjects. Today, according to ClickZ.com and the Computer Industry Alliance, the current internet population worldwide exceeds 1.8B people, just under the population size of India. The Computer Industry Alliance estimates that the global population will reach 2.1B by the end of 2012.

Mobile smartphones and other digital devices allow users to connect to the web, download information and receive automated text messages and alerts, forever severing the need to sit in front of a desktop computer to learn and interact with the publishers of content and the users around them. The topic of using the internet for patient recruitment is broad and varied enough to occupy several chapters of this book. Below are just a few of the different internet based strategies being used today, which you might explore in more detail.

### *Study Specific Website*

A website designed and developed specifically for educating potential study subjects and medical professionals about your clinical trial. These sites are typically online only during the enrollment period of the study and will usually consist of several pages of information about the study including the high level inclusion/exclusion criteria and will include the locations and contact information for investigative sites, as well as a contact form for general inquiries.

### *Trial Listing Database or Registry*

Since 2005, any clinical trials operating under a US IND must be registered on ClinicalTrials.gov, a USFDA website developed to provide transparency into clinical research for patients and professionals. Sponsors, CROs and Sites have also been posting their ongoing trials on CenterWatch.com and other online listing services and databases. These services typically provide summarized easy-to-understand information which links the patient back to the study site for additional details and to see if they qualify.

### *Keyword/Pay-per-Click*

Registering applicable keywords with search engines such as Google and Yahoo. Users conducting an online search on those websites who enter the keyword will be presented with a small text add about your study with a link to a study specific website or to a listing on CenterWatch.com, ClinicalTrials.gov or another listing service or registry.

### *Banner Advertising*

It involves delivering custom designed ads about clinical trials on websites that would have users fitting the profile of the patient. Newer technologies are allowing advertisers to better tailor their message in realtime to patients on a site and to only have their advertisements delivered when applicable patients are present (i.e. live in the same geographic area as one of the investigative sites involved in the study).

### *Social Networks*

According to the publishers of each site, nearly a half billion people now have accounts on Facebook.com and MySpace.com combined, two of the largest online social networking sites) as of the publishing date of this book). These websites have created a viral platform for people to connect with friends and colleagues around them and interact with them in real time, sharing information, polling, distributing customized written, photographic or videographic content and much more. The clinical trials industry has begun to embrace these forums as well and groups have established applications and pages on these sites to inform users about currently enrolling clinical trials and even build databases of potential study participants.

**Investigative sites: Use of internet to recruit patients**

According to a 2006 CenterWatch survey of investigative sites:

- 58% of sites increased usage in the previous 3 years
- 79% of sites were recruiting patients online
- 60% of sites planned to increase usage in the next 3 years

## GENERAL TIPS FOR EFFECTIVE RECRUITMENT

### Customer Service is Key for Investigative Sites

### *Convenience and Responsiveness*

Site should provide evening and weekend hours. Staff should be easily reachable and calls to the site should be answered or returned the same day. The following items can also be provided to make participation easier:

- Prepaid debit cards—nominal amount to account only for convenience related charges (transportation, phone calls, etc.)
- Prepaid phone cards
- Prepaid transportation vouchers.

### *Be Informative*

In addition to the informed consent form, patients and their caregivers may find it useful to receive a fact sheet with a high level overview of the study,

study requirements and expectations. A brochure specifically focused on the role of caretakers can be useful for studies requiring the input or support of a caregiver, guardian or loved one. Keep in mind that these studies may need to be translated.

### *Personal Connection*

Keep a log with basic personal information about the patient in order to establish a personal connection. Sending greeting cards for anniversaries, holidays and with study related reminders can also be effective in keeping patients engaged.

### *Listen and Care*

Truly listen to patients and try to understand their needs and concerns. They will appreciate it and they will understand that they can trust you and the information that is being provided. Ensure that they are aware that all information has been reviewed by an IRB/EC and explain the role of those groups in protecting patient safety.

## Be Organized, Be Prepared

Fundamentals to consider while developing your recruitment plan are as follows:

- Review protocol and be intimately familiar with inclusion/exclusion criteria
- Understand the target patient population and understand geographic areas of highest disease prevalence
- Develop a list of potential investigative sites
- Conduct study feasibility analysis
- Using feasibility analysis data, investigator feedback and protocol review, develop a list of potential challenges
- Develop draft recruitment strategies to address expected study challenges

  *Create a staffing plan:* Who will be responsible for development and execution of strategies
- Ensure that adequate funding is available to support the recruitment budget
- Create timeline of strategies including date of design, production, distribution and execution of all materials and activities
- Communicate plan to all members of the study team, especially the investigative sites prior to and during the investigator meeting if possible
- Develop success parameters and determine which metrics will need to be captured and tracked in order to determine progress.

### Performance Management

In order to be successful with execution of your study, you need to first define what success is and then outline the steps that you think are necessary to get there. From there on out, it will be critical for you to put tools in place to track your performance. While there are all sorts of software available today to manage your study, tracking your performance does not have to be complicated. Most of your reports can be developed in Microsoft Excel, or a similar spreadsheet program such as freely available and Microsoft Office compatible office suite Open Office found at OpenOffice.org. There are a few fundamental metrics that you will want to track as part of your performance management program on a study. First of all you need to understand and define:

- Available patient pool at site and through referring sites (if applicable)
- Expected IRB/EC approvals and site initiation dates
- Predicted enrollment per site
- Enrollment timeline/deadline
- Enrollment rate per month and per site per month
- Gantt chart with timeline showing enrollment targets to use for tracking and comparing projections vs actual
- Time to First Patient In (FPI) from site initiation vs projected
- Source of patients
- Enrollment per recruitment initiative vs projected
- Cost per patient referral
- Cost per patient enrolled
- Number of patients screened vs projected
- Number of screen failures
- Reason for screen failures
- Number of qualified patients who do not participate
- Lost to follow-up.

**Potential Challenges with Recruitment**

Are there competing trials at site and locally competing for the same patients?
Is the protocol designed to challenging requiring too many visits or invasive procedures?
Are the inclusion/exclusion criteria too stringent?
Will caregivers or loved ones have any objections to participation?

## DEVELOP A GENERAL STRATEGY THAT CAN BE ADAPTED TO EACH STUDY

- Evaluate and refine tools and methods that have been effective in the past:
  - Discuss strategies with site personnel
  - Site to review strategies with other sites

- Consider possible new approaches:
  - Read periodicals and books
  - Glean insights from other sites/sponsor/consultants
  - Attend professional meetings and conferences
- Continually refine, revise, re-evaluate, review and re-examine methods used
- Be courteous, kind and care.

## BONUS MATERIAL

### Global Scenario Examples

*Recruitment Tips When Entering a New Market*

- Critical to develop expertise in regards to the regulatory landscape including:
  - Which types of patient recruitment initiatives are allowed
  - The ways in which patients can be engaged at the investigative site
  - Which recruitment materials require EC approval
  - Ethics committee structure and approval timelines
- Important to understand the cultural differences that exist and how patients find out about clinical trials
- Must understand which types of initiatives prove successful when supporting sites—only gained from experienced in India
- Engage CRAs and CRCs, as they provide a critical link with the investigative site.

### Asia

*China*

- Limited use of formalized patient recruitment and direct-to-patient initiatives
- Heavy reliance on investigators to inform patients about the study; secondarily, use of posters and flyers in waiting rooms at accredited clinical trial sites
- Other less used methods include newspaper advertising and electronic media
- Patients not compensated for participation
- Advertising is done in accordance with GCP guidelines and written approval from IEC is required.

*India*

You may be surprised to learn that despite popular belief and growing hype, having success with clinical trials in ascending markets such as India takes more than simply identifying key opinion leaders or the most well known hospitals and clinics. Although India offers many benefits for

conducting clinical trials: a huge treatment naïve patient population, leading physicians, a growing pool of experienced clinical investigators and a favorable regulatory environment, India can be a remarkably difficult and complex place to succeed without proper planning, strong local knowledge, a comprehensive site support model and an understanding of the unique cultural dynamics within the patient population

Sponsors are finding that day-to-day site management is critical in India since there are often first time investigators involved in a study and more importantly, the patient loads and activity level at each site, warrant the placement of and support from a full-time CRC. In general, sponsors are finding that patients are enrolled faster, retained better and that there is higher quality data coming from the site. In profiling more than 900 sites across India, a study revealed that only 15% of all sites have a full-time CRC. If a CRC is present, they are typically spread across multiple studies.

- Site management support is critical in India given the newness of the industry and investigators, the significant patient loads and the sensitivities around clinical research in the general public
- Investigators see huge patient loads and lack the time to handle day-to-day study conduct activities
- Site personnel require ongoing training and support, including GCP, SOPs, IRB set-up and guidelines and more
- Onsite CRC placement provides crucial support, ensuring high quality data reporting, patient screening, enrollment and retention.

### Other Factors for Consideration

- Clinical research is largely unknown across India
- Estimated 30 K of India's 1.2 billion patients have participated in clinical trials
- Most people are treatment naïve when compared to western standards and alternative medicine is very common
- Health care decisions and decision to participate in a clinical trial typically involves several members of a family
- Roughly 11% of India's population has health insurance with only 2 to 3% having private health insurance
- Only 25% of India's population has access to western medicine (allopathic), practiced mainly in urban areas.

### One Country—Many Cultures (Table 14.2)

- Expect the unexpected
- Cultural differences
  - Vacation time varies among regions
  - Religious events/social practices can change course of the study
  - Patient care still No. 1 priority
  - Avoid government institutions for summer start ups
- Develop risk/contingency plans.

**Table 14.2:** Sample recruitment portfolio for a small cell lung cancer study (Location: India)

| *Strategy* | *Usage in trials* | *EC approval required* | *Probability of EC approval* | *Effectiveness (study dependent)* |
|---|---|---|---|---|
| Dear colleague Letter | High | Yes | 100% | Very effective |
| Physician packets | Medium | Yes | 75% | Effective |
| Physician dinners/ Luncheons | Medium | Yes | 50% | Effective |
| Patient awareness and educational materials | Low | Yes | 50% | Somewhat effective |
| Community outreach | Medium | No | N/A | Very effective |
| Caregiver awareness/ Educational materials | Low | Yes | 25% | Unclear |
| public advertising | Low/rare | Yes | 10-25% | NA |

## Central and Eastern Europe

### *Example: Hungary*

*Patient recruitment landscape*

- Direct-to-patient advertising possible (but very rare) in accordance with European clinical trial directive
- Advertising materials must be approved by central EC
- Like many CEE countries, formalized patient recruitment initiatives are uncommon
- Most patients found via physicians and large clinics.

*Rapid enrollment factors*

- Wide availability of treatment-naïve patients
- Low availability of treatments
- Patient willingness to participate in studies sponsored by global BioPharma's.

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CHAPTER

# 15 Essentials of Medical Writing

## INTRODUCTION

The health sector has gone through an enormous change during the last decade with people getting more aware and conscious about their health. The online searches have contributed tremendously towards the health awareness. The patient started exploring about the information related to different diseases and their treatment through the internet and became well versed with the indications and contraindications of the drugs compelling the pharma companies to search for new molecules. Growing demands of the people for different healthcare products such as pharmaceuticals, alternate medicines, neutraceuticals, special nutritional supplements, cosmetics, and herbal products have intensified the competition between various national and multinational companies who boast about their health care products through massive campaigns. A sudden boom in advertisements, promotional materials for marketing, and materials for creating awareness amongst the health care professionals as well as the patients using print or other media has occurred. All these have resulted in the need of well structured documents that spread the information clearly and concisely to the targeted audience by the pharmaceutical industry. This eventually has led in the growing demand of specialized writers who can very well collaborate with pharma companies, patients, health professionals and others involved in this business. These specialized writers are the medical writers who are not necessarily a doctor or writer by qualifications. The growing need of various pharmaceutical products has accentuated the role of medical writers. Amalgamation of science knowledge, research skills, flair for writing with the understanding of the audience makes one a successful medical writer.

## FUNDAMENTALS OF GOOD MEDICAL WRITING

### Goal

Medical writing includes various forms of publications like original publications, reviews, short communications, documents for regulatory approval, marketing collaterals, web contents, etc. for different target audiences. Therefore, with such varied users and audiences the medical

writer should define the goals and key objectives to produce a specific, concise and enthralling material. The writer should aim to represent the research of scientists and health care professionals as accurately as possible, amuse his readers by imparting knowledge and awareness. Complex scientific material should be made simpler, graspable and interesting targeting public-oriented communities.

### Opportunities

The medical writers have opportunities in scientific and nonscientific areas. Writers having high degree in science and allied subjects excel in scientific communications in contrary to writers with high degrees in language who excel in nonscientific or marketing communications.

a. Scientific medical writing includes preparing manuscripts of the research outcomes for the journals, abstracts, full length research articles, short communications, review articles, letters to editor, monographs, presentations, posters, editing and reviewing scientific articles, CD-ROMs, web pages, medical education materials, regulatory documents and white papers.
b. Job opportunities for such writers lie with clinical research organizations (CROs), hospitals, academic institutions, pharmaceutical companies, publishers, websites, regulatory agencies, medical educational centers or societies, etc. CROs conduct clinical trials for the pharmaceutical companies so that the products can be registered with the national / international regulatory authorities. The approval processes are quite cumbersome and time consuming. The documents to be submitted to the regulatory authorities should be well written to avoid further delay. Therefore, the medical writer in a CRO has responsibilities of preparing study protocols, investigator brochures, study reports and several papers which are to be submitted to the regulatory authorities. However, marketing medical writing includes promotional pamphlets, brochures, advertisements, posters, sales training manuals, etc. The prospective clients and employers of the marketing medical writers could be medical advertising or communication agencies, pharmaceutical companies, publishers, websites, hospitals, academic medical centers, associations, foundations, etc.
c. Persons who have the initiative and flair for writing, with working knowledge of human anatomy, and wish to work in flexible hours can become freelance writers. One can be a fulltime freelance writer or a part-time writer earning while learning, sharing other responsibilities at home or even after retirement. A freelance writer can write in different formats and styles for varied audiences. The person can choose from being a research writer, translator, proofreader, copy editor, reviewer, ghost writer, webcontent writer, etc. Becoming a freelance writer needs motivation and work organization. The personal and life should not be

intermingled or else there will be a great mess. A clear line should be drawn between personal and professional time so that even while working from home a professional attitude is maintained. The writer should be able to build up contacts and generate regular work. Strict timelines should be followed while writing a document or else the person looses its credibility.

### Characteristics

Thorough research, accuracy, logical organization, clear thinking and writing, and readability are the main characters of the good medical writing. A good medical writer delves into the subject he is going to write about, he does a thorough research in the subject so that the information he is about to provide is accurate. All information gathered should be organized and written in a coherent manner so that it can be logically understood by the audience he intends to write for. The writing should be such that the reader becomes more interested in the matter as he moves further with the reading.

### The Writer's Role

The medical writer's role is important in the sense that he has to plan and produce scientific/medical quality content in a specific discipline or various therapeutic areas. To accomplish this, interaction with the clients and the staff he is working with, is needed. He should be very good in communicating with his colleagues or with people from other disciplines to gather information. Writing a document not only requires gathering of specialized information but attention to details should also be given utmost importance. Paying attention to small things and attending to the details earnestly helps in improving the quality of the end result. The responsibility of the finished scientific or medical content lies with the medical writer.

### Assessing the Audience

It is very important to know who are the readers; unless it is assessed, a good presentation of the writing cannot be made. The writer should first assess the level of experience or knowledge of the audience, writing for general public will be definitely different from the writing meant for highly professional audience. The terminologies used in the write-up vary accordingly. Selecting highly technical terms is not appropriate for general audience; the terms used should be simple or may be elaborated or explained. The background information should be included according to the level of the audience; it should be very clear to the author who is the audience and what is the purpose of the audience to go through the document. One should also keep in mind that whether the document prepared is informative and meant for the general public or for convincing a more professional audience. The writer should also consider that whether the audience would read the document as narrative or read it in sections.

### Take Home Points

The document prepared should have a clear take home message. The article can be summed up giving a brief description of the research and its results, the controversies arising from it or the lacuna in the research, and finally, what the author expects from the reader to do with this new piece of information.

## TYPES OF MEDICAL WRITING

The writer should choose the field he wants to write for. Medical writing can be scientific or promotional marketing writing. The scientific medical writing for the pharmaceutical industry can further be categorized as follows.

### Regulatory Medical Writing

Various rules and regulations have been imposed for drug development and its marketing for the benefit of people. Need for well written documents for regulatory submission becomes essential for the pharmaceutical companies or clinical research organizations so that they can pass through the scrutinizing eyes of the reviewers without being rejected. Since the approval process is quite cumbersome and time consuming, the companies are compeled to hire trained persons for preparing the documents that comply with regulatory, journal, or other guidelines in terms of content, format and structure to avoid unnecessary delay. The regulatory writing also known as clinical research writing includes the preparation of documents required by the regulatory agencies for the approval process for drugs, devices and biologics. Clinical trial protocols, informed consent forms, patient information sheets, investigator's brochure, interim/study completion reports, new drug applications (NDA) are examples of such documents and their preparation requires a sound knowledge of current and emerging regulatory requirements or guidelines.

### Educational Medical Writing

It consists of documents written for general audiences, students or healthcare professionals such as doctors, nurses, pharmacists, etc. Educational writing can be further categorized into the following.

#### *Scientific Writing*

It is presenting the information gathered by consulting libraries, reading books, attending educational institutions or conducting research in a concise, simple, logical and organized way.

Original research articles, reviews, letters to the editors, short communications, editorials, poster or powerpoint presentations for the

conferences or the meetings, study modules for the various courses or continuing medical education fall in this category. The audience for scientific writing is highly specialized.

*Consumer Health Writing*

People are becoming aware about their health and are eager to get information related to various types of diseases, how they are caused, what are the risk factors, latest treatment available, is there any side effect of the prescribed drug, or is there any alternate medicine. All these information is gathered either from the books, magazines or Web. Reviews of clinical trials or research studies help in disseminating information to the patients or general public. Feature articles on a new disease, new treatment or device interests the readers. All information related to health improvement whether it is a medicine, device, lifestyle modifications reach to the consumers through health magazines, dictionaries, encyclopedias, newspapers, advertisements, blogs and websites.

### Medicomarketing Writing

It is crucial for the financial growth of any pharmaceutical industry. Production of marketing collaterals such as sales brochures, instrument manuals, demonstration advertisements, web contents, posters, etc. of new health products, be it a drug or a medical instrument or device, meant for the healthcare professionals has enhanced the opportunities of medical writers in the pharma sector.

## TYPES OF RESEARCH PUBLICATIONS

### Original Articles

The publications in which the authors/researchers detail their research methods, and discuss the results and its possible implications. These articles can be published in peer reviewed journals of the concerned field. Such publications have a very specialized audience like students (mostly of a particular discipline), researchers or professionals.

### Review Articles

Reviews are not original publications instead they are a coherent narrative of the information gathered from a collection of articles on a single topic. They give comprehensive information about the work conducted in the particular field and also provide journal references to the original research. These are published in many journals or books.

### Short Papers

These are original research articles meant for publishing in journals, proceedings, etc. The length of these articles is comparative less than the full length paper.

### Case Reports

Any novel or unusual episode or incidence is usually described in case reports. A case report of a patient is a detailed report describing symptoms, signs, diagnosis, treatment and follow-up. Demographic profile of the patient may also be included in it. These are published by some of the medical journals. Certain journals exclusively publish case reports like *Journal of Medical Case Reports*.

### Editorial

It is the article which gives the opinion of the editor of a periodical on a current topic or issue reflecting the opinion of the periodical. The editorials are published mostly in newspapers and magazines with a wide audience.

### Letters

A short communication containing outcomes of original research can be sent to the journals for faster publication as they are thought to be urgent.

### Special Publications

Proceedings of the conferences, monographs, transactions of meetings of the members of societies or publications related to a particular topic come under this category.

## REQUIREMENTS FOR WRITING RESEARCH ARTICLES

Any advancement in the field of science or medical science should be communicated to the public in order to enrich their knowledge. It is the obligation of the researchers to publish their work in the reputed journals so that the people all over the world may be benefited. To achieve this, the research outcome should be presented in such a manner that it becomes graspable and others, if interested, can repeat and see the results. Publication of a research article needs to fulfill certain requirements of the selected journal. Most of the journals have almost similar requirements having a title, body and references. The body of the text can be divided into different sections or subsections.

### Title

The preferred title of the paper should be short and informative. It should also clearly identify the general field as well as the specific branch under consideration.

### Title Page

The title page generally contains the title of the paper, name of the contributors and their affiliations, name, address, phone numbers, email address of the corresponding author and a short running title.

### Abstract

An abstract helps the reader to quickly have an idea about the article contents. The reader can then decide whether he wants to continue reading or can save time by switching to other article. Generally every research/review article and case reports contain a short abstract of usually 200 to 300 words. The abstract may be unstructured or structured with introduction, aims and objectives, method, results and conclusions. The abstract briefly describes the objectives, scope of the investigation and research outcomes. Unnecessary abbreviations, acronyms and references should be avoided. Five to six key words may be given at the end of the abstract.

### Introduction

It contains the statement of the problem on which one is working and related background information. The reader is introduced to the relevant literature and comes to know about the relevance of the current work by a clear statement on scope and objectives. The introduction can gradually lead to the objectives of the study so that continuity is maintained.

### Materials and Method

The methodology and the materials used should be provided to the reader so that the reader can repeat the work and the results can be reproduced. The results should be reproducible when scientifically performed. The details of the study design should be given along with the techniques used for evaluating the results. If the technique is new full details should be provided whereas in case of standard techniques a citation of the journal article should be incorporated. The detail such as number of replicates used, study duration, temperature, measurements, amounts, animal species, sex and weight may be given. Results should not be given with procedure. Details of statistical analysis should not be given only a brief mention of the method used will suffice the need. Past perfect tenses are used when writing materials and method.

### Results

The findings of the study are described with the help of tables, line diagrams, figures and images. The results should be clearly explained in a simple manner. The data should be well explained neither too condensed nor elaborate.

The data given in the table should not be repeated. Like materials and method results should also be written in past perfect tense.

### Discussion

The results of the study are discussed in this section of the article. Most important findings are summarized in the discussion. The conclusions that can be drawn from the results are given here. Does the findings support the hypothesis or not, or the findings are in accordance with the previously published articles on the similar problem or there are contradictions, the plausible explanation should be given for this.

### Conclusion

This section should indicate major contributions of the paper and what are the related untouched areas on which researches can be conducted.

### Acknowledgment

The author(s) can add a line of acknowledgment for any financial assistance or assistance in preparing the manuscript or using any facility, etc.

### References

References to support the research study are cited in the text and are enlisted at the end of the paper. The references are written in Harvard or Vancouver style depending upon the style of the selected journal. There are different ways of writing the reference of journals, books or websites. Each journal or book has their own guidelines. The instruction to authors should be read carefully prior to writing the research article.

## CAREER OPPORTUNITIES

A person gets many opportunities as a medical writer. A writer with the managerial skills can be involved in the management of team of writers assigning or undertaking job responsibilities at local or international level or be engaged in the marketing of the pharmaceutical products. To satiate his interest he can choose from various categories of medical writing. He can become a part of pharmaceutical company, clinical research organizations, hospitals or health care agencies. If the person has imaginative powers or creativity he can also be involved in the medical advertising agencies or can be involved in designing web contents. A person with a strong observation skill can be a good proofreader and become a part of some publishing house. Editing and reviewing articles can also be a good option for some. Persons not able to carry out a full time job due to other responsibilities can be freelance writers with flexible timings and can work from anywhere. They can enjoy variety in writing while serving for varied clients (Fig. 15.1).

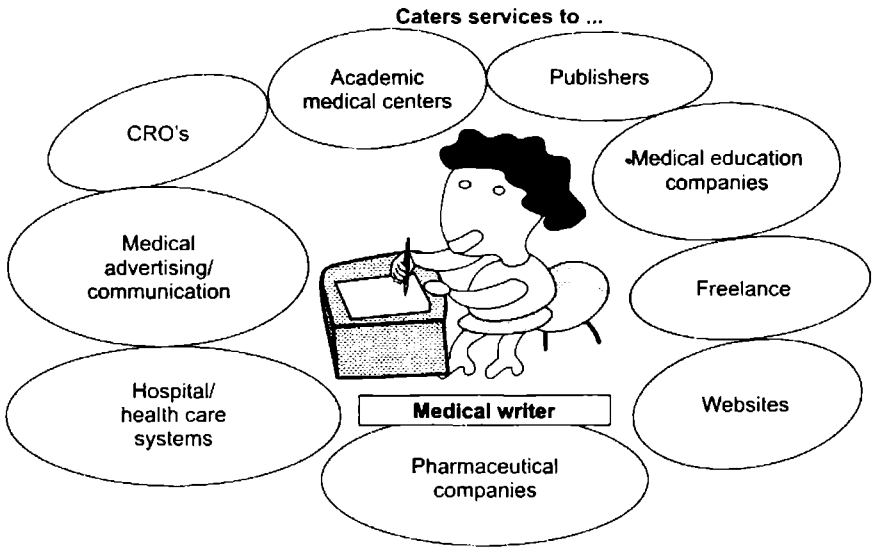



**Fig. 15.1:** Career opportunities for medical writer

## QUALIFICATIONS AND SKILLS NEEDED

The term medical writer does not mean that the writer is from medical background. No particular technical training is required to become a medical writer. A graduate degree in science, medicine, pharmacy, journalism, mass communication, English or allied fields would suffice. However, the person should be conversant with the medical terminologies used in preparing varied type of documents. The most important thing needed is the inclination and flair for writing. The person should possess a good communication skill so that he can interact with people of different background and expertise, interview them and gather information related with their field or expertise. The person should be able to interact with people other than his close associates. The person should possess good writing skills, editing and proof reading skills (common symbols used for proof reading and editing are given at the end of the chapter), knowledge of grammar, know how to search information quickly and above all he should be able to stick to timelines. The person should be able to meet the deadlines fixed for the article.

## INITIATING THE WRITING CARRIER

Starting a carrier in medical writing does not primarily involve a degree in medicine or mass communication. However some training whether informal or formal helps in moving forward in the field.

## Informal Training

There are number of ways to get the informal training to be a medical or scientific writer through books, journals, internet, etc. To start with, a medical writer can take help of many online and offline resources.

*Online Resources*

i. Several online medical dictionaries available such as Dorland's online medical dictionary or Stedman's online medical dictionary are wonderful aid in getting the information related to various diseases or getting familiar with medical terminologies.
ii. Assistance of software can be taken for learning medical terminologies and spell check. A variety of them are available online for free.
iii. A range of online medical and pharmaceutical journals are available for free. These journals can provide information related to a particular disease, its pathology, treatment modalities, and recent advances in therapeutics. They are a very good source for preparing background information for investigator's brochure or materials for health care professionals or marketing, etc.
iv. Besides, there are lots of free online books available that can assist in gathering information regarding the subject or the disease selected.
v. The author may need information about the latest drugs used for the medical therapy of diseases and regulations for the drug trials and marketing. He should be well acquainted with such regulations. Country wise regulatory guidelines are available at the site of most of the regulatory authorities. Some of the regulatory authorities are CDSCO (India), FDA (US), ANVISA (Brazil), MHRA (UK), WHO, EU (Europe) whose websites are given below.
vi. A medical writer also gets aware of the latest happenings in the world of health care, be it developments in pharmaceutical industry, health care centers, new regulations imposed on medicines, devices, research, etc. using online internet services. The writer becomes informed about the new drug molecules in the pipeline in pharma industry.

**Pharmaceutical, Medical and Health-related Government and Regulatory Bodies around the World**

**International**

- International Conference on Harmonisation (ICH) (http://www.ich.org/)
- World Health Organization (WHO) (http://www.who.int/en/)
- World Trade Organization (WTO) (http://www.wto.org/)

**Australia**

Therapeutic Goods Administration (TGA) (http://www.tga.gov.au/)

**Brazil**

National Health Surveillance Agency (Anvisa) (http://www.anvisa.gov.br)

**Canada**

Health Canada (http://www.hc-sc.gc.ca/)

*Contd...*

*Contd...*

**China**

State Food and Drug Administration (SFDA) (http://eng.sfda.gov.cn/eng/)

**Europe**

- EU Legislation—Eudralex (http://ec.europa.eu)
- European Medicines Agency (EMEA) (http://www.ema.europa.eu/)

**France**

Agence Française de Sécurité Sanitaire des Produits de Santé (http://www.afssaps.fr/)

**India**

- Central Drug Standard Control Organization (CDSCO) (http://www.cdsco.nic.in)
- Indian Council of Medical Research (ICMR) (http://www.icmr.nic.in/)
- Ministry of Health and Family Welfare (MoH&FW) (http://www.mohfw.nic.in/)

**UK**

- Medicines and Health care Products Regulatory Agency (MHRA) (http://www.mhra.gov.uk)
- National Health Service (NHS) (http://www.nhs.uk)
- National Institute for Biological Standards and Control (NIBSC) (http://www.nibsc.ac.uk)

**USA**

- Centers for Disease Control and Prevention (http://www.cdc.gov/)
- The Food and Drug Administration (FDA) (http://www.fda.gov/)
- National Center for Complementary and Alternative Medicine (NCCAM) (http://www.nccam.nih.gov/)
- National Institutes of Health (NIH) (http://www.nih.gov/)

### *Offline Resources*

It is always good to read and grasp the information from different sources. The more a person reads the better he can reproduce. Books, medical or scientific journals/magazines can also be purchased or issued from a public library at a nominal fee or through membership. Some basic knowledge of the statistics is also beneficial.

### *Technical Skill*

In addition to the above mentioned resources that contribute in gaining the knowledge about the topic to be taken up for writing, few technical skills are also needed.

*Language:* The command over the language in which the documents are being written is of utmost importance. Since English is the universally accepted language most of the scientific literature is written in English. Therefore, writers having control over English language, grammar and a flair for writing have added advantage. A well written document, grammatically correct with appropriate punctuations can clearly communicate the message to the readers creating an interest in them to indulge further in reading.

*Computer knowledge:* One of the most important requirements for preparing different types of documents is to improve one's computer skill. A computer savvy writer has added benefits. He will be more efficient in gathering information, preparing computer generated documents, graphics or illustrations. Preparing presentations, posters, materials for market promotion or for the physicians or even publishing a book becomes easy, dependency on others is reduced and lot of time and money is saved.

### Formal Training

Unlike these informal trainings a person can also get formally trained in medical writing. He can choose appropriate courses and get formally trained in medical writing. Some of the courses are given below which can be of assistance:

a. A degree in basic science or pharmacology can be pursued if not interested in studying medicine.
b. A degree in English or mass communication or journalism with working knowledge of human anatomy and physiology or
c. A course in biostatistics will have additional significance.
d. He can opt for a career in medical writing by getting enrolled in medical writing courses or programs offered by any one of the several organizations. Details can be found online. AMWA is one such organization that imparts training in medical writing.

**List of some of the websites related with Medical Writing Courses**

a. http://www.emwa.org/training.html
b. http://iocbindia.org/medicalwriting.htm
c. http://www.infocusrx.com/icme/about.html
d. http://www.infocusrx.com/icme/about.html?tcsrc=www.training-classes.com
e. http://www.emagister.co.uk/medical_writer_courses-ec170147415.htm
f. http://www.aagmedicalwriting.co.uk/medical_writing_training_course.html
g. http://www.sfep.org.uk/pub/train/training.asp
h. http://medicalwritingtraininguk.co.uk/
i. http://www.medicalwritingtraining.com/
j. http://www.cfpie.com/showitem.aspx?productid=CMWP

## REMUNERATION

The salary of the medical writer depends upon the qualifications and experience. A medical writer having regular employment can earn between $ 65000-85000 annually in USA depending upon the nature of the job, company's profile, etc. Some extraordinary writers can have six digit salaries. On the contrary, the earning of a freelance writer relies on the number of pages of the document produced or hours devoted for the writing.

## TOOLS

A good document can be created using variety of tools. These tools assist the writer to create usable information with illustrations and graphics or a web page. There are no defined tools which are used by the writers; however some of the broadly used basic tools are described below:

### Publishing Tools

These are the basic tools for technical writing that can create a document, edit and format the text, insert the tables and graphics. A number of word processors are available, the most commonly used are MS-Word and Adobe FrameMaker.

### Image Capturing and Graphics Tools

Most of the documents contain graphics and illustrations to make the information more communicative. The medical writer should possess a basic knowledge about capturing, editing, creating illustrations. Adobe Photoshop is the most popular graphics editing program. Besides Illustrator and CS4 (by Adobe) Corel Draw, SnagIT, are some other graphics tools used by the technical/medical writers.

### Help Authoring Tools

Many tools like RoboHelp, Flare, Doc To Help are used for producing printable user manuals and online help files in .htm, .rtf, .chm formats, each having its own merits and demerits.

Some other help tools include Paper Killer, HelpStudio, Fast-Help, AuthorIt, Digipedia, Help-Producer, OfficeHelp, HTMLHelp Workshop,

### Web Tools

Designing a web site or a web page requires efficient web tools. Several web tools are available such as WebTools Pro, Google Web Toolkit (GWT), HTML editors, search engine tools, GOOGLE tools, YAHOO tools, MSN tools and many more. Most of the tools can be downloaded for free or trial versions with limited features.

## SOFTWARE NEEDED

Basic software required by a medical writer includes following:

- A *web browser* to bring information resources to the writer.
- *Office 2003/2007* for creating, opening, editing or saving the text files, workbooks and presentations in Microsoft Office Word, Excel and Power Point.
- A *programme* to view, create, edit or mange files in portable document format (PDF) such as Adobe Acrobat Professional.
- *Spellchecker*, software to check the spelling errors in the printable document or web pages.

- An *online Dictionary and Thesaurus* to search for any definition or meaning instantaneously.
- *Antivirus software* for complete protection from the computer virus, worms or any other malware.

## PROFESSIONAL GAINS

Good medical writing can stimulate the company's economic growth. Well written documents and communications can:

i. Save unnecessary repetitions of clinical trials.
ii. Reduce the time taken for the product marketing approvals.
iii. Increase the marketing duration of the product under patent protection.
iv. Lead to the successful marketing of the product.
v. Reduce the period of the product marketing approval process.

## ORGANIZATIONS FOR MEDICAL AND SCIENCE WRITERS

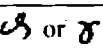
Several medical writing organizations are working in a direction to provide an opportunity to writers to meet and share their experience and expertise. These organizations help in promoting the professional development and excellence in documentation. The writers are also benefited by finding career opportunities. These organizations offer fundamental medical writing training to amateurs.

**Organizations for Medical and Science Writers and their Websites**

i. American Medical Writers Association (AMWA) (http://www.amwa.org)
ii. Australasian Medical Writers Association (AuMWA) (http://www.medicalwriters.org)
iii. European Medical Writers Association (EMWA) (http://www.emwa.org)
iv. Indian Medical Writers Association (IMWA) (http://imwa.webs.com)
v. Drug Information Association (DIA) *(www.diahome.org)*
vi. Association for Communication Excellence in Agriculture, Natural Resources and Life and Human Sciences (ACE) (http://www.aceweb.org)
vii. Association of British Science Writers (ABSW) (http://www.absw.org.uk)
viii. Guild of Health Writers (UK) (http://www.healthwriters.com)
ix. Health and Science Communications Association (H&SCA) (http://www.hesca.org)
x. National Education Technology Writers Association (NETWA) (http://www.netwa. org)
xi. New England Science Writers (NESW) (http://neswonline.com/)
xii. Canadian Science Writers' Association (CSWA) (http://www.sciencewriters.ca)
xiii. International Science Writers Association (ISWA) (http://internationalsciencewriters. org)
xiv. World Association of Medical Editors (WAME), for editors of peer-reviewed medical journals (http://www.wame.org)
xv. World Federation of Science Journalists (WFSJ) (http://wfsj.org)

Medical writing as a career has given many people a satisfaction of fulfilling their dreams. Though it is tough and sometimes demanding, still it gives a job satisfaction, a wide circle of friends and unexpected job opportunity at the later stage of life with good remuneration.

**PROOFREADERS' MARKS**

| Symbol | Meaning | Example |
|---|---|---|
|  | Delete | take it out |
|  | Close up | print as o ne word |
|  | Delete and close up | clo se up |
|  | Caret | insert here (something |
|  | Insert a space | put onchere |
|  | Space evenly | space evenly where indicated |
|  | Let stand | let marked ~~tekt~~ stand as set |
|  | Transpose | change order the |
|  | Used to separate two or more marks and often as a concluding stroke at the end of an insertion | |
|  | Set farther to the left | too far to the right |
|  | Set farther to the right | too far to the left |
|  | Set as ligature (such as ) | encyclopaedia |
|  | Align horizontally | alignment |
|  | Align vertically | align with surrounding text |
|  | Broken character | imperfect |
|  | Indent or insert em quad space | |
|  | Begin a new paragraph | |
|  | Spell out | set 5 lbs. as five pounds |
|  | Set in capitals | set nato as NATO |

*Contd...*

*Contd...*

| Symbol | Meaning | Example |
|---|---|---|
| sm cap or s.c. | Set in small capitals | set signal as SIGNAL |
| lc | Set in lowercase | set South as south |
| ital | Set in italic | set oeuvre as *oeuvre* |
| rom | Set in roman | set *mensch* as mensch |
| bf | Set in boldface | set important as **important** |
| = or -/ or ⁀ or /H/ | Hyphen | Multicolored |
| 1/N or en or /N/ | En dash | 1965-72 |
| 1/M or em or /M/ | Em (or long) dash | Now-at last!-we know. |
| ∨ | Superscript or superior | $x^2$ as in $\pi r^2$ |
| ∧ | Subscript or inferior | $H_2O$ as in $H_2O$ |
| ∧/∨ or ∨/∧ | Centered | $p \cdot q$ for a centered dot in $p \cdot q$ |
| ❟ | Comma | |
| ❜ | Apostrophe | |
| ⊙ | Period | |
| ; or ;/ | Semicolon | |
| : or ⊙ | Colon | |
| « » or ❛ ❜ | Quotation marks | |
| (/) | Parentheses | |
| [/] | Brackets | |
| OK/? | Query to author: has this been set as intended? | |
| ⊥ or ⊥[1] | Push down a work-up | an untended ⊥ mark |
| ⊙[1] | Turn over an inverted letter | inverted |
| wf[1] | Wrong font | wrong size or style |

[1]The last three symbols are unlikely to be needed in marking proofs of photocomposed matter.
Source: http://www.merriam-webster.com/mw/table/proofrea.htm

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# CHAPTER 16 Clinical Research and Pharmacovigilance of Herbal Drugs

## INTRODUCTION

Traditional herbal medicine has not only been continuously in use for primary health care by the poor in developing countries, but has also been used in countries where conventional medicine is predominantly used. There are approximately 4 billion users of herbal medicines worldwide as per estimates of World Health Organization (WHO) (Farnsworth et al. 1985). Herbal medicine is a major component in all indigenous traditional medicine and is the most common form of alternative/traditional medicine (Brody, 1998).

With the tremendous expansion in the use of traditional medicine worldwide, safety and efficacy of herbal and traditional medicines have become important concerns and the medicines with insufficient evidence of safety are not justifiable because such products carry serious health hazards. This has necessitated a move from traditionally followed observations to the current concepts of research (Katiyar, 2006).

In developed countries, a resurgence of interest in herbal medicines has resulted from the preference of many consumers for products of natural origin. In addition, manufactured herbal medicines often follow in the wake of migrants from countries where traditional medicines play an important role. In both developed and developing countries, consumers and healthcare providers need to be supplied with up-to-date and authoritative information on the beneficial properties, and possible harmful effects, of all herbal medicines.

The potential benefits of herbal medicines could lie in their high acceptance by patients, efficacy, relative safety and relatively low costs. Patients worldwide seem to have adopted herbal medicines in a major way. The efficacy of herbal medicines has been tested in hundreds of clinical trials, and it is wrong to say that they are all of inferior methodological quality, but this volume of data is still small considering the multitude of herbal medicines—worldwide several thousand different plants are being used for medicinal purposes.

The status of herbal research and product development in India is largely unsatisfactory; however after the 'WHO' emphasis to motivate the herbal or traditional medicine research, there is growing concern in this area (Annan 2003; Hassan 2002; Angell and Kassier 2004). At the same time, Indian traditional medical knowledge and the medicinal plant resources are

vanishing under the influence of modern medicine and axed plant habitat. Moreover, the situation further worsened largely due to lack of adequate research funding, poor laboratory and human capacities among several other reasons.

Some of the scientists feel that current approach to medical use of herbal or traditional medicine without subjecting them to some rigorous scientific evaluation like their western counterparts is irrational. However, we need to understand that herbal medicines are different from synthetic ones in several aspects. Some of them are given below while others shall be discussed further in this chapter.

- Plants are polypharmacy themselves with active principles frequently unknown
- Standardization, stability and quality control are feasible but not easy
- The availability and quality of raw materials are frequently problematic
- Well-controlled double-blind clinical and toxicological studies to prove their efficacy and safety are rare
- Empirical use in folk medicine is a very important characteristic
- They have a wide range of therapeutic use and are suitable for chronic treatments
- The occurrence of undesirable side effects seems to be less frequent with herbal medicines, but few well-controlled randomized clinical trials have revealed that they also exist
- Most of the time they are used in holistic manner along with various restrictions on diet and deeds, especially when prescribed by a traditional medicine physician. In such cases, though, more often than not, single drug (single or polyherbal) is seldom prescribed
- They usually cost less than synthetic drugs.

Since, the present day scientists are trained in contemporary science and western medicine and have very limited knowledge on the traditional/ herbal medicines; they advocate a particular way of looking at herbal drugs, which includes the quality control, toxicity, proven efficacy through clinical trial using double blind placebo controlled methodology followed by post marketing surveillance with a view to monitor the adverse drug reactions. This approach was advocated by those countries, which do not have a rich tradition of health care like Ayurveda or Chinese medicine. On the other hand, many advocates for the use of herbal traditional medicines argue that the current universal scientific procedures are simply not applicable to remedies that are already accepted and used by some communities based on their long history of use because traditional herbal medicines did not evolve from fundamental or basic science. Rather, they rely on traditional method of knowledge transfer from generation to generation. There is no doubt that the situation with herbal traditional medicines research offers a great opportunity to develop new strategies for the exploitation of these valuable resources.

The objective of clinical trial itself, therefore, becomes radically different for both new chemical entity and a traditional medicine herbal product.

Before designing a clinical trial protocol for a traditional medicine herbal product, it must be understood that the purpose of trial should ideally be to elicit any side effects rather than finding the efficacy, as these traditional medicine herbal products are already in human use for centuries. Let us not forget that traditional use for centuries provides much better parameter of efficacy evaluation than a clinical trial conducted for few days to few months on a representative population, that too in controlled manner. Probably this is the reason why there have been no cases of withdrawal of the herbal products from the market in contrast to certain classes of synthetic drugs internationally.

Various practices of traditional medicine have been developed in different cultures in different regions without a parallel development of international standards and appropriate methods for evaluating traditional medicine. The challenges posed by the application of the universal ethical guidelines to the research and development of herbal traditional medicines have not been properly addressed.

In developed countries, majority of the clinical trials are double-blind placebo controlled trials, however, among the clinical trials conducted in India, most are randomized open trials, and very few double-blind placebo controlled trials. Further majority of clinical trials conducted in India have shown significant efficacy and had no mention of the adverse events encountered during the course of the trial. After evaluating the collected data from the clinical trials funded/conducted on traditional medicine herbal products in India, the authors feel, though may not be totally true, that a certain degree of bias exists among the researchers and mindset also plays an important role in it. As far as trials conducted in India are concerned, majority of the trials seemed to be biased to prove efficacy whereas the trials conducted in other countries seem to prove inefficacy of traditional medicinal herbal products.

## DEFINITIONS AND CLASSIFICATION

Herbal medicines are broadly covered under the category of complementary/traditional medicines globally.

In India Ayurvedic, Unani, Homeopathic, Siddha systems of medicine are quite popular and are licensed accordingly.

Ayurveda, Siddha or Unani (ASU) drugs include all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in the authoritative books of Ayurveda, Siddha and Unani systems of medicine, specified in the first Schedule of Drugs and Cosmetics Act, 1940.

These products contain herbs, minerals, metals, animal origin products and marine products. Recent years have witnessed introduction of European

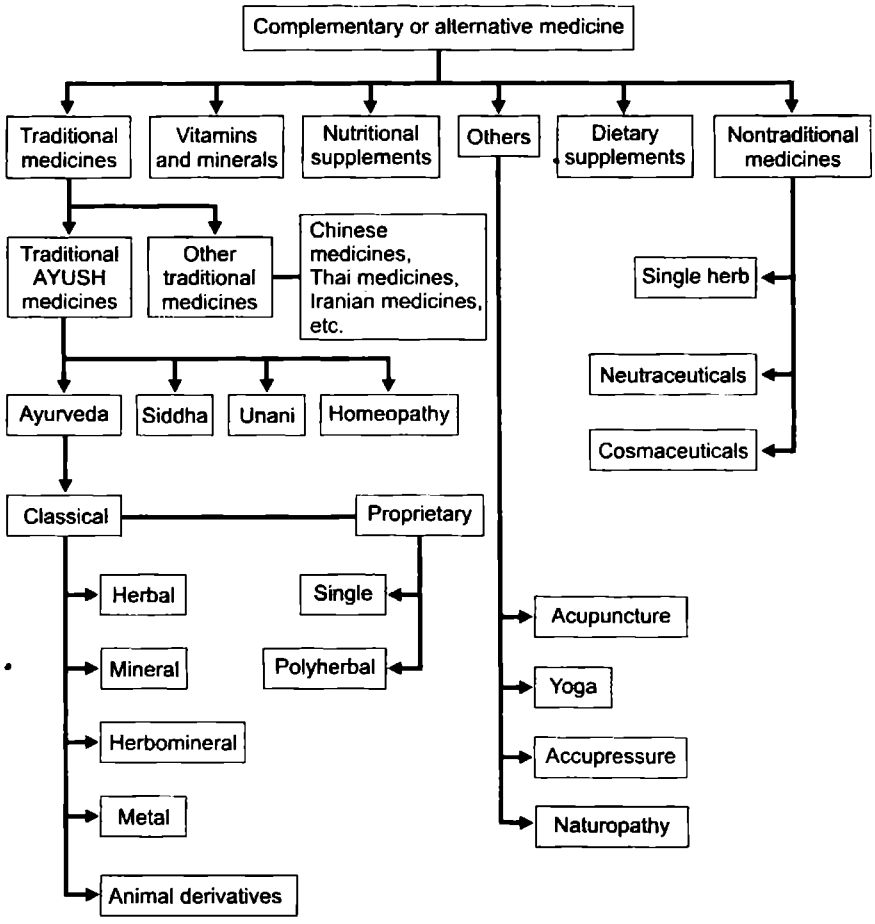


**Fig. 16.1:** Classification and components of complementary/alternative medicine

herbal products also in Indian markets, they however, are sold as dietary supplements.

World Health Organization (WHO, 2000) have specified the definitions of crude herbs, processed herb and finished herbal products, besides traditional medicines. All the related definitions and terminology are discussed in Figure 16.1 and analyzed below.

## Traditional Medicine

Traditional medicine has a long history. "It is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses". The term complementary and alternative medicine is used in some countries to refer to a broad set of healthcare practices

that are not part of the country's own tradition and are not integrated into the dominant healthcare system.

### Herbs

Herbs include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

### Herbal Materials

Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.

### Herbal Preparations

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

### Herbal Medicines

WHO defines herbal medicines as "Finished, labeled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Plant material includes juices, gums, fatty oils, essential oils, and any other substances of this nature. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant material combined with chemically defined active substances, including chemically defined, isolated constituents of plants are not considered to be herbal medicines". Exceptionally, in some countries herbal medicines may also contain, by tradition, natural organic or inorganic active ingredients, which are not of plant origin.

### Finished Herbal Products

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

## HISTORICAL ASPECTS

Physical evidence of use of herbal remedies goes back some 60,000 years to a burial site of a Neanderthal man uncovered in 1960 (Solecki, 1975). In a cave in northern Iraq, scientists found what appeared to be ordinary human bones. An analysis of the soil around the bones revealed extraordinary quantities of plant pollen that could not have been introduced accidentally at the burial site. Someone in the small cave community had consciously gathered eight species of plants to surround the dead man. Seven of these are medicinal plants still used throughout the herbal world (Bensky and Gamble, 1993). All cultures have long folk medicine histories that include the use of plants. Egyptian, Indian and Chinese traditional medicines are considered as oldest system of medicine of the world. Ayurveda, the science of life, prevention and longevity is the oldest and most holistic or comprehensive Indian medical system. The first comprehensive documented treatise on Ayurveda is available in the form of *Charak Samhita*, which is almost 3000 years old (*Charak Samhita*, 2005). Sushruta was an ancient Indian surgeon (who was possibly born in 7th century BC) and is the author of the book *Sushruta Samhita*, in which he describes over 120 surgical instruments, 300 surgical procedures and classifies human surgery in 8 categories. Chinese traditional medicines also have the history of thousand of years; however, reliable historical records are not available before 722 BC. Three thousand year ago on Oracle bones (tortoise shells and animals bone) from the shell dynasty (1766 to 1122 BC) records of illnesses, medicines and treatments were found inscribed in China. Acupuncture has been used as a therapeutic method in China for all over 2000 years ago. The earliest Chinese text, the *Huang Ti Nei Jing Su Wen Ling Shu'* (The Yellow Emperor's Classic of Internal Medicine), is ascribed to the 2nd and 1st centuries BC.

Even in ancient cultures, people methodically and scientifically collected information on herbs and developed well-defined herbal pharmacopeias. Indeed, well into the 20th century much of the pharmacopeia of scientific medicine was derived from the herbal lore of native people. Many drugs, including atropine, quinine, strychnine, aspirin, vincristine, taxol, metformin, and ergotamine, etc. are of herbal origin. About one-quarter of the prescription drugs dispensed by community pharmacies in the United States contain at least one active ingredient derived from plant material (Farnsworth and Morris, 1976).

The past decade has seen a significant increase in the use of herbal medicines. As a result of WHO's promotion of traditional medicine, countries have been seeking the assistance of WHO in identifying safe and effective herbal medicines for use in national healthcare systems. In 1991, the Director-General of WHO, in a report to the 44th World Health Assembly, emphasized the great importance of medicinal plants to the health of individuals and communities. Earlier, in 1978, the 31st World Health Assembly (WHA) had

adopted a resolution (WHA31.33) that called on the Director-General to compile and periodically update a therapeutic classification of medicinal plants, related to the therapeutic classification of all drugs; subsequently, resolution of WHA40.33, adopted in 1987, urged member states to ensure quality control of drugs derived from traditional plant remedies by using modern techniques and applying suitable standards and good manufacturing practices; and resolution WHA42.43, of 1989, urged member states to introduce measures for the regulation and control of medicinal plant products and for the establishment and maintenance of suitable standards. Moreover, the International Conference on Primary Health Care, held in Alma-Ata, USSR, in 1978, recommended, inter alia, the accommodation of proven traditional remedies in national drug policies and regulatory measures.

## REGULATION OF HERBAL/TRADITIONAL MEDICINES

The regulation and legislation on traditional herbal medicines varies from country to country (WHO, 2005). Their review draws the attention to the fact that safety and efficacy do not form the mandatory requirements in most of the countries. This may be due to the fact of long traditional usage, or other ethnic or cultural diversities.

Several regulatory models for herbal medicines currently exist, including prescription drugs, over-the-counter drugs, traditional medicines and dietary supplements, nutraceuticals (WHO, 2005). WHO, therefore, emphasizes the need to establish global and/or regional regulatory mechanisms for regulating herbal drugs. According to a global survey undertaken by WHO in 141 member states enquiring about the laws controlling traditional/conventional alternative medicines 54 countries (38%) confirmed having laws or regulations while 84 countries (60%) did not have any law to control traditional/conventional alternative medicines.

WHO initiative for regulation of traditional medicine were based on the recommendation of a workshop on the regulation of herbal medicines by The Fourth International Conference of Drug Regulatory Authorities, held in Tokyo in 1986, and another workshop on the same subject held as part of the Fifth International Conference of Drug Regulatory Authorities, held in Paris in 1986. Both workshops confined their considerations to the commercial exploitation of traditional medicines through over-the-counter labeled products. The Paris meeting concluded that the World Health Organization should consider preparing model guidelines containing basic elements of legislation designed to assist those countries wishing to develop appropriate legislation and registration.

The objective of these guidelines, therefore, is to define basic criteria for the evaluation of quality, safety, and efficacy of herbal medicines and thereby to assist national regulatory authorities, scientific organizations, and

manufacturers to undertake an assessment of the documentation/ submission/dossiers in respect of such products. As a general rule in this assessment, traditional experience means that long-term use as well as the medical, historical and ethnological background of those products shall be taken into account. The definition of long-term use may vary according to the country but should be at least several decades. Therefore, the assessment should take into account a description in the medical/pharmaceutical literature or similar sources, or a documentation of knowledge on the application of a herbal medicine without a clearly defined time limitation. Marketing authorizations of similar products should be taken into account.

These efforts concentrate on herbal medicines, but might at a later stage be the basis for the assessment of other traditional medicines not covered by these guidelines. In the meantime, it is up to the national authorities to adapt the guidelines for assessment of traditional medicines and other herbal drugs.

Prolonged and apparently uneventful use of a substance usually offers testimony of its safety. In a few instances, however, investigation of the potential toxicity of naturally occurring substances widely used as ingredients in these preparations has revealed previously unsuspected potential for systematic toxicity, carcinogenicity and teratogenicity. Regulatory authorities need to be quickly and reliably informed of these findings. They should also have the authority to respond promptly to such alerts, either by withdrawing or varying the licenses of registered products containing suspect substance, or by rescheduling the substance to limit their use to medical prescription.

WHO has emphasized on four aspects of herbal medicines, viz. quality, safety, efficacy and affordability. Regulatory guidelines can be formulated by the member countries keeping these basic factors in view.

A summary of the regulatory agencies and processes related to herbal drugs of some selected countries is presented below.

### Australia

Therapeutic Goods Act (TGA, 1990) Working Party established by the Australian Parliament reviews the natural and nutritional supplements quality, safety, efficacy and labeling of herbal and related products. In Australia, complementary medicines referred for medicinal products containing herbs, vitamins, minerals, and nutritional supplements, homeopathic medicines and certain aromatherapy products. These are regulated as medicines under the *Therapeutics Goods Act, 1989* (the Act). TGA states that traditional claims for herbal remedies be allowed, providing general advertising requirements are complied with and providing such claims are justified by literature references.

### China

The State Pharmaceutical Administration of China, the Division of Drug Administration in the Ministry of Health, and the Division of Traditional

Chinese Medicine in the Traditional Chinese Medication Administration Bureau were merged into the State Drug Administration (SDA) in 1999. The new organization revised major provisions of herbal drug regulation that had lagged behind the times and added new provisions and guidances. These regulations covered the drug registration procedure, new drug protection and technology transfer, Good Clinical Practices (GCPs), and Good Laboratory Practices.

### European Union

European Union, after giving due consideration to increasing popularity of herbal products have recently released a comprehensive directive which allows simplified registration of Traditional Herbal Medicinal Products (THMPs). However, in order to be eligible for simplified registration these traditional herbal remedies should be in use for more than 15 years in any of the EU member countries in addition to more than 30 years in country of origin. This directive which came in 2004 will be mandatory from 2011 for herbal drugs registration in European countries. Under this regulation, a company needs to demonstrate the safety and efficacy of the herbal medicine through traditional use within the EU for at least 30 years (or 15 years within the EU and 30 years outside the EU). Further, the herbal medicine must now be manufactured under GMP (Good Manufacturing Practice); however, the Traditional Herbal Medicines Product Directive does allow claims to be made on the label of the final product, although restriction does apply.

### India

Central Drugs Standard Control Organization (CDSCO) and Department of AYUSH (Ayurveda, Unani, Siddha, Homeopathic medicines, Naturopathy and Yoga) Ministry of Health and Family Welfare, Government of India are the drug regulatory bodies for approval and control of Ayurvedic, Unani and Siddha medicines. The Chapter IVA section 33C of The Drugs and Cosmetics Act, 1940 and The Drugs and Cosmetics Act and rules, 1945 has laid down the provisions relating to Ayurvedic, Siddha and Unani drugs.

### United States of America

Herbal medicines have been regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994. On the basis of this law, herbal medicines are not evaluated by the FDA and most importantly, these products are not intended to diagnose, treat, cure, or prevent diseases. However, herbalist may also apply under existing guidelines for approval of new herbal drugs, but this will be a huge financial burden similar to the total cost of bringing a new pharmaceutical drug.

The US government has established the Office of Alternative Medicine at the National Institutes of Health (NIH) with the following aims: 1. to explore the potential role of dietary supplements in the improvement of health; 2. to

promote the scientific study of supplements for maintaining health and preventing chronic diseases; 3. to compile a database of scientific research related to supplements; 4. to coordinate NIH funding for dietary supplements related to the treatment of chronic disease. The regulatory lockout of natural remedies has crippled natural products research in US universities and hospitals. There is no dedicated level of support by the Federal Government for herbal medicine research.

As per current US laws all the dietary supplements must be registered with FDA before the same can be marketed in US, otherwise these cannot be sold in US from Jan 2010 onwards.

### United Kingdom (UK)

The MHRA (Medicines and Health Care Products Regulatory Authority) is the executive arm of the United Kingdom's Drug Licensing Authority and is responsible for all aspects of the regulation of medicines in the UK. In January 2002, the European Commission adopted formal proposals for a Directive on Traditional Herbal Medicinal products. The MHRA held a full public consultation during the summer of 2002, which was extended following a request from Ministers for a greater degree of dialogue between the herbal sector and the Agency. Informal consultation continued through 2003 with representatives of the herbal sector attending meetings to discuss many aspects of the Directive, as proposed at that time. The MHRA and the herbal sector agreed that key priorities in the negotiations were greater flexibility in relation to acceptance of evidence of traditional use from outside the European Union, and the possibility for companies to include vitamins and minerals with traditional herbal remedies. These objectives were achieved in European negotiations.

## REGULATORY ASPECTS ON CONDUCTING THE CLINICAL TRIALS

Considering long-term usage of traditional/herbal medicines in several countries including India and China, clinical trials have not been made mandatory by the regulatory authorities as a prerequisite to market authorization. Recent resurgence of herbal/traditional medicines has generated interest among the scientific community and they have started demanding the evidence of efficacy through the clinical trials. Most of the clinical trials currently are conducted to generate the data to validate the claim. In the absence of any harmonized guideline on clinical trials on traditional/herbal medicines, *sui generis* systems are being followed by the enthusiasts.

Currently, there are no specific laid downregulations or guidelines that should be adopted to do clinical trials on herbals/Ayurvedic/alternative medicines. The guidelines available for allopathic stream of medicines may not be directly applicable to herbal medicines. However, few organizations have developed broad directional guidelines, few of which are summarized below.

### Indian Council of Medical Research (ICMR) Guidelines

ICMR guidelines have classified herbal drugs in three categories and have suggested to follow different approaches for their clinical evaluation. The herbal products can belong to any of the three categories given below:

- A lot is known about the use of a plant or its extract in the ancient Ayurveda, Siddha or Unani literature or the plant may actually be regularly used by physicians of the traditional systems of medicine for a number of years
- When an extract of a plant or a compound isolated from the plant has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different, it should be treated as a new drug
- An extract or a compound isolated from a plant which has never been in use before and has not ever been mentioned in ancient literature, should be treated as a new drug.

Clinical trials with herbal preparations should be carried out only after these have been standardized and markers identified to ensure that the substances being evaluated are always the same. The standard recommendations regarding informed consent, inducements for participation, information to be provided to the subject, withdrawal from study and research involving children or persons with diminished autonomy, all apply to trials on plant drugs also. These trials also have to be approved by the appropriate scientific and ethical committees of the concerned institutes. However, it is essential that such clinical trials be carried out only when a competent Ayurvedic, Siddha or Unani physician is an investigator or co-investigator in such a clinical trial.

### World Health Organization (WHO) Guidelines

The WHO has published guidelines in order to define basic criteria for evaluating the quality, safety, and efficacy of herbal medicines aimed at assisting national regulatory authorities, scientific organizations and manufacturers in this particular area. Furthermore, the WHO has prepared pharmacopeial monographs on herbal medicines and the basic guidelines for the assessment of herbal drugs. Originally, WHO guidelines for GCP have been adapted from ICH guidelines. These guidelines specify the requirements for clinical trial protocol and protocol amendment(s); background information about the name and description of the investigational product(s); trial objectives and purpose and trial design selection and withdrawal of subjects; treatment of subjects; assessment of efficacy and safety; statistics; direct access to source data/documents; quality control and quality assurance; description of ethical considerations relating to the trial; data handling and record keeping; financing and insurance if not addressed in a separate agreement; publication policy if not addressed in a separate agreement; pharmaceutical assessment of preparations; stability and safety aspects.

### Good Clinical Practices (GCP) Guidelines

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. Objective of ICH GCP Guidelines is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The ICH guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization. India has also developed its own GCP guidelines.

### AYUSH, India

AYUSH is a nodal agency for all the coordinating works such as education, research and health care through Indian Systems of Medicine, Ayurveda, Homeopathy, Naturopathy, Siddha and Yoga. This department funds several extramural projects besides having a research council called Central Council for Research in Ayurveda and Siddha (CCRAS), dedicated to research in Ayurveda, through its several laboratories. In order to lay down standards on medicinal plants, Department of AYUSH has prepared 326 monographs on medicinal plant parts through Ayurvedic Pharmacopeia Committee. Under this program, monographs of all the 326 medicinal plant parts have been published.

### Central Drugs Standard Control Organization (CDSCO), India

Drug and Cosmetic Act in India covers the regulations for conducting clinical trials in India under Schedule Y. However, all the concepts laid down in this schedule are basis modern medicines that may not be sometimes as such applicable to ayurvedic/herbal category of drugs.

### Ethical Issues

Ethical and economical issues are important in the management aspects of herbal medicines research. The main players in the exploitation of herbal medicines include the traditional medicine practitioner, the research scientists, pharmaceutical industry that will bring forth the medicines and medicinal products of research to the public and the larger society that will ultimately benefit in health and disease. National governments are also involved as they have responsibility of ensuring the welfare and safety of citizens. All the parties mentioned are interested in developing herbal medicines for public use. However, in the clinical development of herbal

traditional medicines, the tripartite relationship between the researcher, the traditional practitioner and the research participant is of paramount importance.

Treating physicians have the obligation of judging the material risks of their medical treatments, and this may include the risks associated with complementary medicine. Most patients and many healthcare professionals view traditional medicine as virtually risk free, a notion that is often misguided. Complementary medicine is likely to become relevant to the informed consent obligation of GPs (Ernst, 2004).

Informed consent (IC) is an integral part of research by which we create understanding on the research projects. Informed consent is a 'process of weighing up any possible risks and benefits to be derived. IC has become the cornerstone of research ethics because it affords the research participants the ability to exercise their rights to beneficence and autonomy. Nevertheless, informed consent as contained in the international guidelines focuses mainly relationship between the researcher and the research participant. As the popularity of complementary medicine grows, and as informed consent becomes more and more comprehensive, its relevance for clinical trial practice is important. At present, however, GPs' ethical obligations still exceed the legal ones.

Traditional medicine may be less risky than most conventional therapies but it is not totally devoid of adverse effects. Treating physicians have the obligation of informing about the adverse events. Many modern practitioners believe that all forms of traditional medicine lack evidence of efficacy. This is clearly not the case. If Cochrane reviews are anything to go by, several herbal remedies are of proven efficacy, for instance, St John's wort is an effective symptomatic treatment for mild to moderate depression (Kessler et al, 1995), so is horse chestnut seed extract for primary venous insufficiency (Creamer et al, 2001), and ginkgo for dementia (Stein et al, 2000).

Researchers should also remember that herbal medical care is a long time cultural duty of the traditional medicine practitioner within the community. He or she holds this responsibility on trust for the community but it is also his/her source of livelihood. These are important considerations in the consent process. Therefore, the need for understanding IC before research commences is strongly advocated. The concerns and benefits of all the stakeholders who share in the burden of herbal medicines research should be defined and determined. This measure should be considered as part and parcel of submissions to regulatory and ethical review committees (Karniyus and Carel, 2004). There should be clear terms on outcome of research regarding benefit and royalties. This should be included in the IRB/EC review process of herbal traditional medicines.

Schedule Y of Drugs and Cosmetic Act in India gives the format of informed consent as well as the format for ethics committee structure and its functions. ICMR has developed detailed guidance in 2000 that has been

revised in 2006. This document very nicely covers almost all the broad ethical issues and concerns related to clinical research.

## REVIEW OF CLINICAL TRIAL DESIGNS ON TRADITIONAL/HERBAL MEDICINES

Katiyar (2006) reviewed the representative clinical trials conducted in India, through National Center of Complementary and Alternative Medicines (NCCAMs), USA and other international studies with a view to analyze the clinical trial designs followed. The search was conducted using Internet search engines Pubmed and Google, studies compiled by Central Council for Research in Ayurveda and Siddha (CCRAS), New Delhi, Indian research journals published by CCRAS, ICMR, New Delhi, Indian Journal of Clinical Practice and other Indian journals. Phytomedicine, International Journal of Complimentary and Alternative Medicine, Journal of American Medical Association, New England Journal of Medicine and other relevant journals were also screened for the purpose besides the NCCAM website.

The review of clinical trials collated using above mentioned resources (without modifying the words used to describe the designs followed) revealed that several researchers have conducted clinical trials on Ayurvedic/herbal medicines in India. These researchers belong to both modern medicine as well as traditional medicine streams. It was observed that there was no harmonization in the trial designs of 68 Indian clinical trials reviewed which are shown in Table 16.1.

Among the 68 trials reviewed from India, approximately 41 percent were randomized open trials and about 19 percent open comparative trials. Approximately 10 percent were double-blind placebo controlled trials. These trials were conducted on single herbal Ayurvedic medicines (viz. *Pluchea lanceolata, Pterocarpus marsupium, Glycyrrhiza glabra, Emblica officinalis, Withania somnifera, Crataeva nurvala, Clerodendrum serratum, Boswellia serrata, Picrorhiza kurroa, Bacopa monniera, Saraca asoka, Swertia chirayata, Terminalia arjuna, Commiphora wightii, Inula racemosa, Smilax china, Streblus asper, Tecoma undulata, Acorus calamus, Centella asiatica, Terminalia belerica, Hedychium spicatum, Gymnema sylvestre, Tribulus terrestris* and *Bergenia lingulata, Zingiber officinale*), polyherbal and herbomineral formulations (viz. AYUSH-64, Rhumayog, Rhumayog Gold, K-4, Brihat Vata Chintamani Rasa, Shweta Parpati and Kshaar sutra).

Clinical trials conducted through NCCAM, USA were also reviewed to find out the designs followed for these studies. Table 16.2 provides the analysis of the same.

It was observed that, 23 (46%) were randomized double-blind placebo controlled parallel trials and 9 (18%) were randomized open and other trials were conducted using different designs. The trials have been conducted on black cohosh (9), red clover (6), borage oil (4), gingko (3), garlic (3), mistletoe (1),

**Table 16.1:** Designs followed in Indian clinical trials on Ayurvedic/herbal medicines

| *Number of trials reviewed (India): 68* | | |
|---|---|---|
| *S. No.* | *Trial design* | *No. of trials* |
| 1. | Double-blind placebo-controlled | 7 |
| 2. | Double-blind comparative | 3 |
| 3. | Open comparative placebo-controlled | 3 |
| 4. | Single-blind placebo-controlled | 5 |
| 5. | Open non-comparative | 1 |
| 6. | Randomized open | 28 |
| 7. | Open add-on | 1 |
| 8. | Flexi-dose open | 1 |
| 9. | Double-blind crossover | 1 |
| 10. | Open add-on comparative | 1 |
| 11. | Open comparative | 13 |
| 12. | Single-blind reference-controlled | 4 |

**Table 16.2:** Analysis of reviewed clinical trials conducted through NCCAM

| *Number of trials reviewed (NCCAM): 50* | | |
|---|---|---|
| *S. No.* | *Trial design* | *No. of trials* |
| 1. | Randomized double-blind placebo-controlled, parallel | 23 |
| 2. | Nonrandomized open-uncontrolled | 3 |
| 3. | Randomized open | 9 |
| 4. | Open label | 3 |
| 5. | Non-randomized open active control crossover | 1 |
| 6. | Randomized double-blind placebo-controlled crossover | 2 |
| 7. | Randomized double-blind placebo-controlled parallel dose-escalation | 2 |
| 8. | Randomized double-blind active control parallel | 1 |
| 9. | Nonrandomized open active control | 1 |
| 10. | Randomized double-blind active control crossover | 1 |
| 11. | Nonrandomized single-blind placebo controlled | 1 |
| 12. | Randomized single-blind placebo-controlled | 2 |
| 13. | Randomized double-blind | 1 |

chamomile (1), cranberry (2), echinacea (3), dehydroepiandrosterone (1), flax seed (1), ginger (1), St. John's wort (6), milk thistle (1), soya isoflavones (4), pycnogenol (1), saw palmetto (1), valerian (1) and broccoli (1).

In the 179 clinical trials conducted internationally on herbs and herbal products, the methodologies, which have been adopted, are listed in Table 16.3. The herbs or products on which these trials have been conducted are: *Cimicifuga racemosa* (10), *Serenoa repens* (18), *Hypericum perforatum* (35), *Zingiber*

*officinale* (20), *Ginkgo biloba* (45), *Piper methysticum* (15), *Valeriana wallichii* (10) and *Echinacea purpurea* (26).

Out of these 179 clinical trials, 62 percent were found to be randomized double blind placebo-controlled studies, approximately 19 percent were double blind comparative and 10 percent were single-blind placebo-controlled studies.

Table 16.4 depicts the comparative percentage of randomized double blind placebo controlled (RDBPC), single-blind placebo-controlled (SBPC) and double-blind comparative (DBC) clinical trials conducted in India, through NCCAM, USA and other studies conducted internationally.

Single herbal drugs subjected to clinical trials using any one of the above designs have recently been reported to be ineffective in few papers published in international journals. Some of them are echinacea for cold (Taylor et al, 2003), guggulu for high cholesterol (Szapary et al, 2003) and more recently saw palmetto for benign prostrate hypertrophy (Stephen et al, 2006). This is in contrast to the several other studies on the same products proving their efficacy in earlier conducted clinical trials using almost similar designs. Moreover, review of the trial methodologies and results obtained provided the debatable conclusion that none of the above methods followed for conducting clinical trials are fool proof with respect to traditional medicines, which includes ayurvedic/herbal medicines as well. Numerous trials on same product even using conventional design for clinical trial give inconsistency in results. Therefore, the conventional approach of conducting clinical trials on single drug as a component of treatment may not be appropriate for traditional/herbal medicines.

**Table 16.3:** Analysis of reviewed clinical trials (International)

| *Number of trials reviewed (International): 179* | | |
|---|---|---|
| *S. No.* | *Trial design* | *No. of trials* |
| 1. | Randomized double-blind placebo-controlled | 111 |
| 2. | Double-blind comparative | 33 |
| 3. | Crossover double blind | 4 |
| 4. | Single-blind placebo-controlled | 17 |
| 5. | Placebo-controlled single-blind comparative | 2 |
| 6. | Parallel group comparative | 12 |

**Table 16.4:** Trial design wise comparative percentages

| *Trial methodology* | *India* | *NCCAM* | *International* |
|---|---|---|---|
| RDBPC | 10% | 41% | 62% |
| SBPC | 7% | 4% | 10% |
| DBC | 5% | – | 19% |

## LIMITATION WITH HERBAL/TRADITIONAL MEDICINE WITH REFERENCE TO CLINICAL TRIALS

Several factors make the task of conducting clinical trials on traditional/herbal medicines daunting. Few important ones are discussed below.

- Trial design
- Randomized controlled trials
- Blinding
- Placebo
- Clinical equipoise
- Standardization or quality of products
- Ayurvedic perspective.

### Trial Design

Herbal/traditional medicine presents special challenges in the design and execution of studies, with respect to both internal validity and generalizability. These problems relate to the tension between specifying the intervention sufficiently that others can apply it and desire to study traditional medicine as it is applied in traditional medicine practices; they also concern the difficulties in controlling expectation bias (the systematic effect on the results of the participants' belief that a certain therapy will help them). Most traditional medicine interventions are investigated only after they are so widespread that they can no longer be ignored, and by that time, the traditional medicine practices are highly diversified in practices, personal experiences, biases, and expectations. A single research strategy will not fit all circumstances and all traditional medicine interventions; hence there is need for flexibility in designing of trials, e.g. randomized trial, single case, black box, ethnographic, etc. The study design may be chosen from a whole spectrum of clinical research designs which are suitable for assessing traditional medicine.

### Randomized Controlled Trials (RCTs)

The most powerful method for testing the effect of a conventional medical intervention is a randomized clinical trial, which however is not suitable for many traditional medicines. Standard RCTs consisting of two or three study arms, large numbers of patients in each study arm, one specific, standard treatment or dose of treatment per study arm, and 1 or 2 years of follow-up may be ill-suited to answer questions about the long-term effects of complementary and alternative medicine. In many other traditional medicine therapies, however, the conceptual basis for the therapy requires an interaction between the practitioners and patient that modifies the therapy to the individual. Among Indian traditional medicines, especially ayurvedic medicine requires individualization of treatment based on examination and

understanding of the patient's condition using concepts that do not have an analog in western allopathic medicine. Consequently, traditional medicine/ CAM advocates have criticized randomized clinical trials that reported no effect for not having allowed the necessary tailoring of the intervention.

### Blinding

Blind assessment is a critical component of conventional evaluation of therapeutic interventions. Though treatment blinding in the evaluation of herbal medicines should adopt the approach of conventional medicines, e.g. using active and control formulations with similar color, taste, aroma, etc. However, in the evaluation of efficacy of traditional therapies, it can be difficult, impractical or impossible for the practitioner to be kept ignorant of what treatment the patients are receiving. It is important, however, to reduce any bias introduced by non-blinded treatment by carrying out a blinded assessment of the primary outcomes of the study. If the herbal medicine cannot be administered in a predetermined standardized formulation, it will be impossible to keep the treatment blinded.

### Placebo

Use of a placebo may not always be possible as they may involve ethical issues as well as technical problems. For example, it may not be possible to have a placebo control if the herbal medicine has a strong or prominent smell or taste, as is the case for products containing certain essential oils. In addition, patients who have been treated previously with the herbal medicine under investigation that has a characteristic organoleptic property cannot be randomized into control groups. In the case of herbal medicines with a strong flavor, placebo substances with the same flavor may have a similar function. This problem may become more compounded in case of semisolid formulations like Chyawanprash. In such cases, it may be advisable to use a low dosage of the same herbal medicine as a control. Alternatively, a positive control, such as well-established treatment, can be used.

### Clinical Equipoise

Ayurveda or herbal medicine does not have another herbal clinical equivalent, rather clinical trial with herbal equipoise are discouraged. Herbal traditional medicine research, comparing the activities of the herbal remedies to standard care is paramount in order to achieve clinical equipoise. Without equipoise, the research will not be scientifically valid as some of the participants may receive inferior treatment and the effort will not contribute to increasing knowledge about best treatment. The drawback in this approach is that some of the intangible holistic values of the herbal remedies are masked by the western approach and are not put into consideration. Therefore, the

control group in herbal medicines research should be placed on the standard clinical care of allopathic medicines where it is available. Furthermore, we suggest that the issue of continued care after completion of the study should be raised in such studies before commencement.

## Standardization or Quality of Products

Plants are polypharmacy themselves containing hundreds of constituents and some of them are present at very low concentrations. Standardization of herbal products is a burning issue being discussed and debated from academic to regulatory fora. Quality of the finished product depends upon the quality and authenticity of the crude raw material, geographical location of collection, time of collection, method of harvesting, storage, processing, microbial load, heavy metal contamination, etc. Most critical point to achieve standardization is identification, isolation and characterization of the marker compounds. It is followed by developing appropriate analytical methods to test the qualitative and quantitative presence of the compounds not only in the crude plant material, but also in the intermediates like extracts and their finished formulations. Intense efforts are ongoing globally to evolve and develop the pharmacopeial standards of the medicinal plants used in the traditional medicines.

## Ayurvedic Perspective

The word Ayurveda is derived from *Ayu* (life) and *Veda* (knowledge) therefore, it is knowledge of life. Its objectives are two-fold, viz. to maintain the health of a healthy person and if by chance despite following all the instructions of leading a healthy life, somebody falls ill then cure the disease. With a view to remain healthy for 100 years in order to achieve *dharma, artha, kama and moksha* (Charak Samhita, 2000), Ayurveda has prescribed both nontherapeutic and therapeutic measures. Therapeutic measures again are of two types: (i) life sustaining and (ii) disease alleviating. Both of the above include three-fold measures:

- Dietary regimen
- Behavioral modalities
- Drugs.

Ayurveda or other traditional systems of medicine seldom use mono-herb based therapy. In most of the cases, traditional medicine physicians follow the approach of multiple therapies coupled with dietary and behavioral modalities to achieve therapeutic effectiveness. Rheumatoid arthritis is a typical example in which oral drugs (mostly polyherbal), topical application of medicated oils along with strict dietary restrictions are common features.

## NEED OF ALTERNATIVE APPROACH FOR CLINICAL TRIAL ON TRADITIONAL MEDICINE

The conventional methods of 'controlled' and 'randomized controlled clinical trial' is considered a gold standard, however, while applying it to evaluate herbal/traditional medicine especially ayurvedic medicines, its limitations come to fore. A careful study of holistic approach of treatment followed in traditional medicines suggests that the current method of conducting clinical trials have serious limitations in evaluating the evidence of efficacy of ayurvedic or traditional medicine products and the reason being that the treatment regimens used by traditional medicines are holistic in nature; while the treatment approach in contemporary medicine is generally reductionist. Several limiting factors make the task of conducting clinical trials on traditional/herbal medicines in conventional way, daunting. Few important ones are discussed below.

There is a quest for appropriate method for assessment of ayurvedic or herbal products. Ayurveda does not consider body as separate from mind and soul and treat these three components together for complete healing of individuals.

An integrated/holistic approach is essential while undertaking the clinical trial with Ayurveda drug and the following factors need to be considered as variables individually and should be accommodated while designing the clinical trial protocols for ayurvedic/herbal medicine.

Essential elements of an ayurvedic therapeutic regimen are DEEDS, DIET and DRUGS in addition to the following:

- Complex (individualistic) treatment approach—Psychosomatic constitution (*prakriti*), etc.
- Multifactorial patient (*rogi*) and disease examination (*roga pariksha*)
- Interventions at different stages of disease (*kriyakala*)
- Close relationship of food (*pathya apathya*), medicine, vehicle (*anupana*), time of drug administration, etc.
- Quality of drug to be tested (batch-to-batch consistency)
- Doctor-patient relationship
- Use of treatment regimen rather than single drug.

### Complex (Individualistic) Treatment Approach—Psychosomatic Constitution (Prakriti)

Prakriti of an individual is determined at the time of conception and can be defined as a 'psychosomatic constitution' of an individual. Total population can be divided in 7 psychosomatic types. *Prakriti pariksha* is based on physical and mental traits and influenced by *Tridosha* (*Vata, Pitta and Kapha*). Ayurvedic system of medicine believes in individualistic treatment. This is the reason while different patients with same disease are prescribed different drugs depending upon several factors including their psychosomatic constitution.

This may also partly explain why most of the ayurvedic medicines are polyherbal in composition.

### Multifactorial Patient (Rogi) and Disease Examination (Rog Pariksha)

Integrated/holistic approach of Ayurveda does not differentiate the disease from the patient. Rather both are considered simultaneously. This approach puts insurmountable challenges in deciding the inclusion and exclusion criteria in clinical trial of ayurvedic medicines following ayurvedic principles.

### Interventions at Different Stages of Disease (Kriyakala)

Ayurveda proposes different interventions at different stages of disease (*Kriyakala*) in the same patient providing another variable in a clinical trial.

### Diet (Pathya-Apathya)

Diet component may also affect the treatment outcome in clinical trial. Administration of *Maha Yogaraj Guggulu* (a formulation having anti-inflammatory effect) with restriction of rice, curd, brinjal, etc. will give positive outcomes, however in similar kind of patients without restriction of rice, curd, brinjal, etc. will give negative outcomes of therapy.

### Vehicle for Drug Administration (Anupana)

Component of Ayurveda is also accountable for therapeutic efficacy of ayurvedic medicines. Most of the time the drug is recommended to be administered with a specific vehicle like honey, sugar, jaggery, buttermilk, curd, ghee, warm water, expressed juice of a herb, etc. An *'Anupana'* is a half-medicine in itself. An interesting example is of *Mrityunjaya Rasa* used for fever in ayurveda, is given with different *anupana* (vehicle) in different kind of fevers. For example, in *vataja jwara* with buttermilk, in *sannipata jwara* with *ardraka swarasa* (Ginger juice), in *ajirna jwara* with *nimbu swarasa* (Lemon juice), in *vishama jwara* with *krishna jeeraka* and jaggery.

## PROPOSED METHODOLOGIES FOR CLINICAL TRIALS ON AYURVEDIC HERBAL DRUGS

The authors propose that proper way of conducting clinical trials in case of ayurvedic medicine is to subject the whole treatment regimen to the test rather than its individual component and the best way to achieve this is to follow the concept of observational research rather than double-blind placebo-controlled clinical trials.

One strategy could be to use pragmatic trial approach; however it has its own problems. In a pragmatic trial, patients are assigned to a traditional

practitioner rather than a tightly specified traditional therapy. The traditional practitioners can provide their treatments in their usual fashion, individualizing the therapy for each particular patient. While this strategy allows the conventional practice to occur in its traditional fashion, it makes blinding or otherwise controlling expectation bias very difficult.

Furthermore, while in one way individualizing the therapy increases generalizability, it also increases the sensitivity of the results to the skill of the practitioners. Since, the intervention relies on practitioner expertise in understanding the patient and delivering the therapy, the study results are more difficult to apply to other practitioners. Thus, pragmatic trials should discuss the training and experience of the traditional practitioner. Large pragmatic trials that include many practitioners and that compare a traditional therapy with a credible control or alternative therapy would be particularly useful in assessing traditional medicine.

The most appropriate method to generate efficacy data on classical ayurvedic therapeutic regimen appears to be observational research as it involves: (i) Efficacy of whole treatment regimen, (ii) It is conducted in real life situation, (iii) Data generated by this method can be used by other physicians as well, (iv) Change in mindset is required among traditional medicine physicians to start proper documentation of their practice to generate the data; though it will be acceptable to both WHO as well as to drug regulatory agencies as documented evidence of traditional use.

Observational studies collect findings on a therapeutic or prophylactic treatment under routine conditions. The special feature of these studies is that they seek, as far as possible, not to influence the individual doctor–patient relationship with respect to indications, and the selection of and carrying out the treatment. These studies may be conducted with or without a control group. The specific details of the study (e.g. the time and extent of examination for each individual patient, the number of patients involved) and the envisaged methods (e.g. data recording and evaluation) must be adapted to the question investigated in the study (e.g. safety or appropriate posology). Observational studies have specific advantages in studying aspects of clinical safety. The use of such studies to prove efficacy is limited because bias in patient selection may occur. Nevertheless, the level of evidence on efficacy of traditional medicine can be significantly increased by well-designed observational studies.

Some of the methodological approaches specific to the assessment of traditional medicines through clinical research are given below:

- Evaluate traditional medicine in its own theoretical framework—this approach is related to clinical evaluation of holistic multipronged therapeutic approach basis the traditional system of medicine practices.
- Evaluate traditional medicine in the theoretical framework of conventional medicine—this approach refers to certain cases of ayurvedic drugs where single herbs are used as standalone medicine in traditional medicine.

- Compare the efficacy of different traditional practices within a system of traditional medicine—this approach refers to clinical evaluations of nontherapeutic or semitherapeutic practices, e.g. *panchakarma* which involves use of medicated oil or yogic practices which do not involve any medicine.
- Evaluate the efficacy of pure active phytochemicals under the rigorous current scientific procedures or conventional methods for clinical trials.

## PHARMACOVIGILANCE OF TRADITIONAL/HERBAL DRUGS

Pharmacovigilance refers to identifying side effects of drugs, their treatment, documentation, reportage and regulatory decisions based on these findings. In general, pharmacovigilance is the science of collecting, monitoring, assessing and evaluating information from healthcare professionals and consumers on the undesired effects medications including herbal and traditional drugs.

Worldwide movement for the improvement of patient safety is gaining momentum; hence the subject of drug safety becomes even more prominent in the present day scenario. Nowadays, herbal medicines are being used by various communities throughout the world. Herbal formulations have reached widespread acceptability as therapeutic agents like cough remedies, hepatoprotectives, antidiabetics, etc. Herbal medicines are traditionally considered harmless since these belong to natural sources. However, this is not true as there are several case reports of adverse reactions of herbal drugs mentioned in published literature.

The following examples demonstrate the range of problems encountered with the use of herbal medicines and products (WHO 2004):

- Some herbal products were found to contain 0.1 to 0.3 mg of betamethasone per capsule after some patients developed corticosteroid-like side effects.
- Owing to misidentification of the medicinal plant species, plant materials containing aristolochic acid were used for manufacturing herbal products, which caused severe kidney failure in patients in several countries.
- Reports have been received by drug safety monitoring agencies of prolonged prothrombin times, increased coagulation time, subcutaneous hematomas and intracranial hemorrhage associated with the use of *Ginkgo biloba*.
- One of the most well known traditionally used herbal medicines caused severe, sometimes fatal cases of interstitial pneumonia when used in conjunction with interferon.

Although most traditional therapies are presumed to be safe, there is still the problem of how to assess and quantify the possibility of very rare adverse events. If the benefit for any alternative medicine therapy is modest or unproven, then the presence of even a very small increased risk for a serious event is enough to tip the scales against use of the alternative medicine therapy.

RCT data will almost never be sufficient to prove or disprove a causal relationship between an alternative medicine therapy and a rare adverse event. Indeed, for a future randomized trial to have sufficient power to assess adverse events occurring at a rate of 1 per million, it was calculated that such a study would need to enroll about 3 million treated patients (Paul et al, 2005). Clearly, this threshold will not be crossed for any interventions for that matter. With RCT data insufficient to draw conclusions, the next place to look for evidence is hypothesis testing observational studies. The case–control study is the traditional epidemiologic tool for evaluating possible relationships between exposure and rare events (Paul et al, 2005).

The inclusion of herbal medicines in pharmacovigilance systems is becoming increasingly important given the growing use of herbal products and herbal medicines globally. For example, in the United States of America, some US$ 17 billion was spent by more than 158 million Americans in 2000. Further, a recent study indicated that more than 70 percent of the German population reported using "natural medicines" and that, for most of them, herbal medicinal products were the first choice in the treatment of minor diseases or disorders. The worldwide consumption of herbal medicines is enormous, so that, in terms of population exposure alone, it is essential to identify the risks associated with their use. Safety of herbal medicines is therefore an important public health issue. Herbal medicines are frequently used in conjunction with other medicines, and it is essential to understand the consequences of such combined use and monitor whether any adverse effects are arising. This can be achieved most readily within existing pharmacovigilance systems.

Diverse regulatory scenario regarding registration of herbal drugs poses a special challenge in pharmacovigilance of herbal drugs. National regulation and registration of herbal medicines vary from country to country. Where herbal medicines are regulated, they may be categorized as either prescription or nonprescription medicines. Herbal products may also be categorized other than as medicines. National regulatory information on herbal medicines is not fully shared among national regulatory authorities, and is often not shared between national regulatory authorities and national safety monitoring/pharmacovigilance centers. Almost all new medicines are introduced to the market as prescription medicines, and a significant volume of postmarketing safety data from spontaneous reporting will have been realized over time. At some stage, some of these medicines will subsequently be reclassified as nonprescription medicines and will become major sources of self-medication. However, in many countries, a significant proportion of herbal products enter directly into the non-prescription medicines category rather than by reclassification from the prescription medicines category.

The World Health Organization (WHO) has set up specific guidelines for assessment of the safety, efficacy and quality of herbal medicines. WHO has specified the causality criteria, the details of which are given in the Table 16.5.

**Table 16.5:** WHO causality criteria

| *The causality categories described by the Uppsala Monitoring Center* |
|---|
| 1. *Certain:* A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drugs (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. |
| 2. *Probably/Likely:* A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. |
| 3. *Possible:* A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. |
| 4. *Unlikely:* A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. |
| 5. *Conditional/Unclassified:* A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination. |
| 6. *Unassessable/Unclassifiable:* A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified. |

In India, National Pharmacovigilance Program under the control of Central Drug Standards Control Organization (CDSCO) has already been started since 2003. WHO had emphasized that it should include traditional medicines in pharmacovigilance system and has published guidelines on safety monitoring of herbal medicines in Pharmacovigilance systems in 2004. Department of AYUSH, Ministry of Health and Family Welfare, Government of India, New Delhi, has initiated the National Pharmacovigilance Program for ASU drugs. National Pharmacovigilance Resource Center for ASU (NPRC-ASU) is coordinating the countrywide pharmacovigilance program for ASU drugs.

Worldwide movement for the improvement of patient safety gains momentum, the subject of drug safety becomes even more prominent. Pharmacovigilance is the science dedicated to reduce the risk of drug-related harms to the consumers. Looking in to the conditions prevailing in the present scenario, it is high time to deliberate over the burning issues regarding traditional and classical Ayurvedic, Siddha and Unani products and practices; A need to constitute a National Pharmmacovigilance Center for ASU Drugs in India was felt.

The program shall be coordinated by National Pharmacovigilance Resource Center (NPRC), Institute for Postgraduate Teaching and Research in Ayurveda (IPGT and RA), Gujarat Ayurved University (GAU), Jamnagar under the supervision of a National Pharmacovigilance Consultative Committee (NPCC) for ASU, which would monitor the program and also recommend regulatory interventions based on the generated Adverse Drug Reaction (ADR) data.

The first national consultative meet of National Pharmacovigilance Program for ASU Drugs was organized at Department of AYUSH, Ministry of Health and Family Welfare, New Delhi on 29th and 30th August 2008, where the draft protocol was technically reviewed and finalized.

As per National Pharmacovigilance Program for ASU drugs, a serious adverse event or reaction is defined as any untoward medical occurrence that at any dose:

- Results in death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is life-threatening.

### Frequency of Adverse Drug Reactions

It is always difficult to estimate incidence on the basis of spontaneous reports, owing to the uncertainty inherent in estimating the denominator and degree of underreporting. However, whenever possible, an estimate of frequency should be provided in a standard form. Standard categories of frequency are recommended in Table 16.6.

Though for centuries ASU drugs are considered as safe and innocuous drugs, this perception is likely to change in the light of some recent occurrence of incidences of ADR during their use. This along with increased wide spread use, both at national and international levels, is likely to lead to increased interaction of these drugs with diverse genomic profiles. This is likely to produce more incidences of expression of unexpected effects, which may be useful or adverse in nature. Thus, it should be considered as the right time to evolve a mechanism to record ADR of ASU drugs. Since there are considerable social and economic consequences of adverse drug reactions and the positive benefit/cost ratio of implementing appropriate risk management there is a

**Table 16.6:** Categories of frequency of ADRs

| | | |
|---|---|---|
| Very common | ≤ 1/10 | (≤ 10%) |
| Common (frequent) | ≤ 1/100 and < 1/10 | (≤1 % and < 10 %) |
| Uncommon (infrequent) | ≤ 1/1,000 and < 1/100 | (≤ 0.1 % and < 1 %) |
| Rare | ≤ 1/10,000 and < 1,000 | (≤ 0.01% and < 0.1%) |
| Very rare | < 1/10,000 | (< 0.01%) |

need to engage healthcare professionals and the public at large, in a well structured program to build synergies for monitoring adverse drug reactions of ASU medicines. The purpose of the program is to collect and collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public.

Since ages Ayurveda, Siddha and Unani systems are being practiced in India. Now in this era of globalization certain concerns are raised with regards to their safety. On Indian plants or Indian plant based products severe toxicity is yet to be reported. Ayurveda has categorized toxic plants separately and for their use special processing is essential. There is a widespread misconception that all drugs of "natural" origin are "safe". There is also a common belief that long-term use of a medicine based on traditional (ASU) medicines are used in conjunction with other medicines there is the potential of serious adverse drug interactions. There are also examples of traditional (ASU) medicines being adulterated or contaminated with allopathic medicines, chemicals such as corticosteroids, nonsterodial anti-inflammatory agents, etc. Further many ASU drugs are manufactured for global use and they have moved beyond the traditional and cultural framework for which they were originally intended. Currently, the majority of adverse events related to the use of herbal/traditional products that are reported are attributed either due to poor product quality or to improper use.

ASU systems of medicines have their own principles, have their own pharmacopeia, but are practiced in the country as OTC drugs without an authentic prescription. A recent WHO survey showed that around 90 countries, less than half of WHO's member states, currently regulate herbal medicines.

Inclusion of traditional medicines in pharmacovigilance systems is becoming increasingly important given the growing use of ASU products and medicines globally. Pharmacovigilance is defined as the detection, assessment and prevention of adverse drug reactions in humans.

The National Pharmacovigilance Program for ASU drugs aims to provide adverse drug reaction data related to various ASU drugs available in the country. The program will be supervised by the National Pharmacovigilance Resource Center for ASU (NPRC–ASU) constituted by Department of AYUSH, Ministry of Health and Family Welfare, Govt. of India. The program would comprise of the following steps:

- To ensure harmonized implementation of the program, efforts shall be made to arrive at a uniform understanding of the operational systems, along with standardized formats to document and analyse ADRs. An induction training program shall be arranged for health care professionals participating in the NP for ASU Drugs.
- All data generated (including reporting forms) will be stored and preserved for the purpose of archiving for a minimum period of 5 years, at the NRC.

- Patient's identity is not revealed on the form, only the patient identifier is mentioned. Identity of the patients and related data will be used only for research and regulatory purpose and sufficient measures will be taken to maintain confidentiality of such information.

Overall supervision of participating centers of all levels will be done by NPCC-ASU, through NPRC office as per a predesigned audit protocol, thereby making room for prompt correction of deficiencies so detected. The purpose of the audit activities will be to ensure the quality of ADR information, which must be authentic (including traceability of the patient), complete (all essential data elements filled-in), timeline compliant, and legible. The audit activity will also look into overall compliance with SOPs. The overall cost-effectiveness analysis of the program will also be evaluated by the audit process. This would refer to regularity of the key personnel, particularly the dedicated program staff, and the average time they devote in the project work.

The National Pharmacovigilance Program for ASU drugs (NP-ASU) shall encourage reporting of all suspected drug related adverse events, including those suspected to have been caused by interaction with any other drugs or food incompatibilities. The reporting of seemingly insignificant or common adverse reactions would be important since it may highlight a widespread prescribing problem.

Any healthcare professional may report suspected adverse drug events. The program shall not accept reports from lay members of the public or anyone else who is not a healthcare professional. Others can report through the physicians under whom he/she had undergone treatment.

The information in the form shall be handled in confidentiality. Peripheral pharmacovigilance centers shall forward the form to the respective Regional pharmacovigilance centers who will carry out the causality analysis. This information shall be forwarded to the National Pharmacovigilance Resource Center. The data will be statistically analyzed and forwarded to the Department of AYUSH, Govt. of India.

In order to avoid receiving fake unauthentic reports or reports by parties having vested interests against any drug (s), it is important that the reporter's identity is clearly stated in the form so that the reporter can be approached to verify the authenticity of the entire report.

## CONCLUSION AND A WAY FORWARD

Last few decades have witnessed tremendous resurgence of interest in herbal medicines globally. This trend has attracted the attention of scientists of various disciplines as well. People with scientific temper started demanding the evidence of efficacy of herbal medicines, taking safety for granted basis their traditional use. Institutions involved in traditional medicines initiated some research using their own methodologies, however, the technological advancements in related put their endeavors far behind. Continued interest

in herbal medicines gave way to interdisciplinary research and soon it was observed that apart from the physicians, pharmacologists, biochemists, biotechnologists, agriculturists, etc. jumped into the fray. As a result today, we know that gugul lipid work by FXR inhibition (Urizar et al, 2002), and Boswellic acids exhibit their anti-inflammatory activity through Cox 2 inhibition. It can be said that most of the convincing researches on herbal drugs have been conducted in the past few decades only and it has been possibly only due to convergence of various streams of scientists as a team.

Concept of evidence-based medicine necessitated clinical evaluation of traditional medicines preferably following the gold standard randomized placebo-controlled clinical trials. After few attempts it was realized that gold standard of evaluating the efficacy of conventional drug does not do justice with traditional medicines. Soon the realization dawned upon the clinical researchers that there is a need of identifying newer techniques to evaluate the clinical efficacy of traditional/herbal medicines.

Normally, clinical research of all types of conventional medicine considers both efficacy and safety, and is conducted according to WHO's guidelines for good clinical practice and the Declaration of Helsinki. Safety evaluation, however, may not be the main focus of clinical research in traditional medicine, because of the long history of traditional medicine. Herbal traditional medicines evolved from traditional knowledge rather than laboratory experimentation. Their development process works backwards from actual use to scientific/laboratory evidence or correlation, often referred to as reverse pharmacology. As drug development process in western medicine is prospective in nature, from preclinical and clinical research, it is reverse in case of knowledge based traditional/herbal medicine (Nicholas 1992). Since the two approaches are fundamentally different, their strategies for development should also differ. Based on their extensive use in humans, herbal traditional medicines may have sufficient information to support limited pilot clinical study with little preclinical testing especially when the herbal remedies are prepared in the same way, used in the original form as the traditional practitioner and if the trial is to be carried out in the same community that use them. However, new compounds, isolates or new formulations of the herbs may bear different characteristics and scientific behavior from the original products. These should therefore undergo full scale preclinical and clinical evaluation to establish their traditional validity using current standards.

The conventional methods of controlled and randomized clinical trial is considered gold standard, however, while applying it on evaluation of traditional or alternative medicine especially ayurvedic medicines, its limitations came to fore. Hence, there is need for a paradigm shift in the clinical research on herbal medicines. Different methodologies should be adopted while evaluating the safety and efficacy of traditional medicine through clinical trials.

Keeping above observations in view, some of the methodological approaches specific to the assessment of traditional medicines through clinical research are given below:

- Evaluate traditional medicine in its own theoretical framework—this approach is related to clinical evaluation of holistic multipronged therapeutic approach basis of the traditional system of medicine practices. For example, in case of *Ama Vata* (Rheumatoid arthritis) Ayurvedic holistic therapeutic approach should be evaluated in totality rather than reducing it to drug trial.
- Evaluate traditional medicine in the theoretical framework of conventional medicine—this approach refers to certain cases of Ayurvedic drugs where single herbs are used as stand alone medicine in traditional medicine, e.g. Guggulu for hyperlipidemia.
- Compare the efficacy of different traditional practices within a system of traditional medicine—this approach refers to clinical evaluations of non-therapeutic or semitherapeutic practices, e.g. *panchakarma* that involve use of medicated oil or yogic practices which do not involve any medicine.
- Evaluate the efficacy of pure active phytochemicals under the rigorous current scientific procedures or conventional methods for clinical trials, e.g. artemisinin, paclitaxel, etc.

The most appropriate method to generate efficacy data on classical Ayurvedic therapeutic regimen appears to be observational research as it involves efficacy of whole treatment regimen conducted in real-life situation. The data generated by this method can be used by other physicians as well; however, change in mindset is required among traditional medicine physicians to start proper documentation of their practice to generate the data.

The pragmatic approach (Paul et al, 2005) of conducting the clinical trial is also suitable for traditional medicines. However, these trials need to be conducted in such a way as to take into account the international guidelines that define such studies. Standardized mixtures can also be tested in the same way as pure drug compounds provided they are used as standalone drugs in actual clinical practice traditionally.

Increasing popularity also invites cynicism followed by criticism. This sometimes leads to innovative solutions to the vexed problems. Identification and validation of one universally acceptable method of conducting clinical trials on traditional/herbal drugs would remain a dream if top brains do not converge to look at this issue after understanding the basic philosophies behind the traditional systems of medicines. Till that happens let us accept that "one size fits all" is not true for knowledge-based traditional medicines. Let us hope that current chaos in clinical trial methodologies on herbal drugs would ultimately lead to more disciplined approaches which would be universally acceptable to the scientific community and regulatory authorities alike.

To conclude, we propose a paradigm shift in approach to conduct clinical trial of traditional medicines. There is huge difference right from objective to evaluation parameters when it is compared to clinical trials on modern synthetic products. Even if we assume that there is need of double-blind placebo-controlled trial, its methodology needs significant modification. There is, therefore, an urgent need to do brainstorming and evolve a harmonized guideline for clinical trials to be conducted on traditional medicine herbal products. Further there is an urgent need to document the safety of herbal medicines through conventional pharmacovigilance methodologies.

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CHAPTER

# 17 Outsourcing Opportunities in Clinical Research

## THE NEED FOR OUTSOURCING: AN INTRODUCTION

The good news: average time for the US Food and Drug Administration (FDA) to approve new medicines has declined recently (to 1.1 years in the period 2005-07). The less than good news: average clinical development time has trended upward. This means combined approval and clinical phase time, as shown in Figure 17.1, is around eight years. Similar trends hold true for drug development elsewhere in the world. Whereas it may appear, at first glance, as if total time to bring new drugs to market has remained essentially unchanged in recent years, progress is indeed being made. To a greater extent than ever before, drug development today focuses on complex diseases, such as cancer, psychiatric and neurological disorders and indications affecting small populations. For many reasons, clinical development design protocols have become more complicated, requiring more resources to run trials. Drug sponsors have responded by improving

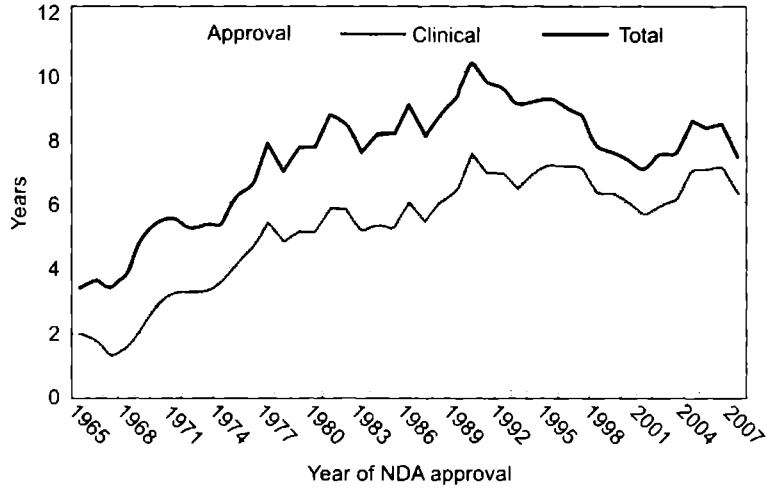


**Fig. 17.1:** Mean US approval and clinical phases for US new drug approvals
*Note:* data are presented as 3-year moving averages
(*Source:* Tufts Center for the Study of Drug Development)

project management and portfolio decision making, expanding reliance on partnerships and licensing arrangements and evolving their approaches to development itself, including greater use of surrogate end-points and adaptive clinical trials.

While much progress has been made, more requires to be done. In drug development, the race—and rewards—will go to the swiftest and most efficient drug sponsors that can deliver safe and effective new medicines. Even before the financial market downturn of last fall, nearly all publicly traded drug companies were under enormous pressure to bring new drugs to market faster and at less cost. That pressure has only increased, making their challenge going forward crystal clear: align with the best people and employ the best technology behind the most promising new drug candidates.

The FDA and sponsors have made a concerted effort in recent years to reduce approval times for new drugs. While average clinical development time appears to have stalled at around eight years recently, it is important to recognize that drugs in development today focus on more complex diseases for which effective therapies remain elusive. http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2009.pdf

Continued high costs and lengthy development times, combined with growing regulatory and economic pressures, will drive drug developers to partner, outsource and in-source to improve R & D productivity (Fig. 17.2).

- More companies will move from a compound-focused approach to development to a mechanistically-based approach to deepen internal expertise and achieve a greater consistency across compounds and within disease areas

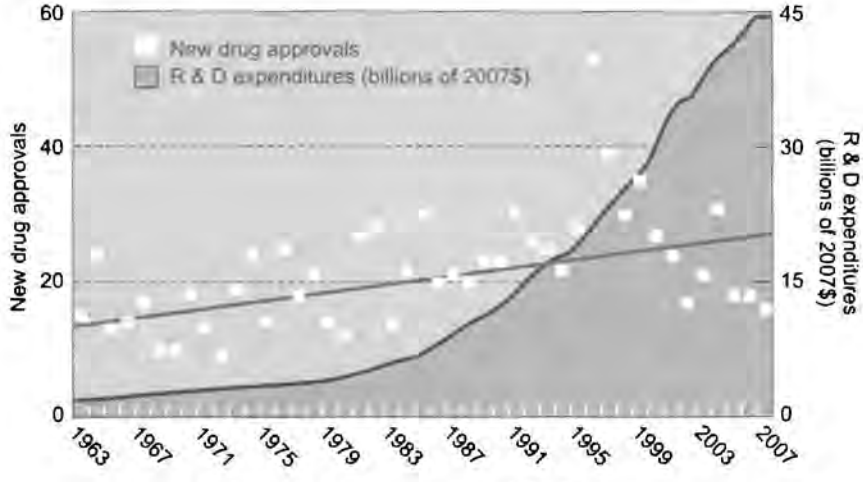


**Fig. 17.2:** New drug approvals and R & D spending
(*Source:* Tufts Center for the Study of Drug Development, PhRMA)

- To increase flexibility and minimize risk, companies will look to combine features of operating structures from large pharma and small/mid-tier biopharmaceutical firms.
- To enhance performance on a sustained basis, firms will strive to make cost-effectiveness analysis of internal processes and productivity improvements core competencies.
- Firms will continue globalization of their preclinical and clinical development activities to overcome local capacity constraints, increase speed-to-market, and expand their presence in emerging markets.
- Companies will further experiment with adaptive clinical trial designs for nonpivotal trials to reduce development timelines and costs.

## ADVANTAGES AND DISADVANTAGES OF OUTSOURCING

Clinical research organizations (CROs) provide clinical development services to the pharmaceutical, biotechnology, and medical device industries. Involved in nearly three quarters of all phase I to III trials not conducted in-house by research sponsors, CRO professionals bring their scientific, regulatory and information management expertise to bear for the completion of timely, accurate and high-quality clinical trials. By partnering with CROs, research sponsors gain the benefits of CRO experience in the drug development process as well as their skilled workforce and resources around the world to help accelerate medical product development.

CROs focus on the unique challenges of biopharmaceutical and medical device development. They offer clients a "readymade" infrastructure of global research personnel, services and facilities, providing a full range of services to efficiently and cost-effectively manage the clinical development process. Capitalizing on CRO capabilities allows clients to focus on their own core strengths, rather than organize, create and administer a complete clinical trial process themselves.

CROs offer an unparalleled depth of regulatory knowledge, therapeutic expertise and integrated services around the world. Acting as true partners in the development process, they provide the kind of on-the-ground capabilities that keep pipelines moving and budgets in line. With established global procedures and the highest commitment to scientific quality and research ethics, CROs play an important role in scientific innovation and have become true partners in the development of critical new medical advances for patients around the world.

## THE GLOBAL PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRY IS IN THE MIDST OF CHALLENGING TIMES, 2008

In 2008, the global pharmaceutical market has grown at the slowest rate in this decade and is expected to slow down further. The market reached

USD 773 billion at a growth rate of 4.8 percent in 2008, which is the slowest growth rate of the decade. The two largest markets, the US and Europe, which contributed almost 73 percent of the global market in 2008, achieved growth rates of 1.4 and 5.8 percent respectively. Going forward, the US market is expected to stagnate or decline further over the next five years while the European market is expected to grow at a sluggish pace with a Compound Annual Growth Rate (CAGR) of 2 to 5 percent for 2008 to 2013 (http://www.expresspharmaonline.com/20091130/retrospective 200907.shtml). There are primarily four reasons for this slowdown.

### Decreased R & D Productivity

During the eight year period between 2000 and 2008, while the total R & D spend of pharmaceutical companies has increased from USD 53 billion to USD 129 billion, the number of drugs approved has declined. This decreased R & D productivity is due to the increased failure rate in trials and higher cost of developing new drugs due to stricter regulatory requirements.

### Current Global Financial Crisis

The crisis has severely affected the liquidity of small biotech companies; with 44 percent of the US biotech companies having less than a year's operating cash and 26 percent having less than six months of operating cash. Further, the consumer spend on healthcare has declined, reflected by a drop in the number of prescriptions in the US by 2 percent for the first time in a decade in 2008 to 09.

### Increasing Penetration of Generics

Penetration of generics in US, in terms of their share in total prescriptions, has increased from 47 percent in 1999 to 63 percent in 2007. Going forward, this is expected to increase further driven by impending patent expiries and measures by governments to reduce healthcare costs.

### Fewer and Smaller Blockbusters

Decreased number of blockbuster approvals to replace the existing ones going off patent and reduced sales potential of recently launched drugs will further decelerate the market growth. The sales of blockbuster drugs have grown only 9 percent in 2007 compared to 24 percent in 2004. Further, projected sales of top 10 new molecular entities (NMEs) launched in 2008 show no potential of achieving a blockbuster status in the next 5 years.

## AREAS OF OUTSOURCING

*Outsourcing is no more an option but a strategic imperative for pharmaceutical companies across the globe*

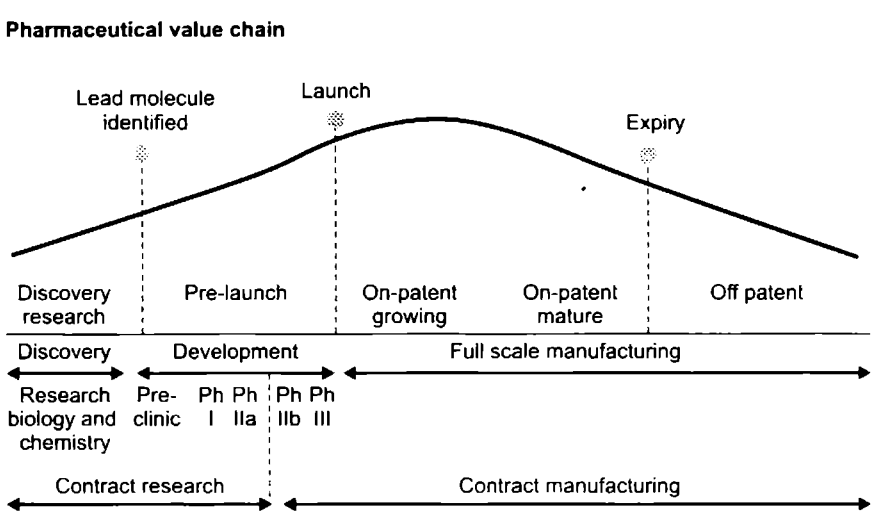


**Fig. 17.3:** Pharmaceutical value chain: Pattern of outsourcing
(*Source:* OPPI and Ernst and Young Report, 2009-Taking Wings)

Over the past two decades, there has been a shift in the pattern of outsourcing. Companies have moved from outsourcing noncore functions to routinely outsourcing a number of core functions such as manufacturing and drug discovery and development. Between 2006 and 2009, percentage of big pharma companies considering outsourcing for strategic advantage has increased from 42 to 57 percent (E and Y report, 2009) (Fig. 17.3).

## THE NEED FOR OUTSOURCING

The global pharmaceutical market has grown at the slowest rate in this decade and is expected to slow down further. This is being shaped by:

- Declining R & D productivity
- The current global financial crisis
- Increasing genericization
- Fewer and smaller blockbuster.

The growth rate of the global pharma market has less than halved in the last decade. The global pharmaceutical market reached USD 773 billion, at a growth rate of 4.8 percent, in 2008, which is the slowest growth rate of the decade. The two largest markets, the US and Europe, which contributed almost 73 percent to the global market in 2008, achieved growth rates of 1.4 percent and 5.8 percent, respectively. The only silver lining in the global pharma market is expected to come from emerging markets, which, according to IMS forecasts, will collectively grow at 13 to 16 percent.

Despite increasing R & D spend and number of active compounds in development, no significant changes in the number of approved NMEs have been seen so far (Fig. 17.4).

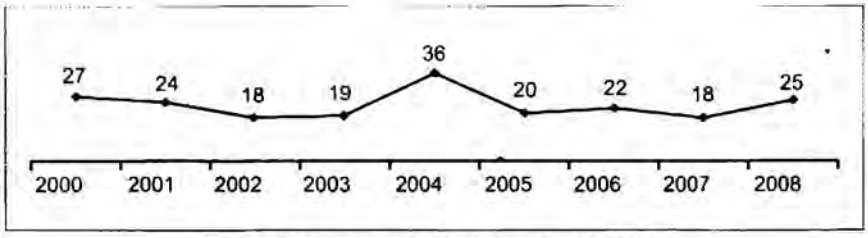


**Fig. 17.4:** Number of NME approvals (2000-2008)
(*Source:* CDER NME, BLA approval, 2008)

*Decreasing R & D productivity but growing R & D expenditures and declining NME approvals*

Although the R & D spend has more than doubled from USD53b in 2000 to USD129 billion in 2008, the number of NCE approvals have shown a largely declining trend with a historic low of only 18 in 2007 before correcting to 25 in 2008. Further, while there has been an increase in the number of approved NMEs in 2008, the percentage of new products, which offered a significant improvement over currently marketed products, fell 52 percent in 2007 to 36 percent in 2008 (Fig. 17.5A).

Over the last five years, the average number of active substances in the development for the first launch has increased steadily across companies. However, this has yet to be reflected in new product approvals.

Declining R & D productivity due to increasing failure rate of NMEs and high costs has incurred in developing molecules for complex therapies.

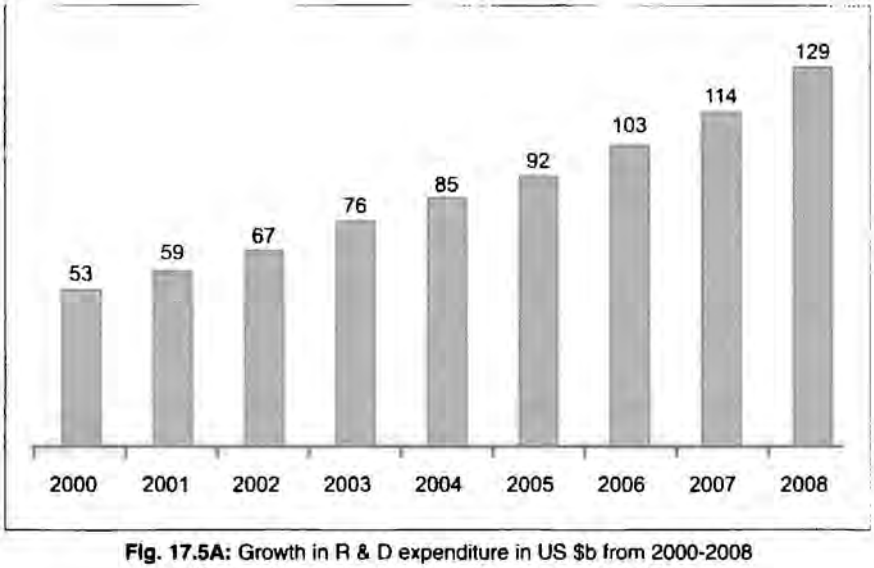


**Fig. 17.5A:** Growth in R & D expenditure in US $b from 2000-2008
(*Source:* Evaluate pharma alpha-world preview 2012.
Center Watch Analysis CDER phRMA industry profile)

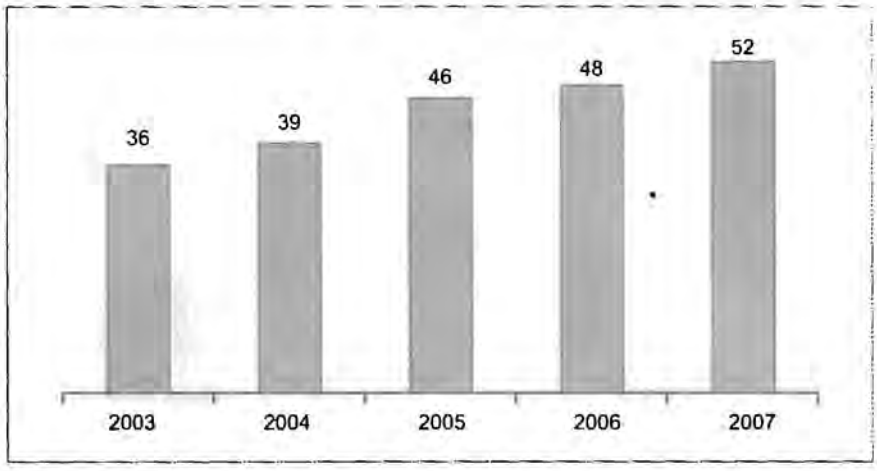


**Fig. 17.5B:** Trend in mean number of active substances developed for first launch (2003-2007)

(*Source:* CDER NME, BLA approval 2008)

(*Note:* Active substance (AS): The active ingredient that is intended to furnish pharmacological acvtivity or other direct effects to a pharmaceutical product—this may be a chemical, biological, biotech or radiopharmaceutical substance that is destined to be made available as a "prescription only medicine", to be used for the cure alleviation, treatment, prevention or in vivo diagnosis of diseases in humans

The decrease in R & D productivity has been due to:

- An increasing number of projects are being terminated at the phase III stage. This has increased by 25 percent between 2002 to 2004 and 2005 to 2007, resulting in fewer NME approvals (Fig. 17.5B).
- The average cost of developing a new drug has increased from USD 1.1 billion in 2004 to USD 1.3 billion in 2008
- Annual drug withdrawal, based on NME, and the withdrawal data for preceding periods indicates a sharp rise ranging from 4 to 10 percent and an average of 7 percent. Thus, stricter FDA regulations have increased the need for more extensive data submissions
- In addition, the FDA requires companies to monitor drugs after their launch for safety, and can at times require specific additional data. Such data are known as postmarketing commitment (PMC). Over the last decade, the number of PMCs has increased by 50 percent, resulting in a significant cost increase
- Increase in time taken for trial completion and drug approval
- Longer trials with higher complexity result in increased costs (Table 17.1)
- Six therapy areas: Oncology, CNS, respiratory, endocrinology, cardiovascular and infectious diseases account for 68 percent of all clinical trial protocols
- These therapies require a larger number of patients per trial, e.g. the mean patient enrollment rates in the therapies mentioned above for phase III trials is nearly twice as much as compared to other therapies.

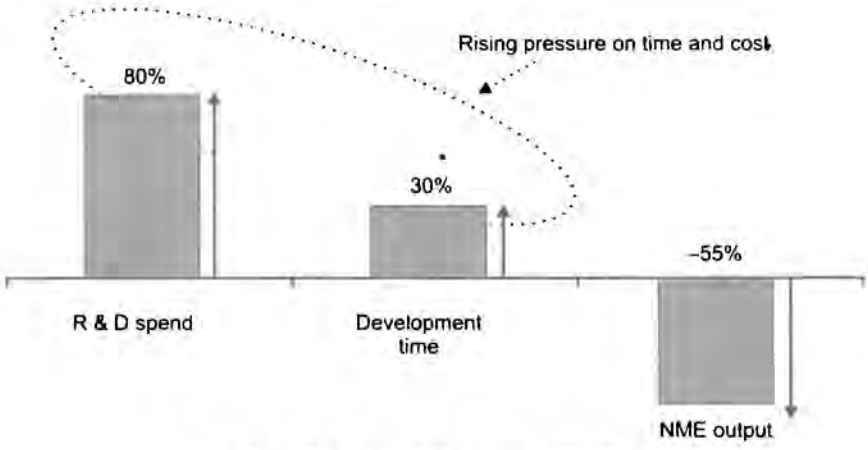


**Fig. 17.6:** Growth % between 1997-2008

**Table 17.1:** R & D productivity evaluation

| *Parameters* | *1999-2002* | *2003-2006* |
|---|---|---|
| Average duration of phase I-III | 5.8 years | 7 years |
| Protocol design to database lock time | 460 days | 780 days |
| Patient recruitment | 75% | 59% |
| Volunteer retention | 69% | 48% |

The clinical research market is mainly concentrated in the western geographies, i.e. the USA and Europe and is valued at US$ 42 billion and constitutes 65 percent of the global clinical research spending. The clinical research market is mainly dominated by the phase I to IV trials to the extent of nearly blanket coverage of the total research spending and is further divided into phase I (6.4%) and phase II to IV (35%). In terms of growth calculations for various phases of trials in the period of 2004-2008, a CAGR value of 21 percent emerges for the phase I (early clinical trials) and phase II and phase IV achieve CAGR of 10 percent each for the same period.

The global clinical research market is facing the challenges related to the development cost, time and productivity. The rising pressure on cost and development has been mounting heavily from the period of 1997 to 2008 according to a report published by Thomson Reuters as illustrated in Figure 17.6.

Clinical trial initiations outside the USA have been rising since the year 2004 (11220) to a figure of 12127 in the year 2008 which indicates that the outsourcing market has been growing at fast paced double digit growth during that period (Fig. 17.7).

The rising trend of clinical trial initiations has started taking its shape since the year 2000 when the evolution of the CRO market started. The concept of outsourcing to India took its shape since then and was expected to achieve double digit dimension.

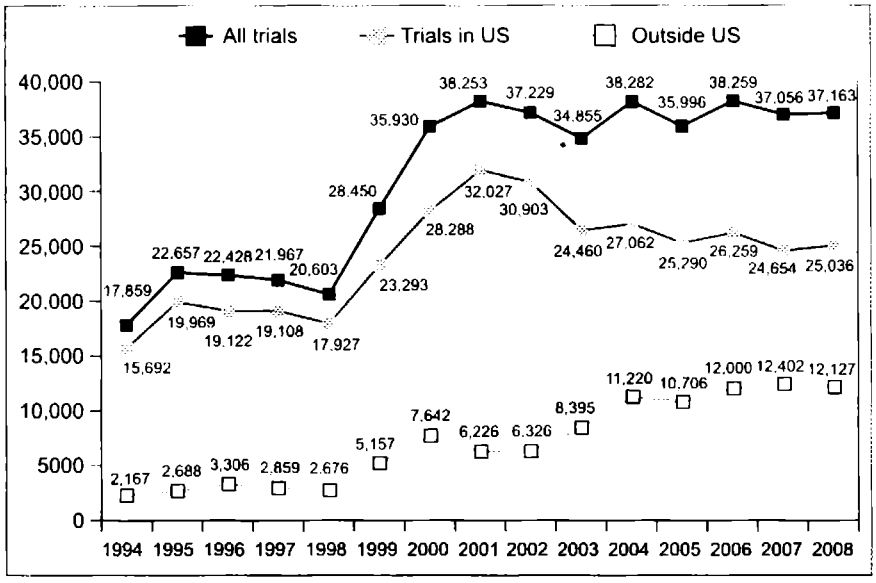


**Fig. 17.7:** Clinical trial initiations (Based on FDA-1572, 1994-2008)

## WINDS OF CHANGE BLOWING IN THE PHARMACEUTICAL OUTSOURCING LANDSCAPE

Increasing pressures in the pharmaceutical industry have resulted in the emergence of the networked model as companies seek alternative ways to drive revenue and profit growth. Outsourcing is a core part of this model and companies are increasing their reliance on third parties to deliver value across drug discovery, development and manufacturing, which have traditionally been considered as core functions. Over the last three years, Big Pharma has increasingly shifted the focus of its outsourcing operations from being tactical to strategic. The outsourcing industry is undergoing a paradigm shift with the rise of a number of new players from emerging economies who offer global capabilities and a substantial cost advantage. This is forcing Big Pharma and Western CMOs to introspect and recognize the need to transition from the West to the East, to fully leverage the benefits outsourcing can offer beyond simple cost-savings to strategic benefits.

## STRATEGIC VERSUS TACTICAL OUTSOURCING

How do pharma companies describe their outsourcing strategy?

- According to a survey conducted by Contract Pharma across more than 200 sponsor-side respondents in 2009, 55 percent of global pharma companies regard their outsourcing as a strategic decision

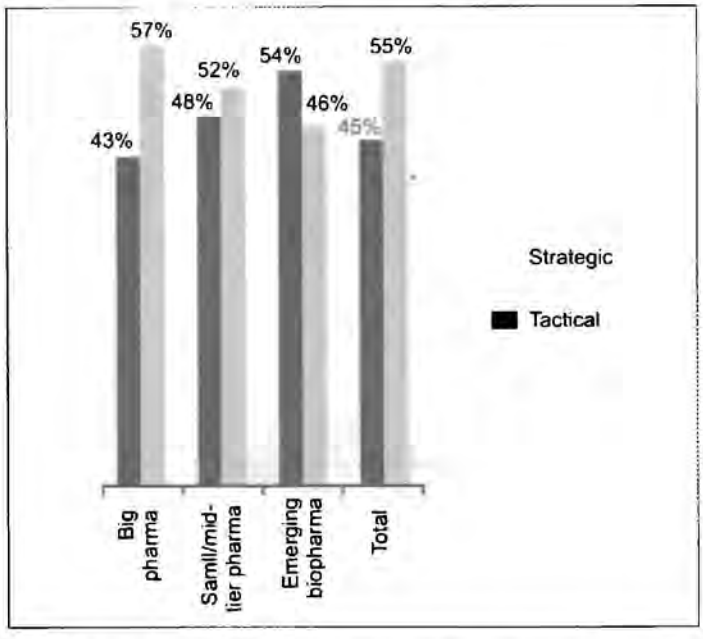


**Fig. 17.8:** Contract pharma study, 2009 (% of respondents)
(*Source:* According to survey conducted by contract pharma across more than 200 sponsor side respondents in 2009)

- Except for responses from emerging biopharma companies, the majority responses from all other types of pharma companies described outsourcing as a strategic decision.

Big pharma companies' inclination to outsource, as a strategic imperative, has increased significantly over last few years. Further, a comparison of the Contract Pharma Survey results of 2009, with the same survey conducted in 2006, shows that 57 percent of Big pharma respondents regard their outsourcing decisions as strategic compared to 42 percent in 2006 (Fig. 17.8).

*Companies increasingly using acquisitions as key strategy for sustained growth*

M and A activities in the pharma and biotech industries have increased over the last three years. The year 2009 has been the landmark year in this area, with a spate of large ticket acquisitions taking place with the aim to augment R & D pipelines and achieve cost benefits through synergies in operations. Big pharma is making acquisitions within itself, with biotech and generics players satisfying its business imperatives and adopting a "networked" operating model as a strategy to boost efficiencies, and gain access to technologies and emerging markets (Fig. 17.9).

Over the past 20 years, pharmaceutical companies have become increasingly reliant on using third parties to improve efficiencies through

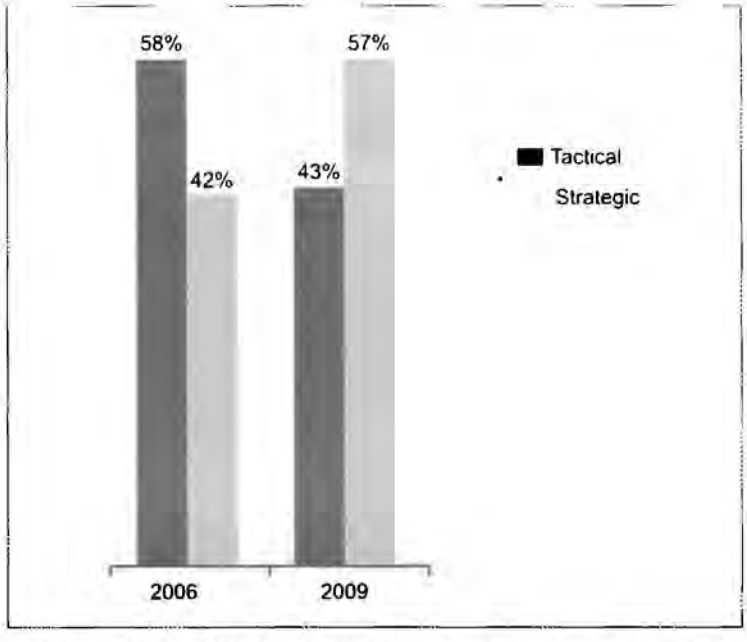


**Fig. 17.9:** Comparison of big pharma responses across two contract pharma surveys (*Source:* According to a survey conducted by contract pharma across more than 200 sponsor side respondents in 2009 and 2006)

in-licensing, out-licensing, collaborations and outsourcing—moving toward a networked pharma operating model.

The degree to which companies have embraced the networked pharma model to date varies extensively; with some heavily reliant on third parties, while others are using third parties to a lesser degree. A networked model with reliable third parties not only enhances capital efficiency but also improves flexibility and the overall cost structure, maximizes access to novel technologies for increasingly complex molecules, optimizes time to market and releases internal capacity/resource for core tasks (Fig. 17.10).

## CRO SELECTION CRITERION

### Selecting the Right/Optimal CRO-Introduction

As the world of product development is getting more complexed and the time to market is critical, the regulatory issues grow more intricate day by day.

CROs offer pharmaceutical, biotechnology and medical device companies the resources, skilled workforce and research expertise to conduct high-quality clinical trials in a manner that's streamlined, efficient and cost-effective. Today, CROs are partners in the drug development

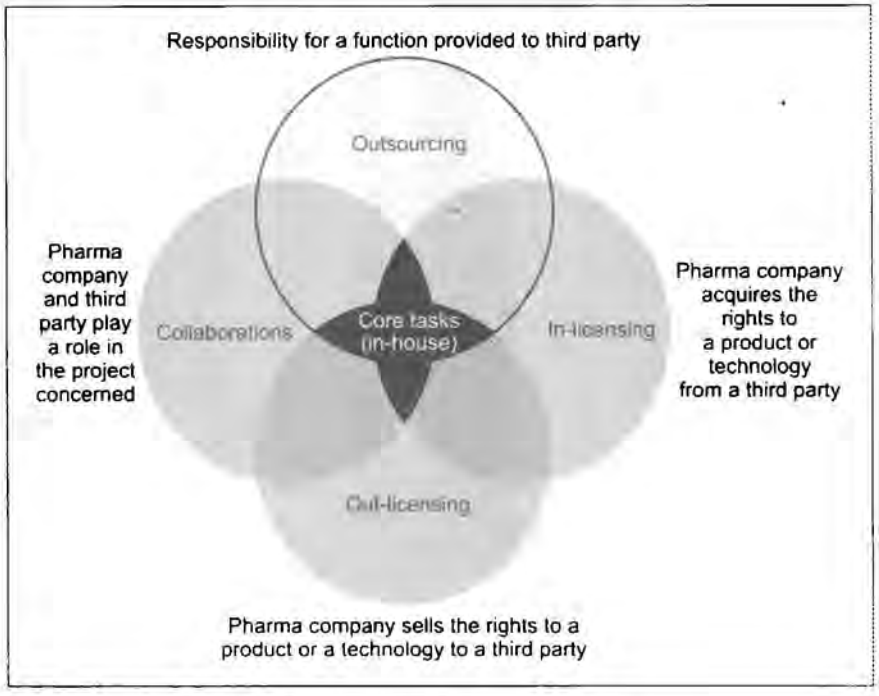


**Fig. 17.10:** Possible outsourcing models
(*Source:* Report- Heavier reliance on 'network pharma' model Healthcare Packaging April, 2007)

process, helping clients address everything from recruitment of participants to data-collection and analysis, from clinical trial planning to regulatory filing.

For a relationship so close, it's important to choose the right partner. Research sponsors need a CRO with whom they can communicate closely and honestly, with whom they can work through bad news as well as good. The CRO-sponsor relationship is one of shared vision, complementary expertise and trust. The CRO's team should understand the demands of your market, seeking ways to make each clinical effort more cost-effective, thorough and timely.

The right CRO is recognized for its professional approach by clients, regulators, even competitors. It subscribes to ACRO's Code of Ethics and its employees comply with rigorous US and international regulations and good clinical practice (GCP) and good laboratory practice (GLP) guidelines. Its commitment to patient safety and research quality should be uncompromising.

Your CRO should provide regulatory expertise appropriate to a product's unique clinical approach and market targets. Studies should be paired with stringent quality assurance procedures and detailed product

management, to make sure deadlines are met and budgets followed. Reporting should be clear, thorough and accurate. *(http://www.acrohealth.org)*

## EVALUATING AND SELECTING A CRO

Outsourcing clinical research may involve one or several strategic and tactical approaches. Sponsors may:

- Opt for full-service outsourcing, whereby a single CRO conducts the entire clinical project.
- Outsource individual services
- Select multiple CROs, depending on their area of expertise, thereby forming an outsourcing network for a particular project.

For each of these approaches, as with any third-party service arrangement, sponsors should assess certain risks before engaging in a contract. The more complex the task covered under the contract, the greater the risk. The potential for risk may increase when clinical protocols are developed by multiple physician-investigators and involve multiple investigational sites and other third parties, for example, if the reporting of adverse events is handled by a safety reporting vendor call center. As more people and systems are involved, greater prudence may be needed.

Some questions to consider when selecting CROs:

- How are the policies of our CRO partner harmonized globally, and how do those policies account for local differences, including culture
- What is the trend in human resources in the market in which a potential CRO partner is located? How might that impact the continuity and quality of our outsourced R & D efforts
- How does the CRO communicate, report, and record adverse events or signs of potential safety effects in early- to late-stage trials
- How and when does the CRO share the draft protocol for the trial
- What controls are in place to govern the final signoff procedures for the protocol

Once a company has decided to outsource clinical trials, the next step is to identify a reliable service provider with a proven track record that best meets the sponsor's requirements. Business continuity is a critical prerequisite in the relationship between a manufacturer and a CRO and sets a strong foundation for success. This requires a manufacturer to screen potential partners using more than the traditional list of vendor selection criteria.

### CRO Selection Criteria

- Compliance with all applicable safety regulations
- Validated experience in target therapeutic areas
- Strong track record of studies performed
- Robust data management and biostatistics capabilities
- Commercial or home-grown IT system stability

- Appropriate pool of human resources (e.g., scientists, project managers, clinical research associates)
- Substantial experience with regulatory submissions in markets of interest
- Validated technical facilities
- Strong relationships/alliances with outside vendors and contractual compliance
- Significant central laboratory expertise
- Ability to manage investigational sites
- Permission to conduct precontract and postcontract audits of personnel, infrastructure, facilities, good laboratory and clinical practices compliance, and quality assurance systems
- Robust processes with strong oversight function and clear roles, responsibilities, and requirements
- Sound financials and adherence to financial processes (e.g., invoice processing)
- Leading IT security and information management practices, e.g., protecting data privacy and compliance with Title 21, Part 11 of the Code of Federal Regulations.

References- (http://www.contractpharma.com)

## PARTNERING IN INDIA

Global pharmaceutical companies continue to increase their R & D activities in India; the CRO market is expected to surpass $1 billion by 2010. In response, multinational and domestic CROs are quickly building capacity. Sponsors are also looking for signs that selected CROs can sustain unexpected workload increases while meeting high standards for clinical operations, quality assurance, business processes and project management.

Given the rapid growth in the local market, CROs need to demonstrate, in addition to their cutting-edge operations, their steadfast commitment to transparency of financial reporting, business processes and compliance controls. They must also show how they are integrating clinical operations into the business context and attaining efficient and effective project tracking and cost management.

Executives at some multinational pharmaceutical subsidiaries in India have expressed some concern about the quality of some newly emerging CROs. They point to high employee turnover and a growing scarcity of qualified management-level executives, from project managers to compliance officers, among their top concerns.

Manufacturers must also address public sensitivities about the growth of clinical trials in India, particularly those conducted by foreign multinationals. India's Union Minister for Health and Family Welfare,

Anbumani Ramadoss, denied that the country has "opened up as a guinea pig," noting that, "if you do clinical trials in India you have to be transparent. We are very, very guarded. We will not allow our population to suffer."

## OUTLOOK

As the pharmaceutical business model relies increasingly on third parties to perform complex and critical processes on their behalf, they will need to continue to monitor their relationships vigilantly and benchmark against others in the industry. For example, the vibrant and growing CRO industry in India provides opportunities for manufacturers to reduce costs, increase RandD productivity, and focus on growing other business areas.

As with any third-party vendor, however, collaborating with CROs raises new risks. As the CRO landscape evolves, manufacturers need to continue mitigating potential compliance, cost management, and patient safety risks involved in outsourcing RandD. Ultimately, the company's reputation — and the welfare of patients and clinical trial subjects — are on the line.

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# ANNEXURES

## ANNEXURE I

# Ethical Guidelines for Biomedical Research on Human Participants: ICMR Code

### CHAPTER I: STATEMENT OF GENERAL PRINCIPLES IN BIOMEDICAL RESEARCH INVOLVING HUMAN PARTICIPANTS

This statement of *Ethical Guidelines* for *Biomedical Research on Human Participants* shall be known as the ICMR Code and shall consist of the following:

a. Statement of General Principles on Research using Human Participants in Biomedical Research.
b. Statement of Specific Principles on Research using Human Participants in specific areas of Biomedical Research.

These Statements of General and Specific Principles may be varied, amended, substituted and added from time to time.

#### BACKGROUND

The shocking details of the post Second World War (1939-45) trial of German medical practitioners accused of conducting experiments on human participants without their consent and exposing them to grave risk of death or permanent impairment of their faculties raised grave concern about subjecting human subjects to medical research. Thus, the first International Statement on the ethics of medical research using human subjects namely, the Nuremberg Code was formulated in 1947. Although informed consent for participation in research was recorded in 1900, the *Nuremberg Code* highlighted the essentiality of voluntainess of this consent. In 1948, *Universal Declaration of Human Rights* (adopted by the General Assembly of the United Nations) expressed concern about rights of human beings being subjected to involuntary maltreatment. In 1966, *the International Covenant on Civil and Political Rights* specifically stated, *'No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his consent to medical or scientific treatment.'*

Based on the preliminary efforts of the Council for International Organizations of Medical Sciences (CIOMS) in 1964 at Helsinki, the World Medical Association formulated general principles and specific guidelines on use of human subjects in medical research, known as the *Helsinki Declaration*, which was revised from time to

time. In February 1980, the Indian Council of Medical Research released a *'Policy Statement on Ethical Considerations involved in Research on Human Subjects'* for the benefit of all those involved in clinical research in India. In 1982, the World Health Organization (WHO) and the CIOMS issued the *'Proposed International Guidelines for Biomedical Research involving Human Subjects.'* Subsequently, the CIOMS brought out the 'International Guidelines for Ethical Review in Epidemiological studies' in 1991 and *'International Ethical Guidelines for Biomedical Research involving Human Subjects'* in 1993. Over the years, various bioethics advisory bodies in national jurisdictions like Nuffield Council of Bioethics and European Commission on Ethics have also laid down general and specific principles in specific areas of scientific research involving human beings as subjects in medical research. These 'national' Codes drawn from the international codes and the universal principles therein provide the 'guidelines' that should be followed in their respective jurisdictions. Meanwhile the international studies conducted in developing countries sponsored or funded by developed countries highlighted the global health divide and the ethical issues related to the 10/90 gap. National Bioethics Advisory Bodies and Funding organizations of developed nations took note of this and to rectify the situation revised guidelines which had relevance to developing countries as evident from Report of National Bioethics Advisory Committee, USA, by 2000 and Guidelines by Nuffield Council of Bioethics, UK and CIOMS, Geneva by 2002. The Helsinki Declaration underwent changes five times, the last one being in 2004. Still the controversy about use of placebo and post-trial access as described in it is being debated. The most recent documents on ethics are those of UNESCO's *"The Universal Declaration on Human Genome and Human Rights"* (1997), *"The International Declaration on Human Gene Data"* (2003) and *"Universal Declaration on Bioethics and Human Rights"* (2005).

## GENERAL STATEMENT

Medical and related research using human beings as research participants must necessarily ensure that -

i. The *PURPOSE*, of such research is that it should be directed towards the increase of knowledge about the human condition in relation to its social and natural environment, mindful that the human species is one of the many species in a planet in which the well-being of all species is under threat, no less from the human species as any other, and that such research is for the betterment of all, especially the least advantaged.

ii. Such research is *CONDUCTED* under conditions that no person or persons become a mere means for the betterment of others and that human beings who are subject to any medical research or scientific experimentation, are dealt with in a manner conducive to and consistent with their dignity and well being, under conditions of professional fair treatment and transparency; and after ensuring that the participant is placed at no greater risk other than such risk commensurate with the well-being of the participant in question in the light of the object to the achieved.

iii. Such research must be subjected to a regime of *EVALUATION* at all stages of the proposal, i.e. research design and experimentation, declaration of

results and use of the results thereof, and that each such evaluation shall bear in mind the objects to be achieved, the means by which they are sought to be achieved, the anticipated benefits and dangers, the potential uses and abuses of the experiment and its results, and above all, the premium that civilized society places on saving and ensuring the safety of each human life as an end in itself.

## STATEMENT OF GENERAL PRINCIPLES

For any research using the human beings as participants, the following principles may be considered:

i. *Principles of essentiality*, whereby the research entailing the use of human participants is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental well being of the planet.

ii. *Principles of voluntariness, informed consent and community agreement*, whereby research participants are fully apprised of the research and the impact and risk of such research on the research participant and others; and whereby the research participants retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by such human participants or someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding. Where any such research entails treating any community or group of persons as a research participant, these principles of voluntariness and informed consent shall apply, *mutatis mutandis* (necessary changes having been made), to the community as a whole and to each individual member who is the participant of the research or experiment. Where the human participant is incapable of giving consent and it is considered essential that research or experimentation be conducted on such a person incompetent to give consent, the principle of voluntariness and informed consent shall continue to apply and such consent and voluntariness shall be obtained and exercised on behalf of such research participants by someone who is empowered and under a duty to act on their behalf. The principles of informed consent and voluntariness are cardinal principles to be observed throughout the research and experiment, including its aftermath and applied use so that research participants are continually kept informed of any and all developments in so far as they affect them and others. However; without in any way undermining the cardinal importance of obtaining informed consent from any human participant involved in any research, the nature and form of the consent and the evidentiary requirements to prove that such consent was taken, shall depend upon the degree and seriousness of the invasiveness into the concerned human participant's person and privacy, health and life generally, and, the overall purpose and the importance of the research. Ethics committee shall

decide on the form of consent to be taken or its waiver based on the degree of risk that may be involved.

iii. *Principles of non-exploitation*, whereby as a general rule, research participants are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research participants kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born. Such human participants should be selected so that the burdens and benefits of the research are distributed without arbitrariness, discrimination or caprice. Each research shall include an in-built mechanism for compensation for the human participants either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive aftercare, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human participant and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary.

iv. *Principles of privacy and confidentiality*, whereby the identity and records of the human participants of the research or experiment are as far as possible kept confidential; and that no details about identity of said human participants, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of the human participant concerned, or someone authorised on their behalf; and after ensuring that the said human participant does not suffer from any form of hardship, discrimination or stigmatization as a consequence of having participated in the research or experiment.

v. *Principles of precaution and risk minimization*, whereby due care and caution is taken at all stages of the research and experiment (from its inception as a research idea, its subsequent research design, the conduct of the research or experiment and its applicative use) to ensure that the research participant and those affected by it including community are put to the minimum risk, suffer from no known irreversible adverse effects, and generally, benefit from and by the research or experiment; and that requisite steps are taken to ensure that both professional and ethical reviews of the research are undertaken at appropriate stages so that further and specific guidelines are laid down, and necessary directions given, in respect of the conduct of the research or experiment.

vi. *Principles of professional competence*, whereby the research is conducted at all times by competent and qualified persons who act with total integrity and impartiality and who have been made aware of, and are mindful of, preferably through training, the ethical considerations to be borne in mind in respect of such research or experiment.

vii. *Principles of accountability and transparency*, whereby the research or experiment will be conducted in a fair, honest, impartial and transparent manner after full disclosure is made by those associated with the research or experiment of each aspect of their interest in the research, and any conflict of interest that may exist;

and whereby, subject to the principles of privacy and confidentiality and the rights of the researcher, full and complete records of the research inclusive of data and notes are retained for such reasonable period as may be prescribed or considered necessary for the purposes of post-research monitoring, evaluation of the research, conducting further research (whether by the initial researcher or otherwise) and in order to make such records available for scrutiny by the appropriate legal and administrative authority, if necessary.

viii. *Principles of the maximization of the public interest and of distributive justice*, whereby the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research participants themselves and or the community from which they are drawn.

ix. *Principles of institutional arrangements*, whereby there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional arrangements required to be made in respect of the research and its subsequent use or application are duly made in a bonafide and transparent manner; and to take all appropriate steps to ensure that research reports, materials and data connected with the research are duly preserved and archived.

x. *Principles of public domain*, whereby the research and any further research, experimentation or evaluation in response to, and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications subject to such rights as are available to the researcher and those associated with the research under the law in force at that time.

xi. *Principles of totality of responsibility*, whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.

xii. *Principles of compliance*, whereby there is a general and positive duty on all persons, conducting, associated or connected with any research entailing the use of a human participant to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions and guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with.

These 12 principles laid down under Statement on General Principles are common to all areas of biomedical research. The specific issues are mentioned under relevant topics.

# CHAPTER II: ETHICAL REVIEW PROCEDURES

## INTRODUCTION

The need for evaluation of research proposals has been emphasized under the Statement of General Principles at item no. 5 pertaining to precaution and risk minimization. It is mandatory that all proposals on biomedical research involving human participants should be cleared by an appropriately constituted Institutional Ethics Committee (IEC), also referred to as Institutional Review Board (IRB), Ethics Review Board (ERB)and Research Ethics Board (REB)in other countries, to safeguard the welfare and the rights of the participants. There are also independent ethics committees [IEC(Ind)] functioning outside institutions for those researchers who have no institutional attachments or work in institutions with no ethics committee. The Ethics Committees are entrusted not only with the initial review of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring of the approved programs to foresee the compliance of the ethics during the period of the project. Such an ongoing review shall be in accordance with the international guidelines wherever applicable and Standard Operating Procedures (SOP) of the WHO available at www.who.int

## BASIC RESPONSIBILITIES

The basic responsibility of an Institutional Ethics Committee (IEC) is to ensure a competent review of all ethical aspects of the project proposals received by it in an objective manner. IECs should provide advice to the researchers on all aspects of the welfare and safety of the research participants after ensuring the scientific soundness of the proposed research through appropriate Scientific Review Committee. In institutions where this is lacking, the IEC may take up the dual responsibility of review of both, the scientific content and ethical aspects of the proposal. It is advisable to have separate Committees for each, taking care that the scientific review precedes the scrutiny for ethical issues. The scientific evaluation should ensure technical appropriateness of the proposed study. The IECs should specify in writing the authority under which the Committee is established.

## SPECIAL SITUATIONS

Small institutions could form alliance with other IECs or approach registered IEC(ind). Large institutions/Universities with large number of proposals can have more than one suitably constituted IECs for different research areas for which large number of research proposals are submitted. However, the institutional policy should be same for all these IECs to safeguard the research participant's rights. A subcommittee of the main IEC may review proposals submitted by undergraduate or postgraduate students or if necessary, a committee may be separately constituted for the purpose, which will review proposals in same manner as described above. The responsibilities of an IEC can be defined as follows :-

1. To protect the dignity, rights and well being of the potential research participants.
2. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.

3. To assist in the development and the education of a research community responsive to local health care requirements.

## COMPOSITION

The IECs should be multidisciplinary and multisectorial in composition. Independence and competence are the two hallmarks of an IEC. The number of persons in an ethics committee should be kept fairly small (8 - 12 members). It is generally accepted that a minimum of five persons is required to form the quorum without which a decision regarding the research should not be taken. The IEC should appoint from among its members a Chairman who should be from outside the Institution and not head of the same Institution to maintain the independence of the Committee. The Member Secretary should be from the same Institution and should conduct the business of the Committee. Other members should be a mix of medical/nonmedical, scientific and nonscientific persons including lay persons to represent the differed points of view.

The composition may be as follows:-

1. Chairperson.
2. One or two persons from basic medical science area.
3. One or two clinicians from various institutes.
4. One legal expert or retired judge.
5. One social scientist/representative of nongovernmental voluntary agency.
6. One philosopher/ethicist/theologian.
7. One lay person from the community.
8. Member Secretary.

As per revised Schedule Y of Drugs and Cosmetics Act, 1940, amended in 2005, the ethics committee approving drug trials should have in the quorum at least one representative from the following groups:

1. One basic medical scientist (preferably one pharmacologist).
2. One clinician.
3. One legal expert or retired judge.
4. One social scientist/representative of nongovernmental organization/ philosopher/ethicist/theologian or a similar person.
5. One lay person from the community.

The Ethics Committee can have as its members, individuals from other institutions or communities with adequate representation of age and gender to safeguard the interests and welfare of all sections of the community/society. If required, subject experts could be invited to offer their views, for instance, a pediatrician for pediatric conditions, a cardiologist for cardiac disorders etc. Similarly, based on the requirement of research area, for example HIV, genetic disorders, etc. It is desirable to include a member from specific patient groups in the Committee.

## TERMS OF REFERENCE

The terms of references should include terms of appointment with reference to the duration of the term, the policy for removal, replacement, resignation procedure, frequency of meetings, and payment of processing fee to the IEC for review, honorarium/consultancy to the members/invited experts, etc. and these should

be specified in the Standard Operating Procedures (SOP) which should be made available to each member. Every IEC should have its own written SOP's according to which the Committee should function. The SOP's should be updated periodically based on changing requirements.

The term of appointment of members could be extended for another term and a defined percentage of members could be changed on regular basis. It would be preferable to appoint persons trained in bioethics or persons conversant with ethical guidelines and laws of the country. Substitute member may be nominated, if meetings have been continuously missed by a member due to illness or other unforeseen circumstances. For this the criteria for number of missed meetings may be defined in the SOP.

## TRAINING

The EC members should be encouraged to keep abreast of all national and international developments in ethics through orientation courses on related topics by its own members or regular training organized by constituted body(ies), so that they become aware of their role and responsibilities. For drug trial review it is preferable to train the IEC members in Good Clinical Practice. Any change in the regulatory requirements should be brought to their attention and they should be aware of local, social and cultural norms, as this is the most important social control mechanism.

## REGULATION

Once the legislation of guidelines occurs which is currently under active consideration by the Ministry of Health, a Biomedical Research. Authority will be set up under the proposed Bill on Biomedical Research on Human Participants (Promotion and Regulation) which would require that all IECs register with this Authority. It will also evaluate and monitor functioning of the IECs, and develop mechanisms for enforcing accountability and transparency by the institutions.

## REVIEW PROCEDURES

The IEC should review every research proposal on human participants before the research is initiated. It should ensure that a scientific evaluation has been completed before ethical review is taken up. The Committee should evaluate the possible risks to the participants with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and the justice issues.

The IEC's member-secretary or secretariat shall screen the proposals for their completeness and depending on the risk involved categorize them into three types, namely, exemption from review, expedited review and full review (see below for explanation).

Minimal risk would be defined as one which may be anticipated as harm or discomfort not greater than that encountered in routine daily life activities of general population or during the performance of routine physical or psychological examinations or tests. However, in some cases like surgery, chemotherapy or radiation therapy, great risk would be inherent in the treatment itself, but this may

be within the range of minimal risk for the research participant since it would be undertaken as part of current every day life.

An investigator cannot decide that her/his protocol falls in the exempted category without approval from the IEC. All proposals will be scrutinised to decide under which of the following three categories it will be considered:

### Exemption from Review

Proposals which present less than minimal risk fall under this category as may be seen in following situations:

i. Research on educational practices such as instructional strategies or effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

*Exceptions*

i. When research on use of educational tests, survey or interview procedures, or observation of public behavior can identify the human participant directly or through identifiers, since the disclosure of information outside research could subject the participant to the risk of civil or criminal or financial liability or psychosocial harm.
ii. When interviews involve direct approach or access to private papers.

### Expedited Review

The proposals presenting no more than minimal risk to research participants may be subjected to expedited review. The Member- Secretary and the Chairperson of the IEC or designated member of the Committee or Subcommittee of the IEC may do expedited review only if the protocols involve:

1. Minor deviations from originally approved research during the period of approval (usually of one year duration).
2. Revised proposal previously approved through full review by the IEC or continuing review of approved proposals where there is no additional risk or activity is limited to data analysis.
3. Research activities that involve only procedures listed in one or more of the following categories:
   Clinical studies of drugs and medical devices only when:
   i. Research is on already approved drugs except when studying drug interaction or conducting trial on vulnerable population, or
   ii. Adverse Event (AE) or unexpected Adverse Drug Reaction (ADR) of minor nature is reported.
4. Research involving clinical materials (data, documents, records, or specimens) that have been collected for non-research (clinical) purposes.
5. When in emergency situations like serious outbreaks or disasters a full review of the research is not possible, prior written permission of IEC may be taken before use of the test intervention. Such research can only be approved for pilot study or preliminary work to study the safety and efficacy of the intervention and the same participants should not be included in the clinical trial that may be initiated later based on the findings of the pilot study.

*Research on Interventions in Emergency Situation*

When proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, physicians may use new intervention as investigational drug (IND)/ devices/vaccine to provide emergency medical care to their patients in life threatening conditions. Research in such instance of medical care could be allowed in patients -

i. When consent of person/patient/responsible relative or custodian/team of designated doctors for such an event is not possible. However, information about the intervention should be given to the relative/legal guardian when available later.
ii. When the intervention has undergone testing for safety prior to its use in emergency situations and sponsor has obtained prior approval of DCGI.
iii. Only, if the local IEC reviews the protocol since institutional responsibility is of paramount importance in such instances.
iv. If Data Safety Monitoring Board (DSMB) is constituted to review the data.

*Research on Disaster Management*

A disaster is the sudden occurrence of a calamitous event at any time resulting in substantial material damage, affecting persons, society, community or state(s). It may be periodic, caused by both nature and humans and creates an imbalance between the capacity and resources of the society and the needs of the survivors or the people whose lives are threatened, over a given period of time. It may also be unethical sometimes not to do research in such circumstances. Disasters create vulnerable persons and groups in society, particularly so in disadvantaged communities, and therefore, the following points need to be considered when reviewing such research:

i. Research planned to be conducted after a disaster should be essential, culturally sensitive and specific in nature with possible application in future disaster situations.
ii. Disaster-affected community participation before and during the research is essential and its representative or advocate must be identified.
iii. Extra care must be taken to protect the privacy and confidentiality of participants and communities.
iv. Protection must be ensured so that only minimal additional risk is imposed.
v. The research undertaken should provide direct or indirect benefits to the participants, the disaster-affected community or future disaster-affected population and *a priori* agreement should be reached on this, whenever possible, between the community and the researcher.
vi. All international collaborative research in the disaster-affected area should be done with a local partner on equal partnership basis.
vii. Transfer of biological material, if any, should be as per Government rules taking care of intellectual property rights issues.

**Full Review**

All research presenting with more than minimal risk, proposals/protocols which do not qualify for exempted or expedited review and projects involving vulnerable population and special groups shall be subjected to full review by all the members. While reviewing the proposals, the following points may be considered for assessing risk/benefit analysis:

a. Collection of blood samples by finger prick, heel prick, ear prick, or veni puncture:
   i. From healthy adults and nonpregnant women who weigh normal for their age and not more than 500 ml blood is drawn in an 8 week period and frequency of collection is not more than 2-times per week;
   ii. From other adults and children, where the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected has been considered and not more than 50 ml or 3 ml per kg, whichever is lesser is drawn in an 8 week period and not more than 2 times per week;
   iii. From neonates depending on the hemodynamics, body weight of the baby and other purposes not more than 10 percent of blood is drawn within 48 to 72 hours. If more than this amount is to be drawn it becomes a risky condition requiring infusion/blood transfusion;
   iv. Prospective collection of biological specimens for research purposes by noninvasive means. For instance:
      1. Skin appendages like hair and nail clippings in a nondisfiguring manner.
      2. Dental procedures—deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction of permanent teeth; supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth.
      3. Excreta and external secretions (including sweat).
      4. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum or by applying a dilute citric solution to the tongue.
      5. Placenta removed at delivery.
      6. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.
      7. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
      8. Sputum collected after saline mist nebulization and bronchial lavages.
b. Collection of data through noninvasive procedures routinely employed in clinical practice. Where medical devices are employed, they must be cleared/approved for marketing, for instance:
   i. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participant's privacy.
   ii. Weighing or testing sensory acuity.
   iii. Magnetic resonance imaging.
   iv. Electrocardiography, echocardiography; electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow.
   v. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
c. Research involving clinical materials (data, documents, records, or specimens) that will be collected solely for nonresearch (clinical) purposes.

d. Collection of data from voice, video, digital, or image recordings made for research purposes.
e. Research on individual or group characteristics or behavior not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

## SUBMISSION OF APPLICATION

The researcher should submit an application in a prescribed format along with the study protocol as prescribed in SOP of IEC concerned. The protocol should include the following: -

1. The title with signature of Principal Investigator (PI) and Co-investigators as attestation for conducting the study.
2. Clear research objectives and rationale for undertaking the investigation in human participants in the light of existing knowledge.
3. Recent curriculum vitae of the Investigators indicating qualification and experience.
4. Participant recruitment procedures and brochures, if any.
5. Inclusion and exclusion criteria for entry of participants.
6. Precise description of methodology of the proposed research, including sample size (with justification), type of study design (observational, experimental, pilot, randomized, blinded, *etc.)*, intended intervention, dosages of drugs, route of administration, duration of treatment and details of invasive procedures if any.
7. Plan to withdraw or withhold standard therapies in the course of research.
8. Plan for statistical analysis of the study.
9. Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and local languages.
10. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory, animal and human research.
11. For research involving more than minimal risk, an account of management of such risk or injury.
12. Proposed compensation and reimbursement of incidental expenses and management of research related and unrelated injury/illness during and after research period.
13. An account of storage and maintenance of all data collected during the trial.
14. Plans for publication of results—positive or negative—while maintaining the privacy and confidentiality of the study participants.
15. A statement on probable ethical issues and steps taken to tackle the same like justification for washout of standard drug, or the use of placebo control..
16. All other relevant documents related to the study protocol like investigator's brochure for trial on drugs/devices/vaccines/herbal remedies and statement of relevant regulatory clearances.
17. Agreement to comply with national and international Good Clinical Practices (GCP) protocols for clinical trials.
18. Details of Funding agency/Sponsors and fund allocation.

19. For international collaborative study details about foreign collaborators and documents for review of Health Ministry's Screening Committee(HMSC) or appropriate Committees under other agencies/authority like Drug Controller General of India (DCGI).
20. For exchange of biological material in international collaborative study a MoU/ Material Transfer Agreement between the collaborating partners.
21. A statement on conflict-of-interest (COI), if any.

## DECISION MAKING PROCESS

The IEC should be able to provide complete and adequate review of the research proposals submitted to them. It should meet periodically at frequent intervals to review new proposals, evaluate annual progress of ongoing ones, review serious adverse event (SAE) reports and assess final reports of all research activities involving human beings through a previously scheduled agenda, amended wherever appropriate. The following points should be considered while doing so :

1. The decision must be taken by a broad consensus after the quorum requirements are fulfilled to recommend/reject/suggest modification for a repeat review or advice appropriate steps. The Member Secretary should communicate the decision in writing to the PI.
2. If a member has conflict-of-interest (COI) involving a project then she/he should submit this in writing to the chairperson before the review meeting, and it should also be recorded in the minutes.
3. If one of the members has her/his own proposal for review or has any COI then she/he should withdraw from the IEC while the project is being discussed
4. A negative decision should always be supported by clearly defined reasons.
5. An IEC may decide to reverse its positive decision on a study, if it receives information that may adversely affect the risk/benefit ratio.
6. The discontinuation of a trial should be ordered if the IEC finds that the goals of the trial have already been achieved midway or unequivocal results are obtained.
7. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.
8. The following circumstances require the matter to be brought to the attention of IEC:
   a. Any amendment to the protocol from the originally approved protocol with proper justification.
   b. Serious and unexpected adverse events and remedial steps taken to tackle them.
   c. Any new information that may influence the conduct of the study.
9. If necessary, the applicant/investigator may be invited to present the protocol or offer clarifications in the meeting. Representative of the patient groups or interest groups can be invited during deliberations to offer their viewpoint.
10. Subject experts may be invited to offer their views, but should not take part in the decision making process. However, her/his opinion must be recorded.
11. Meetings are to be minuted which should be approved and signed by the Chairperson/alternate Chairperson/designated member of the committee.

## REVIEW PROCESS

The method of review should be stated in the SOP whether the review should be done by all reviewers or by primary reviewer(s) in which case a brief summary of the project with informed consent and patient information sheet, advertisements or brochures, if any, should be circulated to all members.

**The ethical review should be done in formal meetings and EC should not take decisions through circulation of proposals.** The committee should meet at regular intervals and should not keep a decision pending for more than 3 to 6 months, which may be defined in the SOP.

## PERIODIC REVIEW

The ongoing research may be reviewed at regular intervals of six months to one year as may be specified in the SOP of the ethics committee.

## CONTINUING REVIEW

The IEC has the responsibility to continue reviewing approved projects for continuation, new information, adverse event monitoring, follow-up and later after completion, if need be.

## INTERIM REVIEW

Each IEC should decide the special circumstances and the mechanism when an interim review can be resorted to by a subcommittee instead of waiting for the scheduled time of the meeting like re-examination of a proposal already examined by the IEC or any other matter which should be brought to the attention of the IEC. However, decisions taken should be brought to the notice of the main committee.

## MONITORING

Once IEC gives a certificate of approval, it is the duty of the IEC to monitor the approved studies, therefore an oversight mechanism should be in place. Actual site visits can be made especially in the event of reporting of adverse events or violations of human rights. Additionally, periodic status reports must be asked for at appropriate intervals based on the safety concerns and this should be specified in the SOP of the IEC. SAE reports from the site as well as other sites are reviewed by EC and appropriate action taken when required. In case the IEC desires so, reports of monitoring done by the sponsor and the recommendations of the DSMB may also be sought.

## RECORD KEEPING

All documentation and communication of an IEC are to be dated, filed and preserved according to written procedures. Strict confidentiality is to be maintained during access and retrieval procedures. The following records should be maintained for the following:

i. The Constitution and composition of the IEC.
ii. Signed and dated copies of the latest the curriculum vitae of all IEC members with records of training if, any.
iii. Standing operating procedures of the IEC.
iv. National and International guidelines.
v. Copies of protocols submitted for review.
vi. All correspondence with IEC members and investigators regarding application, decision and follow-up.
vii. Agenda of all IEC meetings.
viii. Minutes of all IEC meetings with signature of the Chairperson.
ix. Copies of decisions communicated to the applicants.
x. Record of all notification issued for premature termination of a study with a summary of the reasons.
xi. Final report of the study including microfilms, CDs and video recordings.

It is recommended that all records must be safely maintained after the completion/termination of the study for a period of 3 years if it is not possible to maintain the same for more than that due to resource crunch and lack of infrastructure.

### ADMINISTRATION AND MANAGEMENT

A fulltime secretariat and space for keeping records is required for a well-functioning IEC. The members could be given a reasonable compensation for the time spared for reviewing the proposals. A reasonable fees can be charged to cover the expenses related to review and administrative processes. Every institution should allocate reasonable amount of funds for smooth functioning of the IEC.

### SPECIAL CONSIDERATIONS

While all the above requirements are applicable to biomedical research as a whole irrespective of the specialty of research, there are certain specific concerns pertaining to specialised areas of research which require additional safe guards/protection and specific considerations for the IEC to take note of. Examples of such instances are research involving children, pregnant and lactating women, vulnerable participants and those with diminished autonomy besides issues pertaining to commercialisation of research and international collaboration. The observations and suggestions of IEC should be given in writing in unambiguous terms in such instances. Details on these issues are described in the next Chapter on General Ethical Issues.

## CHAPTER III: GENERAL ETHICAL ISSUES

All the research involving human participants should be conducted in accordance with the four basic ethical principles, namely autonomy (respect for person/participant) beneficence, nonmaleficence (do no harm) and justice. The guidelines laid down are directed at application of these basic principles to research involving human participants. The Principal Investigator is the person responsible for not

only undertaking research but also for observance of the rights, health and welfare of the participants recruited for the study. She/He should have qualification and competence in biomedical research methodology for proper conduct of the study and should be aware of and comply with the scientific, legal and ethical requirements of the study protocol.

## INFORMED CONSENT PROCESS

### Informed Consent of Participants

For all biomedical research involving human participants, the investigator must obtain the informed consent of the prospective participant or in the case of an individual who is not capable of giving informed consent, the consent of a legal guardian. Informed consent protects the individual's freedom of choice and respect for individual's autonomy and is given voluntarily to participate in research or not. Adequate information about the research is given in a simple and easily understandable unambiguous language in a document known as the *Informed Consent Form with Participant/Patient Information Sheet*. The latter should have following components as may be applicable:

1. Nature and purpose of study stating it as research.
2. Duration of participation with number of participants.
3. Procedures to be followed.
4. Investigations, if any, to be performed.
5. Foreseeable risks and discomforts adequately described and whether project involves more than minimal risk.
6. Benefits to participant, community or medical profession as may be applicable.
7. Policy on compensation.
8. Availability of medical treatment for such injuries or risk management.
9. Alternative treatments if available.
10. Steps taken for ensuring confidentiality.
11. No loss of benefits on withdrawal.
12. Benefit sharing in the event of commercialization.
13. Contact details of PI or local PI/Co-PI in multicentric studies for asking more information related to the research or in case of injury.
14. Contact details of Chairman of the IEC for appeal against violation of rights.
15. Voluntary participation.
16. If test for genetics and HIV is to be done, counseling for consent for testing must be given as per national guidelines.
17. Storage period of biological sample and related data with choice offered to participant regarding future use of sample, refusal for storage and receipt of its results.

A copy of the participant/patient information sheet should be given to the participant for her/his record. The informed consent should be brief in content highlighting that it is given of free will or voluntarily after understanding the implications of risks and benefits and she/he could withdraw without loss of routine care benefits. Assurance is given that confidentiality would be maintained and all the investigations/interventions would be carried out only after consent is obtained.

When the written consent as signature or thumb impression is not possible due to sensitive nature of the project or the participant is unable to write, then verbal

consent can be taken after ensuring its documentation by an unrelated witness. In some cases ombudsman, a third party, can ensure total accountability for the process of obtaining the consent. Audio-visual methods could be adopted with prior consent and adequate precaution to ensure confidentiality, but approval of EC is required for such procedures. For drug trials, if the volunteer can give only thumb impression then another thumb impression by the relative or legal custodian cannot be accepted and an unrelated witness to the project should then sign.

*Fresh or Reconsent*

Fresh or reconsent is taken in following conditions:

1. Availability of new information which would necessitate deviation of protocol.
2. When a research participant regains consciousness from unconscious state or is mentally competent to understand the study. If such an event is expected then procedures to address it should be spelt out in the informed consent form.
3. When long term follow-up or study extension is planned later.
4. When there is change in treatment modality, procedures, site visits.
5. Before publication, if there is possibility of disclosure of identity through data presentation or photographs (which should be camouflaged adequately).

*Waiver of Consent*

Voluntary informed consent is always a requirement for every research proposal. However, this can be waived if it is justified that the research involves not more than minimal risk or when the participant and the researcher do not come into contact or when it is necessitated in emergency situations elaborated in the previous Chapter. If such studies have protections in place for both privacy and confidentiality, and do not violate the rights of the participants then IECs may waive off the requirement for informed consent in following instances:

i. When it is impractical to conduct research since confidentiality of personally identifiable information has to be maintained throughout research as may be required by the sensitivity of the research objective, e.g. study on disease burden of HIV/AIDS.
ii. Research on publicly available information, documents, records, works, performances, reviews, quality assurance studies, archival materials or third-party interviews, service programs for benefit of public having a bearing on public health programs, and consumer acceptance studies.
iii. Research on anonymized biological samples from deceased individuals, left over samples after clinical investigation, cell lines or cell free derivatives like viral isolates, DNA or RNA from recognized institutions or qualified investigators, samples or data from repositories or registries, etc.
iv. In emergency situations when no surrogate consent can be taken.

**Obligations of Investigators Regarding Informed Consent**

The investigator has the duty to:

i. Communicate to prospective participants all the information necessary for informed consent. Any restriction on participant's right to ask any questions related to the study will undermine the validity of informed consent;
ii. Exclude the possibility of unjustified deception, undue influence and intimidation. Although deception is not permissible, if sometimes such

information would jeopardize the validity of research it can be withheld till the completion of the project, for instance, study on abortion practices.

iii. Seek consent only after the prospective participant is adequately informed. The investigator should not give any unjustifiable assurances to prospective participant, which may influence her/his decision to participate.

iv. Obtain from each prospective participant a signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related to the trial, and in case the participant is not competent to do so, a legal guardian or other duly authorized representative.

v. Take verbal consent when the participant refuses to sign or give thumb impression or cannot do so. This can then be documented through audio or video means.

vi. Take surrogate consent from the authorized relative or legal custodian or the institutional head in the case of abandoned institutionalized individuals or wards under judicial custody.

vii. Renew or take fresh informed consent of each participant under circumstances described earlier in this chapter.

viii. If participant loses consciousness or competence to consent during the research period as in Alzheimer or psychiatric conditions, surrogate consent may be taken from the authorized person or legal custodian.

ix. The investigator must assure prospective participants that their decision to participate or not and will not affect the patient - clinician relationship or any other benefits to which they are entitled.

**Essential Information for Prospective Research Participants**

Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information in the language she or he is able to understand which should not only be scientifically accurate but should also be sensitive/adaptive to their social and cultural context:

i. The aims and methods of the research.

ii. The expected duration of the participation.

iii. The benefits that might reasonably be expected as an outcome of research to the participant or community or to others.

iv. Any alternative procedures or courses of treatment that might be as advantageous to the participant as the procedure or treatment to which she/he is being subjected.

v. Any foreseeable risk or discomfort to the participant resulting from participation in the study.

vi. Right to prevent use of her/his biological sample (DNA, cell-line, etc.) at any time during the conduct of the research.

vii. The extent to which confidentiality of records could be maintained, i.e. the limits to which the investigator would be able to safeguard confidentiality and the anticipated consequences of breach of confidentiality.

viii. Responsibility of investigators.

ix. Free treatment for research related injury by the investigator and/ institution and sponsor(s).

x. Compensation of participants for disability or death resulting from such injury.

xi. Insurance coverage if any, for research related or other AEs.

xii. Freedom of individual/family to participate and to withdraw from research any time without penalty or loss of benefits which the participant would otherwise be entitled to.
xiii. The identity of the research teams and contact persons with address and phone numbers.
xiv. Foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others, clear mention of the same.
xv. Risk of discovery of biologically sensitive information and provision to safeguard confidentiality.
xvi. Publication, if any, including photographs and pedigree charts.

The quality of the consent of certain social and marginalized groups requires careful consideration as their agreement to volunteer may be unduly influenced by the Investigator.

## COMPENSATION FOR PARTICIPATION

Participants may be paid for the inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research. They may also receive free medical services. When this is reasonable then it cannot be termed as benefit. During the period of research if the participant requires treatment for complaints other than the one being studied necessary *free ancillary care* or appropriate referrals may be provided. However, payments should not be so large or the medical services so extensive as to make prospective participants consent readily to enroll in research against their better judgment, which would then be treated as undue inducement. All payments, reimbursement and medical services to be provided to research participants should be approved by the IEC. Care should be taken:

i. When a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses.
ii. When a participant is withdrawn from research for medical reasons related to the study the participant should get the benefit for full participation.
iii. When a participant withdraws for any other reasons she/he should be paid an amount proportionate to the amount of participation.

## CONFLICT OF INTEREST

A set of conditions in which professional judgment concerning a primary interest like patient's welfare or the validity of research tends to be or appears to be unduly influenced by a secondary interest like non-financial (personal, academic or political) or financial gain is termed as Conflict of Interest (COI).

Academic institutions conducting research in alliance with industries/commercial companies require a strong review to probe possible conflicts of interest between scientific responsibilities of researchers and business interests (e.g. ownership or part-ownership of a company developing a new product). In cases where the review board/committee determines that a conflict of interest may damage the scientific integrity of a project or cause harm to research participants, the board/

committee should advise accordingly. Significant financial interest means anything of monetary value that would reasonably appear to be a significant consequence of such research including salary or other payments for services like consulting fees or honorarium per participant; equity interests in stocks, stock options or other ownership interests; and intellectual property rights from patents, copyrights and royalties from such rights. The investigators should declare such conflicts of interest in the application submitted to IEC for review. Institutions and IECs need self-regulatory processes to monitor, prevent and resolve such conflicts of interest. The IEC can determine the conditions for management of such conflicts in its SOP manual. Prospective participants in research should also be informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research. Those who have also to be informed of the secondary interest in financial terms should include the institution, IEC, audience when presenting papers and should be mentioned when publishing in popular media or scientific journals.

Undue inducement through compensation for individual participants, families and populations should be prohibited. This prohibition however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care reimbursement, costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes. Undue compensation would include assistance to related person(s) for transport of body for cremation or burial, provision for insurance for unrelated conditions, free transportation to and fro for examination not included in the routine, free trip to town, if the participants are from rural areas, free hot meals, freedom for prisoners, free medication which is generally not available, academic credits and disproportionate compensation to researcher/team/institution.

However, in remote and inaccessible areas some of the features mentioned above maybe a necessity and culture specific. Therefore, the IEC should examine this on a case-by-case basis, as some of these elements may be justifiable for collecting vital data for national use or necessary to find if some interventions may significantly have direct impact on health policies.

## SELECTION OF SPECIAL GROUPS AS RESEARCH PARTICIPANTS

### Pregnant or Nursing Women

Pregnant or nursing women should, in no circumstances, be the participant of any research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about the fetus, pregnancy and lactation. As a general rule, pregnant or nursing women should not be participants of any clinical trial except such trials as are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable participants.

a. The justification of participation of these women in clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or

preventive benefits. Example of such trials are, to test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child, trials for detecting fetal abnormalities and for conditions associated with or aggravated by pregnancy, etc. Women should not be encouraged to discontinue nursing for the sake of participation in research and in case she decides to do so, harm of cessation of breast-feeding to the nursing child should be properly assessed except in those studies where breast feeding is harmful to the infant. Compensation in terms of supplying supplementary food such as milk formula should be considered in such instances.

b. Research related to termination of pregnancy: Pregnant women who desire to undergo Medical Termination of Pregnancy (MTP) could be made participants for such research as per The Medical Termination of Pregnancy Act, 1971.
c. Research related to pre-natal diagnostic techniques: In pregnant women, such research should be limited to detect the fetal abnormalities or genetic disorders as per the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994 and not for sex determination of the fetus.

### Children

Before undertaking trial in children the investigator must ensure that:

a. Children will not be involved in research that could be carried out equally well with adults.
b. The purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children.
c. A parent or legal guardian of each child has given proxy consent.
d. The assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors from the age of seven years up to the age of 18 years.
e. Research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support.
f. Interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child participant must be justified in relation to anticipated risks involved in the study and anticipated benefits to society.
g. The child's refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/tested, provided the consent has been obtained from parents/guardian.
h. Interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child participant as any available alternative interventions.
i. The risk presented by interventions not intended to benefit the individual child participant is low when compared to the importance of the knowledge that is to be gained.

### Vulnerable Groups

Effort may be made to ensure that individuals or communities invited for research be selected in such a way that the burdens and benefits of the research are equally distributed.

a. Research on genetics should not lead to racial inequalities.
b. Persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them.
c. Rights and welfare of mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders must be protected. Appropriate proxy consent from the legal guardian should be taken after the person is well informed about the study, need for participation, risks and benefits involved and the privacy and confidentiality procedures. The entire consent process should be properly documented.
d. 'Adequate justification is required for the involvement of participants such as prisoners, students, subordinates, employees, service personnel, etc. who have reduced autonomy as research participants, since the consent provided may be under duress or various other compelling reasons.

### Essential Information on Confidentiality for Prospective Research Participants

#### *Safeguarding Confidentiality*

The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual participants.

Data of individual participants can be disclosed under the following circumstances:

a. Only in a court of law under the orders of the presiding judge.
b. There is threat to a person's life.
c. In cases of severe adverse reaction may be required to communicate to drug registration authority.
d. If there is risk to public health it takes precedence over personal right to privacy and may have to be communicated to health authority.

Therefore, the limitations in maintaining the confidentiality of data should be anticipated and assessed and communicated to appropriate individuals or authorities as the case may be.

### Compensation for Accidental Injury

Research participants who suffer physical injury as a result of their participation are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability. In case of death, their dependents are entitled to material compensation.

#### *Obligation of the Sponsor to Pay*

The sponsor whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, in the *a priori* agreement to provide compensation for any physical or psychological injury for which participants are entitled or agree to provide insurance coverage for an unforeseen injury whenever possible.

An Arbitration committee or appellate authority could be set up by the institution to decide on the issue of compensation on a case-by-case basis for larger trials where such a step is feasible. Alternately an institution can also establish such a committee to oversee such claims, which would be common for projects being undertaken by it.

Compensation for ancillary care for unrelated illness as free treatment or appropriate referrals may also be included in the *a priori* agreement with the sponsors whenever possible.

### Post-trial Access

The Helsinki Declaration of the World Medical Assembly (WMA), 2000 states that at the end of the trial every participant should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. This led to a lot of debate globally on account of lack of even basic drugs in most of the developing countries. The Declaration of the WMA in 2004 reaffirmed "its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review." Therefore, whenever possible IEC should consider such an arrangement in the *a priori* agreement.

Sometimes more than the benefit to the participant, the community may be given benefit in indirect way through improving their living conditions, establishing counseling centers, clinics or schools, and giving education on maintaining good health practices. For smaller scale or student projects post-trial benefit to the participants may not be feasible but keeping in mind the post-trial responsibility conscious efforts should be made by the guides and the institution to initiate steps to continue to support and give better care to the participants.

### International Collaboration/Assistance in Biomedical Health Research

Research in biomedical and health areas has gained greater momentum only by the second half of the 20th Century, especially since the 1960s, the scope of international cooperation and collaboration assumed such proportions as to have exploitative connotations with commercial and human dimensions. On the one hand, collaboration in medical research suggests an interest in a humane and civil society, while on the other it could give the impression of experimentation on the population of one country by another. Different levels of development in terms of infrastructure, expertise, social and cultural perceptions, laws relating to intellectual property rights, etc. necessitate an ethical framework to guide such collaboration. The same concerns are applicable even when there is no formal collaboration between countries, but the research is undertaken with assistance from international organizations as sponsors (Governmental like National Institutes of Health, USA, non-Governmental like Bill and Melinda Gates Foundation, Ford Foundation or others like WHO, UNICEF, UNAIDS, etc).

#### *Special Concerns*

1. Given the magnitude and severity of the health problems in different countries, capacity building to address ethical issues that arise out of collaborative research must be promoted on a priority basis. Strategies should be implemented so that various countries and communities can practise meaningful self-determination in health development and can ensure the scientific and ethical conduct of research.

2. The collaborating investigators, institutions and countries can function as equal partners with sponsors even when in a vulnerable position by building appropriate safeguards. Community representatives should be involved early enough while designing the protocol and in a sustained manner during the development, implementation, monitoring and dissemination of results of research.
3. Careful consideration should be given to protect the dignity, safety and welfare of the participants when the social contexts of the proposed research can create foreseeable conditions for exploitation of the participants or increase their vulnerability to harm. The steps to be taken to overcome these should be described and approval taken from concerned IEC/IndEC.
4. Every adult participant in the research should voluntarily give informed consent and child her this assent as may be applicable.
5. As different kinds of research (epidemiological studies, clinical trials, product development, behavioral and social science oriented research, etc.) have their own particular scientific requirements and specific ethical challenges, the choice of study populations for each type of study should be justified in advance in scientific and ethical terms regardless of the place from where the study population is selected. Generally, early clinical phases of research, particularly of drugs, vaccines and devices, should be conducted in communities that are less vulnerable to harm or exploitation. However, for valid scientific and public health reasons, if sufficient scientific and ethical safeguards are ensured it may be conducted in any phase after obtaining relevant regulatory clearances.
6. The nature, magnitude, and probability of all foreseeable harms resulting from participation in a collaborative research program should be specified in the research protocol and explained to the participants as fully as can be reasonably done. Moreover, the modalities by which to address these, including provision for the best possible nationally available care to participants who experience adverse reactions to a vaccine or drug under study, compensation for injury related to the research, and referral for psychosocial and legal support if necessary, need to be described.
7. The research protocol should outline the benefits that persons/communities/countries participating in such research should experience as a result of their participation. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation. The burden and the benefit should be equally borne by the collaborating countries.
8. Guidelines, rules, regulations and cultural sensitivities of all countries participating in collaborative research projects should be respected, especially by researchers in the host country and the sponsor country. These could be with reference to intellectual property rights, exchange of biological materials (human, animal, plant or microbial), data transfer, security issues, and issues of socially or politically sensitive nature. In this context, it is essential for researchers to follow the GOI notification on " Exchange of Human Biological Material for Biomedical Research" issued on 19.11.97 and obtain appropriate regulatory clearances as prevalent in the country for international collaboration and EC approval from all trial sites before the initiation of research.

### Researcher's Relations with the Media and Publication Practices

Researchers have a responsibility to make sure that the public is accurately informed about results without raising false hopes or expectations. It should also not unnecessarily scare the people. Researchers should take care to avoid talking with journalists or reporters about preliminary findings as seemingly promising research that subsequently cannot be validated or could lead to misconcepts, if reported prematurely. Or, the results of research may be reported in such a way that it would seem that the human application is round the corner, only to be told later by the researchers that considerable time has to pass before these findings can be translated into tools for human use. In such circumstances, retractions most often do not appear in the media. Therefore, it is important to avoid premature reports and publicity stunts. The best safeguard against inaccurate reporting is for the researcher to talk to media on condition that the reporter submit a full written, rather than oral version, of what will be reported, so that it enables the researcher to make necessary corrections, if needed, prior to publication.

Investigator's publication plans should not threaten the privacy or confidentiality of participants, for example publication of pedigrees in the report on research in genetics can result in identification of study participants. It is recommended that a clear consent for publication be obtained besides the consent for participation in research or treatment and such a consent should preferably be obtained on two different occasions and not as a blanket one at the commencement of the study. Maintenance of confidentiality while publishing data should be taken care of. In case there is need for publication/presentation of photographs/slides/videos of participant (s), prior consent to do so should be obtained. Identification features should be appropriately camouflaged. The same safeguard should be observed for video coverage.

With regard to authorship, the International Committee of Medical Journal Editors (ICJME) has laid down criteria based on credit and accountability. Only those who make substantial contribution to the article and take responsibility for the published matter can be co-authors. Plagiarism or falsification of data and authorship are important ethical issues in publications. The term 'misconduct in research' means fabrication, falsification, plagiarism, selective omission of data and claiming that some data are missing, ignoring outliers without declaring it, not reporting data on side effects/adverse reactions in a clinical trial, publication of post-hoc analysis without declaring it, gift authorship, not citing others' work, not disclosing conflict of interest, redundant publication, and failure to adequately review existing research. The Commission on Research Integrity in US created by US Congress addresses the scientific, ethical, social and legal issues involving scientific misconduct in research. Consolidated standards of reporting trials (CONSORT) guidelines have been prescribed for publishing results of clinical research especially RCTs (Randomized Controlled Trials) and are available at http://www.consort-statement.org.

# CHAPTER IV: STATEMENT OF SPECIFIC PRINCIPLES FOR CLINICAL EVALUATION OF DRUGS/VACCINES/DEVICES/ DIAGNOSTICS/HERBAL REMEDIES

Human studies designed to evaluate the safety, effectiveness, or usefulness of an intervention includes research on therapeutics, diagnostic procedures and preventive measures including vaccines. The type of experimental procedures that a patient is submitted to have become more complex, multifaceted and varied as the complexities of medical research have increased. It is clearly accepted that it is essential to carry out research on human participants to discover better medical and therapeutic modalities for the benefit of mankind. It is equally clear that such research on normal participants and patients is associated with some degree of risk to the individual concerned. These guidelines have been framed to carry out the evaluation of drugs, vaccines, devices and other diagnostic materials on human participants including herbal remedies, in accordance with the basic ethical principles. These guidelines are important for the protection of research participants against any avoidable risk, guide the researchers in the preparation of research proposals/ protocols and facilitate ECs to review and approve such studies. For the clinical evaluation of proposed research intervention, the framework of guidelines is provided for the following areas:

1. Drug trials.
2. Vaccine trials.
3. Surgical procedures and medical devices.
4. Diagnostic agents - with special reference to use of radioactive materials and X-rays.
5. Trials with herbal remedies.

## GENERAL PRINCIPLES

All the research involving human participants should be conducted in accordance with the four basic ethical principles, namely autonomy or respect for person/ participant, beneficence, nonmaleficence and justice. The guidelines laid down are directed at application of these basic principles to research involving human participants. An investigator is the person responsible for the research trial and for protection of the rights, health and welfare of the participants recruited for the study. She/he should have qualification and competence in clinical trial research methods for proper conduct of the trial and should be aware of and comply with all requirements of the study protocol as enumerated under the General Principles and General Issues in these guidelines.

## SPECIFIC PRINCIPLES

### Drug Trials

As per the revised Schedule 'Y' of the Drugs and Cosmetic Act (2005), "a clinical trial is a systematic study of new drug(s) in human subject to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic, and pharmacokinetics), and/or adverse effects with the objective of determining the

safety and/or efficacy of the new drugs". Clinical trial of drugs is a randomized single or double-blind controlled study in human participants, designed to evaluate prospectively the safety and effectiveness of new drugs/new formulations. The new drug as defined under the Drugs and Cosmetic Rules 1945 (OCR), and subsequent amendments include:

i. A new chemical entity (NCE).
ii. A drug which has been approved for a certain indication, by a certain route, in a certain dosage regimen, but which is now proposed to be used for another indication, by another route, or in another dosage regimen.
iii. A combination of two or more drugs which, although approved individually, are proposed to be combined for the first time in a fixed dose combination (FDC).

The proposed trial should be carried out, only after approval of the Drugs Controller General of India (DCGI ,as is necessary under the Schedule 'Y' of Drugs and Cosmetics Act,1940.The investigator should also get the approval of Ethics Committee of the Institution before submitting the proposal to DCG. All the guiding principles should be followed irrespective of whether the drug has been developed in this country or abroad or whether clinical trials have been carried out outside India or not.

Throughout the drug trials, the distinction between therapy and research should be maintained. A physician/investigator who participates in research by administering the new drug to consenting patients should ensure that the patients understand and remember that the drug is experimental and that its benefits for the condition under study are yet unproven.

*Special Considerations*

i. Use of a placebo in drug trials and sham surgery has been intensely debated and even the fifth version of Helsinki Declaration has not been helpful in providing clarity in this matter. Each such protocol using placebo requires careful consideration before approval. Denial of the available treatment to control (placebo) group of patients is unethical.
ii. Trials of drugs without the approval of the Indian Regulatory Authority and appropriate agencies should be dealt with according to the law of the land.
iii. After the clinical trial is over, if need, the drug is found effective, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country and thereafter at a reduced rate for the participants whenever possible. A suitable *a priori* agreement should be reached on post-trial benefits.
iv. The criteria for termination of a trial must be defined *a priori* in the proposal of the trial and plan of interim analysis must be clearly presented as this is important if the test drug is found to be clearly either more effective or less effective than the standard drug. The trial can be discontinued thereafter and better drug should be given to patient receiving less effective drug.
v. Issues of partner notification and discordant couples should be taken care of before initiating any HIV/AIDS related trial.
vi. For new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I through Phase III and data should be submitted as described in Appendix I of revised Schedule 'Y' (2005) of Drugs

and Cosmetics Act. Permission to carry out these trials shall generally be given in stages, considering the data emerging from earlier Phase(s).

vii. For new drug substances discovered in countries other than India, Phase I data as described in Appendix I of revised Schedule 'Y'(2005) should be submitted along with the application. After Phase I data generated outside India has been submitted to the Licensing Authority, permission may be granted to repeat Phase I or conduct Phase II and subsequently Phase III trials concurrently with other global trials for that drug.

viii. In case of amendment or deviation in the protocol not only the approval of IEC may be obtained but also the Licensing Authority has to be notified of the same.

In order to optimize and expedite drug development for drugs indicated in life threatening/serious diseases or specific diseases of relevance to India—the toxicological land clinical data requirements shall be decided on a case by case basis. In such cases, particular studies may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority and not by ECs.

The Indian Good Clinical Practices (GCP) based on the international guidelines issued by World Health Organization (WHO) and International Committee on Harmonization (ICH) provides operative guidelines for ethical and scientific standards for the designing of a trial protocol including conduct, recording and reporting procedures and should be strictly adhered to while carrying out a trial. They may be accrued at http://cdsco.nic.in/html/GCP.htm.

The clinical trials usually are of 3 types:

i. Studies where intervention is clearly "demarcated research" such as phase I trial of a new compound.
ii. Studies with a mix of standard medical practices and specific research elements, e.g. trials of two competing antinausea drugs following standard chemotherapy.
iii. Studies involving research on therapeutic practices, such as the trial of two already approved antidiabetic drugs.

### *Phases of Clinical Trials*

All phases require approval from EC. The first three of the following four phases of clinical trials of drug require DCGI's clearance:-

*Phase I (Human pharmacology):* This is a nontherapeutic trial and the objective is to determine the safety of a new drug and determine the maximum tolerated dose as also to determine the nature of adverse reactions that can be expected in healthy adults of both sexes. Healthy female volunteers could be included provided they have completed their family or do not intend to have a child in the future. These studies include both single and multiple dose administration and should ideally be carried out at a site that is adequately equipped. The following points should be considered before initiating the trial:

1. At least two participants should be administered each dose to establish the safe dose range using maximum tolerated dose, pharmacokinetic, pharmacodynamic effects, and adverse reactions, if any, with their intensity and nature.
2. As this involves testing in humans for the first time, it is safer to plan the study in cohorts of volunteers by starting from the lowest dose, which is increased to higher doses only after the safety of the lower doses is clearly established.

3. Early measurement of drug activity as preliminary study of activity of potential therapeutic benefit may be conducted in Phase I as a secondary objective such studies are generally performed in later Phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage. This also can be carried on patients, if the drug has cytotoxic potential as in case of cancer or if quicker results are needed as in case of HIV.
4. Pharmacokinetics, i.e. characterization of a drug's absorption, distribution, metabolism and excretion (ADME), should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations. Obtaining pharmacokinetic information in subpopulations such as patients with impaired elimination (renal or hepatic failure), the elderly, children, and ethnic subgroups should also be considered.
5. Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies which relate to blood levels of drug to response (pharmacokinetic/pharmacodynamic studies) may be conducted in healthy volunteers or in patients with the target disease. Such data obtained from patients may guide the dosage and dose regimen to be applied in later studies.
6. Investigator trained in clinical pharmacology should preferably carry out these studies.
7. The duration of time lapsing between two trials in the same volunteer should be a minimum of 3 months. The volunteers should preferably be covered under some insurance scheme.
8. Compensation is given by the sponsors of newly developed drugs. The amount may vary depending upon the discomfort experienced by the participant and the number of samples taken or being subjected to procedures. The EC has to examine this does not tantamount to undue inducement.
9. There should be adequate safeguards for management of adverse reactions, including resuscitative measures as in intensive care.

*Combined Phase I and Phase II:* Such trials are conducted on populations for whom the therapeutic options are exhausted, as in the case of HIV/AIDS and cancer. Toxic drugs like antiretroviral or anticancer drug, cannot be tested in normal healthy volunteers as in Phase I studies as the risk far outweighs any benefit. Hence, such studies are planned in patients suffering from the disease so that the risk-benefit ratio is more favorable. Since here the patient population is a vulnerable group and trial on them has to be planned very carefully. The role of ethics committee assumes great importance here as the weighing of the risk-benefit ratio influences the decision and participation in terminal stages may be considered to be inducement. The researcher also has to consider very carefully the risks involved.

*Phase II (Therapeutic exploratory trials):* These are controlled studies conducted in a limited number of patients of either sex to determine therapeutic effects, effective dose range and further evaluation of safety and pharmacokinetics in patients. Generally due to selection of patients with narrow inclusion criteria to find effective dose the study population is more or less homogenous. The dose used is lesser than the highest dose used in Phase I. Another objective of this Phase II is evaluation of potential study endpoints, therapeutic regimens including concomitant medications

and target populations, and mild versus severe disease, for further studies in Phase II or III. These objectives may be served by exploratory analyses of subsets of data and by including multiple endpoints in trials. Normally 20 to 25 patients should be studied for assessment of each dosage. These studies are usually limited 3 to 4 centers. It is advisable to include a clinical pharmacologist as a coinvestigator in such studies.

*Phase III (Therapeutic confirmatory trials):* The purpose of these trials is to obtain adequate data about the efficacy and safety of drugs in a larger number of patients of either sex in multiple centers usually in comparison with a standard drug and/or a placebo if a standard drug does not exist for the disease under study. This is to validate efficacy and safety found in Phase II. On successful completion of phase III trials permission is granted for marketing of the drug.

Studies in Phase II may also further explore the dose-response relationship to drug concentration in blood and clinical response, use of the drug in wider populations, in different stage of disease, or the safety and efficacy of the drug in combination with other drug (s). For drugs intended to be administered for long periods, trial involving extended exposure to the drug are ordinarily conducted, although they may be initiated in Phase II. These studies carried out in Phase III complete the prescribing information needed to support adequate instructions for use of the drug.

These trials may be carried out by clinicians in the concerned therapeutic areas having facilities appropriate to the protocol. If the drug is already approved/ marketed in other countries, Phase III data should generally be obtained in sufficient numbers of patients distributed over adequate number of centers, primarily to confirm the efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Open noncomparative trials, do not generate any generlisable data and therefore, are unethical. Studies in Phase III may also further explore the dose-response relationships, drug concentration in blood and clinical response, use of the drug in wider population, in different stage of disease, or the safety and efficacy of the drug in combination with other drugs.

*Phase IV:* The Phase IV studies should have valid scientific objectives. After approval of the drug for marketing, phase IV studies or post marketing surveillance is undertaken to obtain additional information about the risks and benefits resulting from long term usage of drug. It is an important aspect of drug trial on the long-term effects of the drugs and the adverse reactions induced by drugs, if any, should be brought to *the notice of the Ethics Committee*. There is a need to correlate the adverse events reported during Phase IV trials with the toxicity data generated in animals, to draw markers for future warnings of potential adverse events likely to occur with other drugs. These trials may not be necessary for approval of new drug for marketing but may be required by the Licensing Authority for optimizing its use. These studies also include those on specific pharmacologic effect, drug-drug interaction(s), dose response studies, trials designed to support use under approved indication(s), e.g. mortality I morbidity studies, clinical trials in a patient population not adequately studied in the pre-marketing phase, e.g. children; and epidemiological studies, etc. Bioequivalence and bioavailability study also falls under this category.

In addition, there are Phase IV studies that are designed to evaluate the marketed drug in specifically designed studies, which have inclusion I exclusion criteria,

objectives and end points. The drug is used for the labeled indication in these studies. Therefore, Licensing Authority permission is not needed. However, EC permission is needed.

A third type of postmarketing study involves evaluation of the drug for a new indication of a marketed drug, ego studies with letrazole. Here, DCGI permission and EC approval are needed which really makes the trial a Phase III study.

### Special Studies

*Bioavailability studies:* For all new drug substances and for new dosage forms administered for systemic absorption which are approved elsewhere in the world, bioequivalence studies with the available formulation should be carried out wherever applicable. Data on the extent of systemic absorption may be required for formulations not meant for systemic absorption. Evaluation of the effect of food on absorption following oral administration should be carried out if the food absorption data is not submitted.

*BA/BE* (bioequivalence) studies are also clinical studies conducted most often in normal volunteers. Hence, all safeguards to protect participants must be in place, including ethical review of protocol, recruitment methods, compensation for participation, evidence of noncoercion and consent procedures. It is in such studies that volunteers often participate at short intervals and may participate at different centers within less than the prescribed period of three months between two studies. Mechanisms to prevent this must be developed at the study site.

*Dissolution studies:* Data on dissolution of all solid oral dosage forms should also be submitted.

Dissolution and bioavailability data submitted in the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulation(s) sought to be marketed and those used for clinical trials during clinical development of the product. Data regarding interaction of the new drug with drugs that are likely to be used concomitantly with it are required to be conducted and should be submitted from nonclinical studies and, if appropriate, from human studies.

### Special Concerns

*Multicentric Trials:* A multicentric trial is conducted simultaneously by several investigators at different centers following the same protocol. Ideally, these trials should be initiated at the same time at all the centers.

i. All the investigators should give a written acceptance of the protocol provided by the sponsor which may be modified to suit the local requirements and should be followed for the trial duly approved by the ethics committee of the host institutes.
ii. Meetings should be organized at the initial and intermediary stages of the trial to ensure uniform procedures at all centers.
iii. Training should be imparted to research staff at the participating centers to familiarize them with the uniform procedures, data entry in the case record forms, ethics and GCP.
iv. Standardization of methods for recruitment and evaluation/monitoring of laboratory procedures and conduct of trial should be carried out.

v. There should be monitoring of adherence to protocol including measures to terminate the participation of some centers, if necessary.
vi. A Central monitoring committee could be set up for this purpose, which could include ethics committee members too.
vii. Specific role of coordinators and monitors should be defined.
viii. Centralized data management and analysis should be planned as per WHO's "Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards".
ix. Drafting of a common final report and publication procedure should be decided at the outset. No individual center should publish any data till appropriate authorities accept the combined report.
x. The code of the administered drug could be broken in the event of a severe adverse reaction occurring during the conduct of a double blind trial necessitating such a step.
xi. It is advisable to establish communication between ECs reviewing multicentric studies in India to discuss ethical concerns of the trial. This is particularly important if any EC does not grant approval for a study at a site for ethical reasons.

*Contraceptives*

i. All procedures for clinical trials are applicable. Participants should be clearly informed about the alternatives available.
ii. In women where implant has been used as a contraceptive for trial, a proper follow-up for removal of the implant should be done, after the trial is over or the participant has withdrawn from the trial.
iii. Children born due to failure of contraceptives under study should be followed up for any abnormalities if the woman does not opt for medical termination of pregnancy.

*Randomized Controlled Trial (RCT):* RCT reduces considerable bias but can also create ethical problems when the comparative arm has placebo. Hence, a proper justification should be provided for using the placebo. In keeping with the Declaration of Helsinki as far as possible standard therapy should be used in the control arm. In the following situations, placebo can be used:

i. Self limited disease.
ii. Where no proven prophylactic, diagnostic or therapeutic method exists.

*Superiority and noninferiority trials:* These terms have recently emerged as a result of newer application of statistical analysis for RCTs. When a trial is conducted to test, if a new drug is superior to the existing one such a trial is termed superiority trial. When the trial is conducted to examine, if the drug is as good as the existing one then it is called noninferiority or active control equivalence trial (ACET). Such a concept evolved due to pitching of clinical reasoning against statistical thinking which earlier gave an indeterminate result when clinically small difference in beneficial effect was expected.

In superiority trials one of the arms can be placebo or active control but in equivalence trials use of placebo arm will be unethical as the drug's efficacy will have to be tested against a proven therapy.

In late 90s CONSORT (Consolidated Standards of Reporting Trials) Statement, including a checklist and a flow diagram, was developed to improve reporting of

randomized controlled trials with primary focus on RCT with 2 parallel groups that assess the possible superiority of one treatment compared with another. This method of reporting has been modified to encourage reporting of non-inferiority or ACET trials which are lesser in number in medical literature. CONSORT guidelines are now being extended to other trial designs too.

### *Monitoring and Reporting Adverse Reactions or Events*

Any adverse event or adverse drug reaction (AE/ADR) can be expected and unexpected. These should be specified in the concerned SOP. Based on medical criteria they can be mild, moderate or severe/serious and causality relationship should be examined. An AE or unexpected ADR requires expedited review by the ethics committee. Unexpected AE/ADRs and all SAE (serious adverse event) should be reported to the sponsor by the investigator within 24 hours and to the ethics committee that accorded approval to the study protocol within seven days. In the event of death the EC should also be informed within 24 hours. Any unexpected SAE as defined in the Indian GCP (Good Clinical Practice) Guidelines occurring during a clinical trial should be communicated promptly within 14 calendar days by the Sponsor to the Licensing Authority and to the investigator(s) of other trial sites participating in the study. The reporting of the SAE to the regulatory authority immediately is to enable it to stop the clinical trials of unapproved drugs or withdraw from market approved drugs based on report of Phase IV studies. All other serious unexpected reactions (ADRs) that are not fatal or life threatening must be filed as soon as possible but not later than 14 calendar days. At the end of the trial, all adverse events whether related to trial or not are to be listed, evaluated and discussed in detail in the final report.

The medical management of the adverse event is the responsibility of the investigator, and the protocol for adverse event management with allocation of responsibilities must be pre-defined in the protocol and submitted to the Ethics Committee. There must be a financial plan (including, if necessary, insurance) to manage adverse events and compensation for trial related injury. The Ethics Committee reviewing the protocol must review these aspects as well before giving approval.

## Vaccine Trials

Vaccines can be prophylactic and therapeutic in nature. While prophylactic vaccines are given to normal participants, therapeutic or curative vaccines may be given to patients suffering from particular disease. Many of the prophylactic vaccines are given to pediatric group. The guidelines to conduct the clinical trial on investigational vaccines are similar to those governing a drug trial. The phases of these trials differ from drug trials as given below:

### *Phases of Trial*

*Phase I*: This refers to the first introduction of a vaccine into a human population for determination of its safety and biological effects including immunogenicity. This phase includes study of dose and route of administration and should involve *low-risk participants*. For example, immunogenicity to hepatitis B vaccine should not be determined in high risk participants. Pharmacokinetic studies are generally not required for injectable characteristics of the immune response to the known or

presumed action of vaccine. The class, subclass, and the function of specific antibody produced and the lag time for appearance and duration of adequate antibody titre is determined. Information about the induction of cell-mediated immunity, the cross reactive antibodies and/or interaction pre-existing antibodies which might affect immune system, is also obtained.

*Phase II:* This refers to the initial trials examining effectiveness (immunogenicity) and dose range in a limited number of volunteers forming the target groups, like, children, adults or those at risk of exposure to pathogens. Pharmacokinetics and safety of the vaccine is also studied. Early Phase II is usually an exploratory trial while the late Phase II is known as pivotal efficacy study.

*Phase III:* This focuses on assessment of safety and effectiveness in the prevention of disease, involving controlled study on a larger number of volunteers (in thousands) through multicentric studies. These studies determine the protection offered by the vaccine and provide pivotal data for licensure. Efficacy in vaccine trials means reduction in incidence of the disease after vaccination compared to the incidence that prevailed before vaccination. Effectiveness on the other hand provides information of protective rate conferred on a given population. It includes measurement of direct and indirect protection to a nonvaccinated person among the defined vaccinated population determined by vaccine coverage area, and correlation of vaccine strains with circulating strains.

*Phase IV Studies (Post-Licensure Evaluation):* These studies are done in the entire population or a subgroup to detect the rarer or unexpected events that may not be seen in smaller Phase II/ III studies. Postlicensure studies of large populations, in a more heterogenous group of people, over longer periods of time are necessary to provide ongoing assessment of vaccine safety and effectiveness.

The pharmacodynamic studies provide information on the vaccines when other routes of administration are claimed, e.g. oral vaccine, or when vaccine contains novel adjuvants or excipients. These are also done to conduct further research on age at vaccination, effect ovaccine strain, and interchangeability of vaccine. Bridging studies in vaccine trials are conducted to support clinical comparability of efficacy, safety and immunogenicity of new formulation when there is change in vaccine composition with regard to adjuvant, preservative, or a change in manufacturing process, site or scale. These are performed either before or after product licensure. The rationale of bridging clinical studies is the goal is to demonstrate product equivalency to that used in earlier preclinical or clinical testing. When serologic bridging studies are to be done, only comparison of sera with historical control from an efficacy trial is warranted, and no clinical trial needs to be undertaken.

### *Combination Vaccines*

Combination vaccines are being used commonly at present. The main goal in efficacy trial design of such vaccines is to evaluate the efficacy of each antigenic component. When correlates of protection are validated for each component, immunogenicity end- points should be used. When they are not validated for each component, prospective controlled trial is required. Further, noninferiority trials should be conducted to demonstrate that the combination vaccine is not inferior in terms of immunogenicity or efficacy, to vaccines with individual components.

*Vaccines Administered Simultaneously with the Combination Vaccines*

Immunogenicity and safety data should be obtained in Phase III (Prelicensure) studies to support the simultaneous administration of a new vaccine with already licensed vaccines that would be given to the same target population using the same (or overlapping) schedule. With regard to immunogenicity, assessment should be performed to show that subjects still attain an acceptable immune response to both the combination vaccine and the other simultaneously administered vaccine. The immunogenicity obtained with such simultaneous administration should be evaluated early in clinical development for all components to detect any possible immunological interference and such assessment would be valuable before proceeding to a large-scale trial of the investigational vaccine. These studies will evaluate safety and interference of the new combination vaccine with one type of simultaneously administered vaccine, e.g. for a new DTaP vaccine, safety and interference will be evaluated in a statistically valid manner with one type of simultaneously administered *Haemophilus influenzae* type b conjugate vaccine. If no such studies have been conducted, it should be stated in the package insert that no safety or immunogenicity data has been generated.

*Special Concerns*

i. Some vaccines that contain active or live - attenuated micro-organisms can possibly possess a small risk of producing that particular infection. The participant to be vaccinated should be informed of the same.
ii. The participants in control groups or when subjected to ineffective vaccines run a risk of contracting the disease. In such an event free treatment for the disease should be given and if it is a disease where lifelong treatment is required then this should be insisted upon by IEC/Ind EC.
iii. The risks associated with vaccines produced by recombinant DNA techniques are not completely known. However, for all the recombinant vaccines/ products, the Guidelines issued by the Department of Biotechnology should be strictly followed.
iv. Post-trial access to the vaccine should be available to the control group. But if the vaccine is for pediatric age group and by the time the study gets over the children in the control arm may cross the age when the vaccine is supposed to be protective. In such instances, the control arm could be some other alternative vaccine for that pediatric age group although this does not restore clinical equipoise. EC may examine the feasibility and ethical aspects on a case-to-case basis.
v. Post-trial access to the vaccine should be given first to the community from which the participants were drawn.
vi. When a trial of HIV preventive vaccine is being conducted, positive serology may result after the vaccination. This may not indicate infection but may create problems for employment and travel purposes. To avoid confusion, a certificate stating that the person is a trial participant in an HIV vaccine trial may be issued.
vii. Children being a vulnerable group, care should be taken to choose the particular age with regard to gender, ethnic background and health profile for testing vaccines for this age especially if they are from over-researched vulnerable community.

viii. In RCTs if no effective vaccine exists as comparator then placebo can be used. The community should be involved to decide on the choice of comparator.

**Clinical Trials with Surgical Procedures/Medical Devices**

Medical and health care technology has undergone rapid transformation in the past two decades. Of late, a series of technological inventions have revolutionized the preventive, diagnostic, rehabilitative,*therapeutic (life-supporting or life sustaining devices) capabilities of medical sciences and biomedical technology has made considerable progress in the conceptualization and designing of bio-equipments. Several biomedical devices and critical care equipment have been imported and successfully deployed in diagnostic and therapeutic services in the country. Similarly, various academic and research organizations as well as private entrepreneurs are taking active interest in the development and manufacture of medical devices. Several important devices such as cardiac valve and spin offs from defence research laboratories like Kalam-Raju Stent, cardiac catheters, eye lasers and external cardiac pacemaker have been successfully developed and many more are in various stages of development. However, only through good manufacturing practices (GMP) can the end products reach the stage of large scale utilization by society. Most of these products are only evaluated by Central Excise testing for taxation purposes, which discourages entrepreneurs to venture in this area with quality products especially when they do not come under the strict purview of the existing regulatory bodies like ISI, BSI and Drugs Controller General. This is evidenced by the very low number of patents or propriety medical equipments manufactured and produced in the country.

Some low technology devices such as thermometers and weighing instruments seek optional certification from Indian Standards Institute (ISD as a proof of quality rather than as a premarket approval requirement. The Bureau of Indian Standards BIS) certifies and regulates few other low technology devices. However, these procedures are not adequate to assure the quality of high technology medical devices. It appears that some imported high technology devices, approved or cleared by the country of origin or by the Federal Drug Administration (FDA) of the United States of America (USA), are permitted for marketing in India. No regulatory mechanisms exist even with the Drug Controller General of India (DCGI) for certification, quality assurance and post market surveillance of both imported and indigenous medical devices. As the capacity of the country in this area is improving day by day the need for a regulatory mechanism/authority is increasingly obvious. The concept of regulations governing investigations involving biomedical devices is therefore relatively new in India. Earlier only needles, syringes and blood bags were covered by the Drugs and Cosmetics Act, 1940. Now, sterile devices like cardiac stents, drug eluting stents, catheters, intraocular lenses, IV cannulae, bone cements, heart valves, scalp vein set, orthopedic implants, internal prosthetic replacements have been included in the list with effect from 1.3.2006.

The attendant health risks through the errors caused by use of implantable devices require systematic and rigorous preclinical and clinical studies to evaluate their efficacy and safety besides the quality. In addition, every implant and installed diagnostic device needs to be assessed for its long-term safety and/or performance through an appropriate mechanism. Execution of these measures, i.e. evaluation, certification, post-market surveillance and regulatory action in the event of any

inadequacy, is possible only through a well conceived regulatory agency, which is supported by adequate legislative safeguards.

All countries which have a medical device industry, have policies and regulatory processes or mechanisms in place. Most of these countries (mainly USA, EU, Australia, and possibly Japan. China, South Korea and Brazil) are attempting to harmonize the medical device regulations of different countries with a view to enhance their export potentials. However, it should be borne in mind that not all the devices permitted for export by other countries have been approved for commercialization in their own countries. Therefore, the Society for Biomedical Technology (SBMT), an interministerial initiative to utilize defense research spin offs for health care sponsored a review of the existing certification procedures and regulatory mechanisms in other countries. As a second step in this direction, it was decided to conceptualize a framework for medical device regulation.

It is proposed to set up the Indian Medical Devices Regulatory Authority (IMDRA) which is being examined by the Health Ministry. Until the guidelines are formulated and implemented by this Regulatory Authority, Bodies like Indian Standard Institute, Board of Indian Standards, Drug Controller General of India, and Nuclear Medicine Board of the BARC constituted for specific purposes under an Act or Administrative authorities should approve clinical trials with biomedical devices on case-to-case basis.

### *Definitions*

*Device:* "An instrument, apparatus, implement, machine, contrivance, implant, *in vitro* agent, or other similar or related article, including a component, part or accessory,

- Intended for use in the diagnosis of disease or other conditions, or in the cure,
- Mitigation, treatment, or prevention of disease in man, or
- Intended to affect the structure or any function of the body of man, and
- Which does not achieve any of its primary intended purposes/uses,
- Through chemical action within or on the body of man, or
- By being metabolized within the body."

*Medical devices:* A medical device is defined as an inert diagnostic or therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body.

*Medicated devices:* These are devices that contain pharmacologically active substances which are treated as drugs.

Medical devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, orthopedic pins and other orthopedic accessories. Their purpose varies from being used primarily for specific affected parts of the body to being used as adjunct to primary therapies, e.g. lithotripsy with drug therapy for kidney stone. Depending upon risks involved the devices could be classified as follows:

a. Noncritical devices: An investigational device that does not present significant risk to the patients, e.g. thermometer, BP apparatus.
b. Critical devices An investigational medical device that presents a potential serious risk to the health, safety or welfare of the participant, e.g. pace markers, implants, internal catheters.

A more appropriate classification and the proposed regulatory and certification procedures for Indian devices are summarized as follows:

All the general principles of clinical trials described for drug trials should also be considered for trials of medical devices. As for the medicated devises, safety evaluation and premarket efficacy of devices for one to three years with data on adverse reactions should be obtained before premarket certification. The duration of the trial and extent of use may be decided in case-to-case basis by the appropriate authorities. However, the following important factors that are unique to medical devices should be taken into consideration while evaluating the related research projects:

- Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered.
- Clinical trials of medical devices are different from drug trials, as they cannot be conducted in healthy volunteers. Hence, Phase I trials are not necessary for trial on medicated devices .
- Medical devices used within the body may have greater risk potential than those used on or outside the body, for example, orthopaedic pins vs crutches .
- Medical devices not used regularly have less risk potential than those used regularly, for example, contact lens vs intraocular lenses .
- Safe procedures to introduce a medical device in the patient should also be followed as the procedure itself may cause harm to the patient.
- Informed consent procedures should be followed as in drug trials. The patient information sheet should contain information on follow-up procedures to be adopted, if the patient decides to withdraw from the trial.
- Study design of the intra body devices like implants can be very challenging and should have adequate protective safeguards. The study should be long enough to detect if there are any late onset ADRs.
- If full assessment of safety is not complete, the Phase III could extend to Phase IV.

**Diagnostic Agents - Use of Radio - Active Materials and X-rays**

In human beings, for investigation and treatment, different radiations - X-ray, gamma rays and beta rays -, radiopaque contrast agents and radioactive materials are used. The relative risks and benefits of research proposal utilising radioactive materials or X-rays should be evaluated. Radiation limits for the use of such materials and X-rays should be in accordance with the limits set forth by the regulatory authority for such materials (BARC - Bhabha Atomic Research Center, Mumbai).

*Special Concerns*

- Informed consent should be obtained before any diagnostic procedures.
- Information to be gained should be gathered using methods that do not expose participants to more radiation than exposed normally.
- In the event of death of a participant with radiological implant, due precaution as 'per radiation guidelines may be taken not to expose the relatives or the close cohabitants to radiation till safe.
- Research should be performed on patients undergoing the procedures for diagnostic or therapeutic purposes.
- Safety measures should be taken to protect research participants and others who may be exposed to radiation.

- The protocol should make adequate provisions for detecting pregnancies to avoid risks of exposure to the embryo.
- Information must be given to participant about possible genetic damage to offspring.
- Nonradioactive diagnostic agents are considered as drugs and the same guidelines should be followed when using them.
- Ultrasound should be substituted wherever feasible.

### Clinical Evaluation of Traditional *Ayurveda, Siddha, Unani*(ASU) Remedies and Medicinal Plants

Self-medication and greater orientation towards preventive health care, the growing desire of the aging population to stay young and healthy, and the increasing health care costs of therapy provided by Modern Medicine have led to more usage of traditional remedies. However, the improved research technology tools and growth deciders like new Biotechnology developments for producing the evidence, together with media publicity have catapulted traditional knowledge to the status of a hidden treasure worth exploring. Nevertheless, subjecting traditional remedies to the same rigours that synthetic drugs undergo to establish their safety and efficacy is a difficult proposition, as most of them are complex combinations leading to difficulty in assessment of their activity and risk/benefit ratio. This involves four sets of issues chemical-manufacturing-control (CMC) issues, nonclinical issues, clinical issues, and ethical issues.

The recognized traditional systems in India are *Ayurveda, Siddha* and *Unani* besides Yoga and Naturopathy and Homeopathy. The two unique features of herbal products used in the traditional Indian medical systems are that they are mostly used in compound forms and are multicomponent mixtures including minerals in some of the formulations, and that substantial information is available regarding their prior human use vouchsafing safety and efficacy of these formulations. Therefore, an approach different from that for evaluation of synthetic drugs is required which concerns two groups, namely, clinical investigators evaluating the benefits and risks of herbal products and the regulatory authorities.

For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic System and which may later be used in allopathic hospitals, the procedures laid down by the office of the Drugs Controller General of India for allopathic drugs should be followed. This does not pertain to guidelines issued for clinical evaluation of *Ayurveda, Siddha* or *Unani* (ASU)drugs or formulations by experts in those systems of medicine, which may be used later in their own hospitals and clinics. All the general principles of clinical trials described earlier pertain also to herbal remedies. However, when clinical trials of herbal drugs used in recognized Indian Systems of Medicine and Homeopathy are to be undertaken in Allopathic Hospitals, association of physicians from the concerned system as coinvestigators/collaborators/members of the expert group is desirable for designing and evaluating the study.

#### *Special Concerns*

The ASU drugs include herbal and herbo-mineral formulations. The herbal products can belong to one of the three categories given below:

1. A lot is known about the use of a plant or its extract, metals, minerals and animal products in the ancient *Ayurveda, Siddha* or *Unani* literature or the plant

may actually be regularly used by physicians of the traditional systems of medicine for a number of years and the substance is to be clinically evaluated for same indication for which it is being used or as has been described in the texts.

2. When an extract of a plant or a compound isolated from the plant and any compound formulation having plants, metals, minerals and animal products as ingredients has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different, it has to be treated as a new substance or new chemical entity (NCE) and the same type of acute, subacute and chronic toxicity data will have to be generated as required by the regulatory authority for synthetic products before it is cleared for clinical evaluation.
3. An extract or a compound isolated from a plant and any compound formulation having plants, metals, minerals and animal products as ingredients which has never been in use before and has not ever been mentioned in ancient literature, should be treated as a new drug, and therefore, should undergo all regulatory requirements before being evaluated clinically.

It is important that plants and ASU remedies currently in use or mentioned in literature of recognized Traditional System of Medicine is prepared strictly in the same way as described in the literature while incorporating GMP norms for standardization. Since traditional remedies have short life, increasing their stability and shelf life, and controlling their batch to batch variation could be challenging tasks for modern scientists and drug controllers to justify the beneficial effects of stored formulations.

*Category I:* For formulations belonging to this category, it may not be necessary to undertake phase I studies. In Phase II dose ranging should be explored to find the effective dose as also maximum tolerated dose. RCTs would be the preferable methodology to validate the claim with placebo or standard drug depending on the ethical requirement. The clinical trials would mostly fall in the noninferiority group, if literature is not available regarding the proven efficacy of the formulation. Superiority trial could be designed, if the control arm is placebo or modern medicine, which is only weakly effective. Sometimes it would also be right to design pilot observational studies to explore feasibility of conducting larger trials for validation if the outcome is encouraging.

It needs to be emphasized that since the substance to be tested is already in use in Indian Systems of Medicine or has been described in their texts, the need for testing its toxicity in animals has been considerably reduced. Neither would any toxicity study be needed for phase II trial. This is the unique reverse pharmacology approach for evaluating traditional formulations for traditional indication. If there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months it would be necessary to undertake 4 to 6 weeks toxicity study in 2 species of animals in the circumstances described above or when a larger multicentric phase III trial is subsequently planned based on results of phase II study. Clinical trials with ASU preparations should be carried out only after these have been standardized and markers identified to ensure that the substances being evaluated are always the same. However, Good manufacturing Practices (GMP) standards for the formulations to be tried would not be required for Phase I and II trials. But for Phase III GMP standards would be required for the formulations to be

used in the trial as the number of participants would be larger and this will be followed by marketing approvals.

*Category II and III:* All the steps involved for regulatory approvals as in the case of synthetic drugs should be followed. However, for formulations falling under category two only limited toxicities as mentioned for category I would apply.

All formulations involving herbal component should satisfy following criteria as prescribed by WHO document "Operational Guidance: Information needed to support clinical trials of herbal products (2005)":

a. **For Phase I/II studies-**

*Herbal substance:*

- Description of the plant: Genus, species (cultivar where appropriate); region(s) and country(ies) of origin; time of harvest; parts to be harvested
- Plant processing: drying, mechanical disruption, solvent extraction (aqueous or organic solvents, others)
- Analytical procedures
- Specification
- Storage conditions/shelf life.

*Herbal product:*

- Amount of active ingredient
- List of excipients
- Type of product (tablet, capsule, etc.) and its method of manufacture
- Analysis of putative active ingredient(s) via chemical or biological parameters
- Analysis of a sizeable chemical constituent (analytical marker compound)
- Analysis via chemical fingerprint (analytical markers)
- Analysis for lack of contamination by pesticides, herbicides, heavy metals, synthetic drug adulterants, microbials, toxins, etc.
- Dissolution studies
- Storage conditions and stability over the length of the trial
- Specification against which a certificate of analysis can be assessed before the clinical trial material is released.

b. **For Phase III studies:** Performing generally the same procedures as for Phase I/II trials, but more extensively and with more stringent oversight.

*Herbal substance:*

- As above for Phase I/II trials.

*In addition:*

- Statement that the plant is cultivated according to Good Agricultural Practices or harvested according to Good Wildcrafting Practices
- Reference batch.

*Herbal product:*

- As above for Phase I/II trials

*In addition:*

- Environmental impact statement.

On account of the substantial use of traditional ASU formulations both in animals and humans this relevant information should be included in the protocol for evaluation of these products. This helps in analysis of the chemistry, manufacturing, and control of the product. The manufacture of the product should ideally be as per traditionally processed formulation to endorse the claim for efficacy as seen in traditional practice.

As the extracts of herbal products and ASU formulations are mixtures of at least partially uncharacterized constituents it is claimed that such a mixture provides a therapeutic advantage, since the unknown constituents may be additive or synergistic in action or may produce a balance to counteract adverse effects of anyone constituent. This may thus provide more efficacy than would be provided by the known constituent alone. Thus, purification of the medicines down to known or otherwise single chemical constituents is not required as it may lead to lose of the advantage provided by the mixture.

For standardization and quality control analysis of the active pharmaceutical ingredient(s) may be best approached by analysis of one or more active biomarker(s), analysis of a chemical constituent that constitutes a sizable percentage of the total ingredients, and a chemical fingerprint of the total ingredients. The latter two analyses would act as surrogates for analysis of the unknown constituents that contribute to efficacy. In order to have the best standards by minimizing variation of content from batch to batch several analytical procedures may be needed to adequately quantify the constituents of herbal products or ASU formulations.

### *Quality Control*

Contaminating herbicides and pesticides levels as well as toxic contaminations must be particularly addressed in maintaining the quality control of the herbal or herbomineral formulation. The presence of adulterants should also be ruled out.

For traditional ASU formulations extraction may be done as per classical method or by a special SOP prepared for it. Information on each individual plant species used as ingredient must be collected and authenticated and maintained as voucher specimens. The plant ingredient should be subjected to pharmacognosy and other relevant analysis in phytochemistry.

Formulations intended for administration in clinical trials should be prepared in bulk after standardization, and quality control. The stability and shelf life studies should also be carried out simultaneously for marketing purposes.

The recommendations made earlier regarding informed consent, inducements for participation, information to be provided to the participant, withdrawal from study and research involving children or persons with diminished autonomy, all apply to trials on plant drugs also. These trials have also got to be approved by the appropriate scientific and ethical committees of the concerned Institutes. *However, it is essential that such clinical trials be carried out only when a competent Ayurveda, Siddha* or *Unani* physician is a coinvestigator in such a clinical trial. It would be neither be ethically acceptable nor morally justifiable, if an allopathic physician, based on references in ancient literature of above-mentioned traditional systems of Medicine, carries out clinical evaluation of the plant without any concept or training in these systems of medicine. Hence, it is necessary to associate a specialist from these systems and the clinical evaluation should be carried out jointly by following the outcome parameters prescribed in each system.

When a folklore medicine/ethnomedicine is ready for commercialization after it has been scientifically found to be effective, then the legitimate rights/share of the Tribe or Community from which the knowledge was gathered should be taken care of appropriately while applying for the Intellectual Property Rights and/ Patents for the product.

# CHAPTER V: STATEMENT OF SPECIFIC PRINCIPLES FOR EPIDEMIOLOGICAL STUDIES

## INTRODUCTION

Epidemiology is defined as the study of the distribution and determinants of health related states or events in specified populations and the application of this study to control health problems. Epidemiological studies are of primary importance in a large developing country like ours, where the natural history, incidence, prevalence and impact on morbidity and mortality of a variety of diseases are not known. Such studies are on large scale and assist in improving the public health which includes patients, healthy people and communities.

It has usually been considered that epidemiology of infectious diseases is of prime importance in our country. However, the evolving pattern of change in the society with upward economic mobility and increasing a number of middle class population would mean that a significant number of lifestyle related diseases, such as Ischemic Heart Disease, are increasing. The Framingham Heart Studies in USA illustrates how epidemiological data collected on risk factors for cardiovascular diseases helped in planning measures to prevent and control them. Such information in India could be undertaken as long-term cohort studies in different population groups.

Epidemiological studies are generally considered in two categories—Observational and experimental. Designs of these studies are based on cross-sectional, case-control or cohort approaches. Epidemiological studies cover research, programe evaluation and surveillance. Ethics in epidemiological studies is multidimensional covering clinical medicine, public health and the social milieu. The code of ethics is much better understood for clinical research, where the interaction between a patient and a clinical researcher is of supreme importance. In epidemiological research, the researcher is dealing with a group of individuals and the questions faced by an epidemiologist are more than a professional nature. These questions would pertain to interaction with an individual participant, sources of funding or employer, fellow epidemiologist and the society at large. Need for a code of ethics for epidemiologists is being recognized globally and the issues for such a code in the context of epidemiological research in India deserve attention.

Epidemiological research differs from clinical research in the context of the large number of study participants and generally a long time frame. If some mistakes or aberrations get detected during the course of conduct of such studies, repeating the whole exercise will be expensive, time consuming and may not even be feasible. Hence, utmost care needs to be taken for various aspects—technical, practical and ethical.

## DEFINITIONS

### Observational Epidemiology

In observational studies, predefined parameters in a defined population group over a specified period and frequency are recorded for studying exposure to risks affecting health. These may be of the following types:

*Cross Sectional Studies (Surveys)*

This is a primarily population based and involves in selecting an entire population or random samples of the representative population based on census data and then using questionnaires to understand the prevalence of various diseases. Its aim is to assess aspects of the health of a population or to test hypotheses about possible cause of disease or suspected risk factors. The study participants are directly contacted only once in the defined period for which informed consent is required to be taken.

*Case Control Studies*

This usually compares the past history of exposure to risk among patients who have a specified condition/disease (cases) with the past history of exposure to this among persons who resemble the cases in such respects as age, sex socioeconomic status, geographic location but who do not have the disease (controls). Case control studies can be done by following-up available records, usually records in a hospital, but in the context of a country like ours, it may require direct contact between research workers and study participants and informed consent to participate in the study is necessary. However, if it entails only a review of medical records, informed consent may not be required and indeed may very often not be feasible but for such waiver of consent approval from IEC would be necessary.

*Cohort Studies*

These are longitudinal or prospective studies of a group of individuals with differing exposure levels to suspected risk factors. They are observed over a long period usually several years. The rate of occurrence of the condition of interest is measured and compared in relation to identified risk factors. It requires a study of large number of participants for a long time and involves asking questions, checking of records, routine medical examination and sometimes laboratory investigations. Individuals are being followed-up as the cohort and it is essential to identify precisely every individual to be studied.

**Experimental Epidemiology**

In experimental epidemiology, the investigators alter one or more parameters under controlled conditions to study the effects of the intervention on health. These are usually randomized controlled trials done to test a preventive or therapeutic regimen or the efficacy of a diagnostic procedure. Although, these are strictly speaking epidemiological studies, they come under the purview of clinical evaluation of drugs/devices/products/vaccines etc. The possibility of use of placebo as one of the arm of the trial should be explained and informed consent taken in such studies.

## GENERAL PRINCIPLES

General ethical principles of respect for persons, duty to maximize possible benefits and minimize possible harm are important considerations in ethical guidelines. At the same time, it is essential that all individuals in an epidemiological research are treated alike keeping in mind the rules of distributive justice. The welfare of the individual has to be balanced against the welfare of the community and society at large. The CIOMS/WHO Guidelines for Epidemiological Research assume that the

individuals or populations being studied are capable of giving informed consent understanding the implications of the study. With large segments of our population, given their level of education, the full understanding in the sense of industrialized countries may not be achievable. How the principle of "do no harm" is ensured under such circumstances without being paternalistic, is a major issue that has to be taken into consideration in ethical guidelines. In cohort or survey techniques for incidence and prevalence of various diseases, a major issue that has to be considered is how much of intervention is justified and whether one is justified in withholding interventions. For example, if you are looking at longitudinal morbidity in a population group, should you give them health education that is well established with regard to preventive aspects or should you leave them alone so that the natural evolution of the disease can be studied? Health education or other interventions including nonhealth interventions can be quite expensive. An alternate strategy that may be followed is to make curative therapy available to the population at their own request. This usually involves in running a clinic which is readily accessible to the population without any other intervention. However, it is generally considered unethical to withhold intervention or services.

Surveillance studies to obtain true disease burden rates most likely to give rise to ethical dilemmas regarding maintenance of confidentiality and prevention of stigmatization. So is the case with studies on postdisaster events, mental health and evaluation of health programs. Wherever applicable anonymisation could solve these problems when the information is required to be placed in public domain.

## SPECIFIC PRINCIPLES

1. *Informed Consent:* When individuals are to be included as participants of any epidemiological studies, the purpose and general objectives of the study has to be explained to them, keeping in mind their level of understanding. It needs to be ensured that privacy will be maintained. In the context of developing countries, obtaining informed consent has been considered many times as difficult/impractical/not meeting the purpose on various grounds such as incompetence to comprehend the meaning or relevance of the consent and culturally being dependent on the decision of the head of the family or village/community head. However, there is no alternative to obtain individual's informed consent but what should be the content of the informed consent is also a crucial issue. In spite of obtaining informed individual consent, it is quite likely that the participants/patients may not be fully aware of their rights. In this context, the role of investigator is crucial and she/he should remain vigilant and conscious of her/his obligations towards the participants/patients, all through the course of the studies.
2. In most epidemiological research, it would be necessary to have the consent of the community which can be done through the village leaders, the Panchayat head, the tribal leaders, etc. who are considered to be gate-keepers of the society/community.
3. In obtaining the consent of individuals or communities, it is important to keep in mind that working through peer groups or through Panchayat etc. may mean that the individuals or community would feel reluctant to disagree and

refuse to give consent because of societal pressures. This is something that has to be carefully avoided.

4. Particularly in a country like India, with the level of poverty that is prevalent, it is easy to use inducements, especially financial inducements to get individuals and communities to consent. Such inducements are not permissible. However, it is necessary to provide for adequate compensation for loss of wages and travel/other expenses incurred for participating in the study.
5. All risks involved including the risk of loss of privacy must be explained to the participants in an epidemiological study. Steps should be taken to maintain utmost privacy which should be informed to the community.
6. Maintaining confidentiality of epidemiological data is absolutely essential. A particular concern is the fact that some population based data may also have implications on issues like national security and these need to be carefully evaluated at the beginning.
7. All attempts should be made to minimize harm to the individuals and society at large. Special consideration for the cultural characteristics of the communities that are being studied is essential to prevent any disturbance to cultural sensitivities because of the investigation.
8. The design of the study should ensure that the benefits of the study are maximized for the individuals and communities taking part in the study. This means that at the onset itself the investigators should design the way in which the results of the study are going to be communicated and also decide whether individuals identified at particular risk during the course of the studies would be informed. It may also be necessary in some instances to inform the concerned family members about the results, for instance, as in AIDS, STD, etc. It may not always be possible to communicate study results to individuals but research findings and advice should be publicized by appropriate available means. It is also important that the beneficial results of epidemiological studies are fed into the health system and necessary training modules should be developed as part of the epidemiological project.
9. In all situations where there is likely to be conflicts of interest, it must be ensured that the interest of the individuals involved in the study are protected at all cost, e.g. for studies on outbreaks, epidemics, disasters and calamities, and epidemiological studies undertaken by providers of relief and rehabilitation.
10. Scientific objectivity should be maintained with honesty and impartiality, both in the design and conduct of the study and in presenting and interpreting findings. Selective withholding of data and similar practices are unethical.
11. Benefits : When epidemiological studies (like those on mortality and morbidity as a result of exposure to an agent) lead to long associations with the community, the results if released in timely manner could give improved health care facilities or educate the community to reduce the impact of adverse environment on health and tackle the problem at their end in time.
12. Ethical Review Procedures: In all Ethical Committees at least one or two individuals with an understanding of the principles of epidemiological ethics have to be included. These Committees should be independent and comprise of epidemiologists, clinicians, statisticians, social scientists, philosophers, legal experts and representatives from community/voluntary groups who should

be aware of local, social and cultural norms, as this is the most important social control mechanism.

13. Distinction between research and program evaluation: It is difficult to make a distinction between epidemiological research and program evaluation. Whenever a program is evaluated and surveillance is launched, the monitoring and evaluating mechanisms should clearly be planned and cleared by IEC before initiation as is done in all epidemiological studies.

It is not always possible to know what will happen to the participants as unexpected results or undesirable events can sometimes occur. Very often the benefits and risks of the research pertain not only to the individual participants but also the community from which they are drawn. Therefore, the participation of local community representatives in planning, conducting and monitoring research is important to avert circumstances which may be detrimental to the participants' welfare. This also helps in improving the vision of the researcher regarding the objectives and the design of study. The inclusion of a community representative to act on behalf of all participants involved in a research study Communities should be informed by the research, possible outcomes (positive and negative), and the result of the research. Research findings belong to participants and their communities as well as the researchers and the research representatives and researchers can work together to make sure that research is conducted in the most appropriate way and the benefits if any, could be shared in a reasonable or workable manner.

## COMMUNITY PARTICIPATION

A community can be defined as a group of people sharing the same location, beliefs, culture, ideals, goals, age, gender, profession, lifestyle, common interests, geographical locations or settings or disease. When research participants are drawn from a specific community, members of that community can be involved to discuss any concerns which may have regarding the research. In different ways such a dialogue can be facilitated. If an ethics committee does not have a member from the community, which may ask a local community representative to be the voice for all participants. On the other had, community representatives can formally join together to form a group termed as Community Advisory Board, Community Working Group, or Community Advisory Group, which takes part in the research at all stages of the study. In international studies, representation from this ensures that the community's health needs and expectations are addressed, informed consent is appropriate and access to research benefits is provided through research that is designed and implemented in the best interests of science and community.

Community representation should be involved before, during and after the study. Before the study is initiated the community is informed to see if it agrees that the research addresses a need or problem relevant to that community and to confirm that the design is culture specific and brings some benefits to research participants or the community. Since, some risk may be associated to the community representation, is needed to assist in developing appropriate ways to protect the participants. During the study, the association with community representatives continues to educate others about the research and to alert the researcher to ethical issues related to the research. After the study is completed, community representatives can help in making the results known to the entire community.

However, application of research findings may take a long time, which the community representatives should be made to understand. The benefits may be participants' and community's access to intervention whose responsibility and conditions under which this would be done, duration of availability of intervention, methods of improving the quality of health care in the community and any expected desirable behavioral change in the community should be clearly explained to community by the Ethics Committee or community representatives.

## CHAPTER VI: STATEMENT OF SPECIFIC PRINCIPLES FOR HUMAN GENETICS AND GENOMICS RESEARCH

### INTRODUCTION

In no other area of biomedical research there has been a greater concern for ethical issues than in the field of human genetics. It has largely stemmed from practice of eugenics by Nazis. In recent years, this concern has grown even further because of the possibility of commercial eugenics. While the advent of recombinant DNA technology has provided one of the most powerful tools in the hands of mankind to unravel the mysteries of the human genome. It has also led to a great deal of concern about our ability to handle such information. With the successful completion of Human genome sequencing in June 2000, clear-cut guidelines were laid and disseminated this information to all stakeholders through media and public debates for improving awareness and understanding of human genetic disorders amongst public, the majority of whom have little knowledge of genetics was initiated.

The knowledge about human genes and genetic diseases prior to 50's was so poor that there was hardly any human genetic experimentation. Since then, especially in the recent decades. In the field of human genetics, there has been a veritable explosion in knowledge which has culminated in gene therapy (the ultimate in therapy for genetic diseases) and various other therapies based on genetic engineering. Termination of pregnancy or selection of embryos to avert birth of a genetically abnormal child, possible discrimination by insurers and employers because of genetic trait, tailored development of stem cells from embryos created by conception, *in vitro* fertilisation or nuclear transfer for regenerative therapy or organ transplantation and potential for producing designer babies as per whims and fancies of parents or even society have been subject of fierce public debate. Serious issues are raised by genetic research because it can potentially create conflict between the rights and freedoms of the individual versus that of the family and the society at large particularly when it involves human embryo and vulnerable population not competent to give informed consent. Besides the Human Rights issues of dignity, autonomy and justice, the Human genome project (HGP) has also precipitated an unprecedented concern for Intellectual property rights. Earlier experiments on cloning sheep and mice have brought human cloning into the realm of active debate raising additional set of ethical, legal and social issues (ELSI). While there should be no restrictions in availing the gains of latest technology, which are beneficial to the mankind, any potential harm should be contained. In fact, ensuring access to genetic services to all irrespective of their ability to pay, particularly to those who need it the most, is an equally important moral concern.

Other issues relate to property rights on biological samples, patenting of DNA sequences and potential for bio-terrorism. In this rapidly evolving field, there is a need to continuous monitor such developments and respond to emerging ethical issues promptly and judiciously.

## GENERAL GUIDELINES

Clinical research in the area of human genetics and human genome, including gene therapy, is subject to general ethical considerations of protection against harm and voluntariness of participation. It concerns not only the individual but also the family, community or society from which she/he has been drawn. Therefore, the additional considerations are:

i. The harm may not only be physical, but also psychosocial which may produce anxiety and depression or damage familial relationship. This should be safeguarded. Appropriate communication skills are necessary for genetic counseling. There is a likelihood of social stigmatization and discrimination in schooling, employment, health and general insurance, which requires much greater care in recruiting participants in research study, obtaining informed consent and maintaining confidentiality of research findings than in any other area of research.

ii. There is a great importance of spoken word in medical genetics, since genetic counseling is akin to therapy in other fields. In that sense in medical genetics, the 'word' is equivalent to drug/intervention in other fields of medicine. Written explanation understandable to layman about presentation and natural course of the disease, interventions available and their outcome as also implication of the information for progeny and family, has special place in clinical research in this field.

iii. Genetic counseling deals with discussion on personal matters such as reproductive options, and the couple may have to make a choice with far reaching social implications. Therefore, it calls for special care that should be documented in research proposals and carefully considered by the Institutional Ethics Committee.

iv. Genetic manipulations have consequences for the future, some of which are unknown. Hence, greater care towards potential dangers is necessary.

v. There is greater likelihood of situations cropping up where there is a conflict of interest between an individual and that of family and society at large. Careful guidelines need to be evolved by peers in the profession to tackle such situations. The professional societies should actively participate in these activities.

vi. The science of Medical Genetics is progressing very rapidly. Therefore, there is a need for frequent updating of any guidelines for research in this field. To meet this challenge not only the guidelines should be flexible but there should also be a built-in mechanism to review the guidelines from time to time.

vii. The Institutional Ethical Committees reviewing research proposals related to research on human genetics should have necessary expertise which includes knowledge of latest developments in the field of human genetics. In areas of doubt, open discussion should be encouraged. This has to be the responsibility of National agencies, e.g. Central Ethical Committee (ICMR) and/or National

Bioethics Committee (DBT) to organize national debates on such issues to evolve consensus on them.

viii. Concerned with the misuse of genetic tests, particularly for the pre-selection of sex, the Government of India has enacted a law known as "The Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act 1994". All researchers in this area, shall follow the provisions of this Act (and such other acts which may be passed in future). In 2003, this Act was amended to include the Preconceptual diagnostic technique also.

## PEDIGREE STUDIES

These involve obtaining history of other members of the family of the proband under investigation. It may reveal information about the likelihood of individual members of the family being either carriers of genetic defects or being affected by the disease. Special privacy and confidentiality concerns arise in genetic family studies because of relationship between the participants. It should be kept in mind that within families each person is an individual who has the right to keep the information about himself or herself confidential. Family members are not entitled to know each other's diagnosis. Before revealing medical or personal information about individuals to other family members, investigator must obtain consent of the individual to do so. In view of the cultural background of our country where woman is still a vulnerable and exploited participant, revealing information to the husband that his wife is the carrier of balanced chromosomal translocation (leading to recurrent abortions or a genetic syndrome in her child) or that she is a carrier of a single gene causing 'X' linked or recessive disease, may lead to grounds for a divorce despite the fact that the husband himself is a carrier of the autosomal recessive disorder. While general principles of counseling require presence of both the spouses, necessary care must be taken not to end up in breaking the families.

### Participant Recruitment

The familial nature of research cohorts involved in pedigree studies can pose a challenge for ensuring that recruitment procedures, are free of elements that unduly influence decision to participate. The very nature of research exerts pressure on family members to take part because more complete the pedigree, the more reliable the resulting information. Problems of the following kind could arise:

i. Revealing who else in the family has agreed to participate may lead to breach of confidentiality.
ii. If a proband is used, out of personal interest she/he may put undue pressure on relatives to enroll in the study.
iii. Direct recruitment by telephone calls, etc. may be seen as an invasion of privacy by family members.
iv. Contact to personal physicians may imply that their health care may get compromised if they do not agree to participate.

There is no satisfactory alternative which can be recommended. The likely problems are listed, so that appropriate caution may be exercised.

### Informed Consent

For biogenetic research involving human participants, certain special considerations have to be kept in mind while obtaining informed consent of the prospective participants enrolled in the study. These are in addition to general principles that are applicable to all medical research. Since genetic research gives rise to information applicable to the community from which the participants were drawn, 'group consent' will have to be taken from culturally appropriate authority like community head where there are no relevant authorities like village panchayat head. The ethic committees should ensure that this has been applied wherever applicable.

### Confidentiality of Data

This includes codification of the biological samples, where necessary.

a. The investigator must establish secure safeguards for the confidentiality of the research data. Participants should be told of the limits of the investigator's ability to safeguard confidentiality and of the anticipated consequences of breach of confidentiality.
b. Genetic data should be delinked to maintain confidentiality. If the result of the research is of benefit to the health of the participant then, with the approval of ethics committee re-link could be established for communication of the result.
c. When commercial companies are involved in research, it is necessary to protect researchers and participants from possible coercion or inducement to participate in the study.
d. Academic institutions conducting research in alliance with industries or commercial companies require a strong review to probe possible conflicts of interest between scientific responsibilities of researchers and business interests (e.g. ownership or part-ownership of the investigator in the company developing a new product). In cases where the Ethics Committee determines that a conflict of interest may damage the scientific integrity of a project or cause harm to research participants, it should advise accordingly. Institutions need self-regulatory processes to monitor, prevent and resolve such conflicts of interest.
e. Prospective participants in research should also be informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research.
f. Undue inducement through compensation for individual participants, families and populations should be prohibited. This prohibition, however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care or of information infrastructure, reimbursement costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes.

### Defining Risks and Benefits

Potential risks and benefits should be discussed thoroughly with prospective participants. In genetic research, the primary of risks are psychosocial rather than physical. Adequate counseling should be given to participants on the meaning of genetic information they receive. Only those persons who are qualified and

experienced in communicating the meaning of genetic information should undertake genetic counseling.

## GENETIC SCREENING

Genetic screening implies search in population of individuals who have, or are susceptible to have a serious genetic disease; or who, though not at risk themselves, are carriers and thus at risk of having children with the particular genetic disease. It is essential that screening must be purposive. Also, besides validation of screening tests, it shall also be ensured that a suitable intervention is possible. Rarely, screening may be permissible to allay anxiety but it should not be forgotten that response of different individuals might vary, therefore, the need may be carefully evaluated by the health care provider. Depending on nature of the genetic defect that is identified and its pattern of inheritance, siblings and other blood relations as well as existing and future offsprings may be affected. This raises ethical questions that differ significantly from the normal rules and standards applied to handling of personal medical records.

- A well informed consent is, therefore, essential. Those being screened are entitled to receive sufficient information in a way that:
  i. They can understand what is proposed to be done.
  ii. They must be made aware of any substantial risk.
  iii. They must be given time to decide whether or not they would like to participate or withdraw from screening.
- Details about the disorder to be screened and its inheritance pattern, reliability of the screening test and what will be done with the samples should be explained. Information about the implications of a positive screening test (abnormal) should also be explained.
- Confidentiality should be maintained in handling of results with emphasis on responsibility of individuals with a positive (abnormal) result to inform partners and family members. It needs to be emphasized that consent for screening or a subsequent confirmatory test does not imply consent to any specific treatment or termination of the pregnancy. Specific consent is required from the affected proband to share his/her genetic information with family members who may be benefited from it. In case of refusal duty of confidentiality shall weigh higher than the duty for beneficence to family members unless sharing of information is vital to prevent serious harm to the beneficiary in the family. In such case appropriate precautions may be taken to ensure that only the genetic information needed for diagnosis/treatment is shared.
- General guidelines have to be followed for a vulnerable individual, i.e. minors, mentally ill, prisoners, students, subordinates and people who do not speak the language of the investigator etc.
- Genetic counseling should be readily available for those who are being screened. Law protects confidentiality of medical information but this is not absolute. Information may be disclosed where it is in the public interest to do so, or if required by the court of law. However, great care is needed in this regard as well.

### Prenatal Testing

It is aimed at detecting presence of abnormalities in the fetus. The fetal sample for examination may be obtained through amniocentesis, chorionic villi sampling, placentocentesis, cordocentesis (blood sampling from the umbilical cord) and skin or other biopsies. Fetal cells in maternal circulation can also be used for prenatal testing. Noninvasive methods should be preferred whenever available.

### Screening New Borns

Screening of newborns is permissible to detect those genetic diseases like phenylketonuria where serious effects of the disease could be prevented by a suitable intervention such as special diet or treatment. It should not be done when there is no immediate cure/intervention for diseases manifesting later in life. The same applies to investigations to detect genetic, chromosomal, metabolic abnormalities, etc. The diseases can be screened as and when intervention/therapy becomes available in future.

### Screening of Children

Children should not be screened merely at the request of their parents. The child's autonomy should dominate over parental autonomy. The genetic testing for children should be deferred until they are able to comprehend and are able to participate in the decision making process, unless the intervention based on result of the test is likely to be of direct therapeutic benefit to them.

### Anonymous Testing

Researchers may conduct anonymous testing on general population in order to establish prevalence of genetic traits/diseases. Blood spots collected for screening newborns for treatable disorders could also be used for this purpose. In case information derived from stored specimens might be useful to an individual, the code of anonymity may be broken with the approval of the Institutional Ethics Committee (IEC).

## THERAPEUTIC TRIALS INCLUDING GENE THERAPY

### Recombinant Protein Products

Genetic disorders, which require replacement therapy like ADA deficiency, do not pose any ethical problem. Replacement with animal products should follow the rules as stipulated for other diseases.

### Gene Therapy

The goal of human genetic research is to alleviate human suffering. Gene therapy is a proper and logical part of this effort. Gene therapy should be subject to all the ethical codes that apply to research involving patients.

#### *Somatic Cell Gene Therapy*

Somatic cell gene therapy is the only method that may be permissible for the purpose of preventing or treating a serious disease when it is the only therapeutic

option. It should be restricted to alleviation of life-threatening or seriously disabling genetic disease in individual patients and should not be permitted to change normal human traits. However, rapid advance in science necessitates periodic review of guidelines in this area. This includes evaluation of safety and efficacy of DNA vaccines and transgenic foods as well.

Gene Therapy trial consists of two parts. The first part is preparation of the 'gene construct' to be administered, and the second part is evaluation of the efficacy and safety of the administered 'gene (construct)'. As far as the first part is concerned, the guidelines and clearance for it, is to be regulated by the National Bioethics Committee under Department of Biotechnology (DBT) and for the second part clearance from the local IEC and Central Ethical Committee (CEC) of the ICMR shall be obtained. Safety should be ensured especially because of the possibility of unpredicted consequences of gene insertion. All gene therapy trials should have the provision for long-term surveillance. Informed consent must be taken especially regarding uncertainties about outcome. Children could be candidates for therapy, if the therapy is meant for a childhood disorder.

### *Germ Line Therapy*

Germ line therapy is prohibited under the present state of knowledge in these areas.

### *Gene Therapy for Enhancement*

Gene Therapy for enhancement of genetic characteristics (so called designer babies) should not be attempted as we possess insufficient information at present to understand the effects of attempts to alter/enhance the genetic machinery of humans. Also, the influence of environmental interaction on the expression of genetic characters is poorly understood. It is not safe or ethical for parents to give, for example, growth hormone to their normal offspring in order to produce very large football or basketball players. Similarly, it would be unethical to use genetic engineering for improvement of intelligence, memory etc. even if specific gene/genes are identified in future.

### *Eugenic Genetic Engineering*

Eugenic Genetic Engineering for selection against personality, character, formation of body organs, fertility, intelligence and physical, mental and emotional characteristics is prohibited.

## HUMAN GENOME PROJECT (HGP)

The human genome project (HGP) was an international research effort, the goal of which was to determine the location of estimated 40 to 1,00,000 genes and to sequence the entire human DNA. Another component of the programme is to analyze the DNA of a set of non-human model organisms, which may contribute to understanding of the human genome. The project began formally in 1990 and has been completed by June 2000. This project has resulted in exploring the potential for profoundly altering our approach to medical care from treatment of advanced disease to prevention, based on the identification of individuals at risk, and designing it specific to targets/individuals. Implications of using this genetic knowledge pose a number of questions for:

i. Individuals and families – whether to participate in testing with whom to share the results, and how to act on them.
ii. Health professionals – when to offer testing, how to ensure its quality, how to interpret the results and to whom to disclose information.
iii. Employers, insurers, the courts and other social institutions – the relative value of genetic information to the decision they must make about individuals.
iv. Governments – about how to regulate the production, use of genetic tests and the information they provide and how to provide access to testing and counseling services for society.
v. The society – how to improve public understanding of science and its social implications and increase participation of the public in science policy making.

The scientific community should address the above mentioned questions before application of this knowledge could be considered as ethically valid.

## DNA AND CELL-LINE BANKING/ REPOSITORY

A biobank/repository is collection of resources that can be accessed to retrieve human biological material and data. Human tissue repositories collect, store, and distribute human tissue materials for research purposes. Repository activities involve three components: (i) the *collectors* of tissue samples; (ii) the *repository* storage and data management center; and (iii) the *recipient* investigators. The term biobank when broadly used may include physical samples as well as databases, and involve bioinformatics.

Biobanks serve as an important resource for studies on understanding the population dynamics and the pathogenesis of a large number of diseases. Human biological samples in biobanks include organs (heart, liver, kidney, lung, pancreas, etc.), tissues, cells (somatic and gonadal), body fluids or samples like serum, buffy coat, DNA, hair, nails, excreta, sweat, buccal scrapings etc. Research on banked human tissue samples is conducted in a laboratory, hence it does not directly involve the individuals. The steps involve the initial process of collecting, processing, freezing, "anonymizing", and storing tissue with its corresponding clinical information in a database. As tissue banking concerns research at a later time, the ethical issues pertain to consent requirements for the banking and further uses of tissue and DNA samples, their control and ownership, and the benefit sharing to the individual or community. Therefore, to prevent any exploitation and protect the rights of participants, the three main requirements are individual *informed consent*, approval of the *IEC* and the *Repository Ethics Committee, wherever applicable.*

### Repository Collections

#### *Unidentified Specimens*

Identifiable personal information was not collected or if collected, was not maintained and cannot be retrieved by the repository.

#### *Identified Specimens*

These specimens are linked to personal information in such a way that the person from whom the material was obtained could be identified by name, patient number, or clear pedigree location (i.e. his or her relationship to a family member whose identity is known).

**Research Samples**

*Unidentified Samples*

Sometimes termed "anonymous," these samples are supplied by repositories to investigators from a collection of unidentified human biological specimens.

*Unlinked Samples*

Sometimes termed "anonymized," these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being.

*Coded Samples*

Sometimes termed "linked" or "identifiable," these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information such as a name or other identifying number.

*Identified Samples*

These samples are supplied by repositories from identified specimens with a personal identifier (such as a name of person/patient number) that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained.

The sample collector must obtain informed consent of the donor for DNA banking or for cell-line transformation and banking. The process of seeking informed consent for purposes of banking must clearly be stated in addition to possible risks and benefits, the conditions under which samples from the Repository shall be provided to other researchers, how long the samples shall be preserved in the Repository and what will be the costs to individual researchers in obtaining samples from the Repository. The sample collector must also clearly inform every donor that he reserves the right to order destruction of his sample from the Repository at any time.

1. If any commercial use is made of the samples in the Repository, appropriate written benefit-sharing agreements, consistent with the policies stated earlier, must be jointly signed by the donor, sample collector and Repository in-charge. It is also desirable that community consultations are held prior to collection of samples to be stored in a Repository, and group consent is obtained before individual consent.
2. Any researcher who intends to use samples from a Repository must submit a statement of Research Intent, which must be approved by the Ethics Committee of the Repository, which shall be responsible for determining whether the intended research is consistent with the informed consent provided by the donor, and where applicable, of the group.
3. Unless scientifically essential, the Repository must not provide to an individual researcher any information linked to the samples. When linked information is to be provided, only the minimal information as required for the intended research shall be provided.
4. There should be appropriate Material Transfer Agreements with the Repository for depositing samples as well as for taking them out with clear reasons. Third parties must be allowed to take samples only after approval from Repository ethics committee.
5. The identity of the Repository from which samples were obtained must be revealed in all reports, patents or copyrights arising out of these samples.

6. Due intellectual property rights should be given while granting access to samples, through a contractual agreement.
7. For any publication resulting out of research from samples taken from repository, appropriate acknowledgement should be given to the original contributor of samples, sponsors of research, repository, donors and participants.

Detailed guidelines are also given in a separate booklet on biobanking or stored biological materials released by the Council in 2006.

### General Principles

An Ethics Committee exclusive to the Repository, the Repository Ethics Committee constituted as per the guidelines in the chapter on Ethics Review Mechanism, should play an important role in looking at the issues related to informed consent, privacy and confidentiality, risk-benefit analysis, benefit sharing, maintain linkages with other biobanks and repositories while adhering to the basic principles of bioethics viz. Autonomy, Justice, Beneficence and Non-maleficence.

#### *Primary Use*

By primary use it is meant that the biological material will be used for the intended purpose as described in the protocol submitted for approval from Ethics Committee. Ownership of the sample lies with the individual, family or community as the case may be. Local Ethics Committee should consider following points for approving primary use:

i. Consent should be in written form, given voluntarily by the donor who has the capacity to do so. The use of the samples shall be reserved for the defined purpose only.
ii. Participants have the right to withdraw at any time. This does not apply to anonymised samples.
iii. If sample is inadequate or contaminated re-contact is necessary for fresh and specific consent. This should be incorporated in the prior consent form.
iv. While obtaining data/samples from vulnerable subgroups with reduced autonomy, Ethics Committee should ensure that informed consent be obtained from legally authorized representatives in the presence of impartial witness. The risks and benefits should be adequately explained.
v. When samples have to be obtained for specific research from participants belonging to specified communities, permission of the group leader/local leader/authorities must also be obtained. However, individual consent should never be compromised even if permission of the gatekeepers/village panchayat.
vi. Group consent of the population/community should be obtained through its culturally appropriate authorities before sampling starts, particularly so for groupspecific research like genetic research.
vii. Samples obtained for archival purposes in a prospective study.

#### *Secondary Use*

Every request for secondary use shall be examined by the Institutional Ethical Committee to ensure that:

i. The proposed use does not transgress the original consent given for the earlier study and the validity of the objectives of the new study.

ii. Provisions for ensuring anonymity of the samples for secondary use are stated.
iii. After anonymising sample, results are not communicated to the donor.
iv. For postmortem uses of samples the permission of the next of kin, legally authorized representative should be obtained.
v. Waiver of consent is given whenever the donor is not traceable or the sample is anonymised.

## DNA DIAGNOSIS

The general principles of informed consent, confidentiality and other criteria used for any investigation in genetics should be followed. Since, the knowledge in this field is new and relatively complicated, a DNA test must be preceded and followed by appropriate genetic counseling.

### Pre-implantation DNA Diagnosis

It is a type of prenatal diagnosis. Some precautions and safeguards should be adopted for this purpose also.

### Pre-morbid Diagnosis in Children

Parents are advised not to get the diagnosis done especially in cases like Huntington's disease etc. for which there is no available intervention till the child reaches the age of proper "consent".

### Pre-morbid Diagnosis in Adults

It may be carried out with informed consent. However, appropriate genetic counseling must be provided and documented before offering such services.

### DNA Diagnosis in Forensics

The laboratories carrying out DNA diagnosis in forensics should follow the guidelines evolved by National Accreditation Board for Laboratories functioning under the Department of Science and Technology.

The consequences of DNA testing for conditions for which no treatment is available or for conditions manifesting late in life, e.g. breast cancer, Alzheimer's disease etc. should be seriously considered before embarking on such studies. Information so derived should not disclose the identity of the individuals.

## PRENATAL DIAGNOSIS

This should be performed only for reasons relevant to the health of the fetus or the mother. Prenatal diagnosis should not be performed solely to select the sex of the child (in the absence of an X-linked disorder). Sex selection, whether for male or female, denigrates the fundamental personhood of those yet to be born, and has the power to harm societies by unbalancing sex ratios. The potential harm to large groups of people outweighs any immediate benefits to individuals or families. The Government of India has already passed legislation banning diagnosis of sex for non-medical reasons. Prenatal diagnosis can be used to prepare parents for the birth of a child with a disability. Therefore, prenatal diagnosis should be available to

such parents who request it but oppose abortion, provided that they understand and are willing to accept the risks to the fetus.

In some cases, prenatal diagnosis may be performed to protect the health of the mother. These include clinically confirmed cases of morbid anxiety or situations where prenatal paternity testing would benefit the mother's mental health (e.g. if rape occurred while a couple was trying to conceive). Professionals should recognize the human and economic costs involved in prenatal diagnosis and should limit its use to situations where there is a clear benefit.

## DEFINITIONS

### Genetic Material/Genome

Genetic material refers to DNA or any other material carrying hereditary information in each cell of an organism. It consists of unique, single copies of genes, which make up approximately 10 percent of the DNA. The total informational content of an individual is known as 'genome'.

### Chromosome

The thread-like DNA in a cell is divided into several separate lengths. Each length forms a structure called a chromosome. There are two copies of each chromosome in every cell. Human cells contain 23 pairs of chromosomes.

### Gene

A gene is a length of DNA that contains the information needed to make one polypeptide. For example, the beta globin gene contains the information needed to make the beta globin polypeptide found in hemoglobin of red blood cells. More than one gene may be involved in making one protein, and more than one polypeptide may be formed from one gene as a result of alternate splicing.

### Genetic Engineering

It is the process of creating new DNA such as by cutting and patching (recombinant DNA technology). Several other technologies such as site directed mutagenesis, vector mediated integration or deletion of DNA, etc. have evolved and are continuing to evolve.

### Heterozygote

Each cell of an organism contains two copies of each gene. In a heterozygote, the two genes of a pair are different from each other (allelic).

### Homozygote

Each cell of an organism contains two copies of each gene. In a homozygote, both copies of the gene are identical to each other.

### Mutation

A process by which the DNA of an organism changes or mutates. In humans this can lead to disease such as thalassemia in which the mutation resultsin decreased

production of beta or alpha globin. The mutant gene is passed on from parent to the offspring, so the condition is inherited. In viruses and other infectious organisms, mutations can lead to emergence of organisms with new characteristics. It can make them more virulent or resistant to antibiotics, thus increasing their infectivity.

### Recombination

A cross-over between two members of a homologous pair of chromosomes results in the formation of a recombined chromosome wherein a new set of gene (allele) arrangement is created.

### Transgenesis

This refers to the introduction of a foreign gene into an animal or other organism. The transferred gene is called a transgene.

## CHAPTER VII: STATEMENT OF SPECIFIC PRINCIPLES FOR RESEARCH IN TRANSPLANTATION

### INTRODUCTION

The practice of transplantation is in its infancy in India. The exceedingly high-cost restricts its application, and also reduces the interest in research into this field. The same reason makes it imperative that Indian scientists should devise means of reducing the cost and improving the success rate, to make it feasible to increase the number of Indians who can benefit by this treatment. At present the protocols devised in the West are followed which are not necessarily ideal. Transplantation raises some specific ethical aspects, and these will have to be weighed in the light of ethical guidelines as applicable to Indian ethos. The problem has been considered with special reference to the following points:

i. Transplants from live or cadaver donors.
ii. Embryonic and fetal tissue and organ transplantation.
iii. Xeno-transplantation.
iv. Transplantation for cosmetic purposes.

### TRANSPLANTS FROM LIVE OR CADAVER DONORS

#### Definitions

*Cadaver*

A dead body. For purposes of this document, the term refers to a dead human body.

*Death*

This was originally defined as entire and continuous cessation of respiration and circulation. It has since been recognized that the heart could continue beating for a time, even for days, though the brain may have lost the ability to maintain respiration and sustain life. Death of the brainstem, also called brain death, has since been

recognized internationally, and in the 'Indian Transplantation of Human Organs Act', 1994.

### *Brain Death*

Specified in 'Transplantation of Human Organs Act, 1994' with 'Transplantation of Human Organs' Rules, 1995' the salient features are as described below:

- Entire, permanent, and irreversible cessation of functions of the brainstem —this is synonymous with brainstem death, since the centers for the control of essential body functions such as consciousness, respiration, and blood pressure are situated within the brainstem. In many countries strict criteria for diagnosis of brain death have been established. These include the presence of deep coma, the absence of any brainstem functions such as spontaneous respiration, pupil reactions, eye movements, gag and cough reflexes, and the exclusion of low body temperature and drugs as relevant to the comatose state. The EEG is a useful (but not essential) confirmatory test. Brain death is when 'damage is judgd irremediable based on its context, the passage of time, and the failure of all attempts to remedy it. Secondly, all possible causes of reversible brainstem dysfunction, such as hypothermia, drug intoxication, or severe metabolic upset, must be excluded. Finally, the absence of all brainstem reflexes must be demonstrated, and the fact that the patient cannot breathe, however strong the stimulus, must be confirmed.
- When testing the brainstem reflexes, the following normal responses must be looked for: (1) constriction of the pupils in response to light, (2) blinking in response to stimulation of the cornea, (3) grimacing in response to firm pressure applied just above the eye socket, (4) movements of the eyes in response to the ears being flushed with ice water, and (5) coughing or gagging in response to a suction catheter being passed down the airway. All responses have to be absent on at least two occasions with an interval of six hours between them. Apnea, which also must be confirmed twice, is assessed by disconnecting the patient from the ventilator, (prior to this test, the patient is fully oxygenated by administering 100 persent oxygen for several minutes to ensure that the patient will not suffer serious oxygen deprivation while being disconnected from the ventilator). The purpose of this test is to establish the total absence of any inspiratory effort as the carbon dioxide concentration in the blood (the normal stimulus to breathing) reaches more than sufficient levels to stimulate any respiratory center cells that may still be alive.

### Guidelines on Live Donor Transplants

1. Donation from a live donor should be restricted to renewable tissues like bone marrow, or to a paired organ, which on removal will not greatly alter, physiological functions, as in the case of the kidney. Since the removal of an eye will compromise binocular vision and produce disfigurement, it should not be permitted in a live donor.
2. Surgery on the donor inflicts bodily harm on him or her, the extenuating circumstances being the saving of another human life. It is imperative that no risk be imposed on the donor beyond that inherent in surgery and the loss of a vital organ. Any manner of experimentation, though it may be intended to improve the survival of the graft, should be prohibited if there is the slightest

extra risk to the donor. Examples are pretreatment of the donor with immunosuppressive or anticoagulants.

3. Every such research project should be preceded by careful assessment of predictable risks and compared to foreseeable benefits and improvement in the success rate of transplantation.
4. The interests of the donor should always take priority over those of the recipient of the transplant.
5. In view of the risk involved, the voluntary consent of the donor is absolutely essential. Further, the donor should be informed of all possible risks in a manner easily understood by the participant before the consent is taken.
6. It follows that the donor should have the legal capacity to give consent and be in a position to exercise free power of choice without the slightest element of force, duress, or coercion, and should have sufficient knowledge and comprehension as the participant to be able to make a decision with full understanding of the consequences. Children and mentally incompetent adults as also individuals with restricted autonomy should not be used as organ donors or as participants for such experiments.
7. Since the experiment would have consequences for the recipient too, the donor must be fully informed of the nature of the procedures and the possible effects on the recipient before consent is taken.
8. The responsibility of providing the above information to the donor, and of making sure that she/he understands fully the implications of what is to be done and what he or she consents to, rests entirely on the individual who directs the research project.
9. The experiment should be such as to yield fruitful results for the overall good of the donee without any risk to the life of the donor. The experiment should be undertaken only if there is no other method available of finding the answer to the question raised.
10. The experiment should be so planned and conducted as to avoid all unnecessary risks to the donor, to the organ to be transplanted, and to the recipient of the organ. Proper precautions should be taken and adequate facilities should be available to protect the donor from the most remote possibility of harm.
11. The donor should be at liberty to withdraw from the experiment and to abrogate the consent given earlier, with no requirement to offer any explanation of the reasons for his or her doing so.
12. If at any time during the course of the experiment the investigator comes to know that there is risk to the donor or to the recipient as a result of the procedure, it is her/his responsibility to terminate the experiment forthwith.
13. This does not preclude any treatment or procedure done on the organ or tissue after removal from the donor's body, aimed at reducing its antigenicity and improving graft survival. Creation of human beings for transplantation purposes should be banned.

**Guidelines on Cadaver Donor Transplants**

1. Every one should give a thought to the need for organ donation after death. In such an event one should make a decision and inform the next of kin, and register oneself with an appropriately constituted authority. Where one is opposed to donating her/his organs, this too, should be made known to the

next of kin, so that this wish of the deceased may be respected after death. Such a *Living Will* is in vogue in a number of countries in the world.

2. If consent for organ donation is given prior to death in the presence of two or more witnesses, consent for transplantation of organs should be presumed and permissible without seeking further consent from relatives.
3. In the absence of such prior directions from the deceased, the person in lawful possession of the body will make the decision to use the organs or not, as he may think fit, after consultation with the family.
4. It is important that the medical team uses the body only for the purpose for which consent has been given.
5. Remaining tissue and organs should be treated with the respect due to a human body, and will not be used for any purpose to which explicit consent had not been given unless anonymized.
6. Under no circumstances should financial gain be made from any such procedure.
7. There shall be no coercion and no monetary inducements offered to the family of the prospective cadaver donor.
8. Confidentiality of the donation must be maintained on both sides: The recipient and her/his family will not be informed of the identity of the donor, and the family of the donor will equally be kept unaware of who receives the donated organ. This is essential to avoid any form of exploitation by the donor's family.

**Guidelines on Recipients of Transplants**

1. The patient with failure of a vital organ is at a particular disadvantage in developing countries due to the enormous cost involved for the available interventions. If the organs involved are the kidneys, most Indians cannot afford to maintain themselves on dialysis. Similarly ventilators are available at very few centers. There are no artificial supports for other organs like the heart, the lungs and the liver, so death is imminent and no means is available to keep the individual alive short of replacing the organ concerned. Thus, a measure of urgency is introduced into the search for a donor organ.
2. A desperate patient may consent to procedures, which put him or her at risk. It is all the more important that every research protocol for transplantation should be carefully reviewed by an appropriate committee of suitably qualified scientists, jurists and other eminent members of society, so that its scientific and ethical basis may be impartially evaluated.
3. The transplant research team should have high-technical expertise.
4. Adequate data management, tissue storage facilities, and surveillance procedures should be available in a center before it is authorized to conduct research into transplantation.
5. If, at any time, a patient should refuse to take part as a participant for a research project, it should in no way interfere with his or her right to receive treatment of the best quality, which the team is capable of providing.
6. Under no circumstances should there be a conflict between scientific content of a study and the best interests of the patient. Should there be need to choose, the experiment should be abandoned and the patient should receive the best treatment possible.

## EMBRYONIC AND FETAL TISSUE

### Introduction

Human fetal tissue has been used in research for a wide range of purposes over decades. The thought of using fetal cells as transplants was first occasioned when scientists attempted to find ways of treating patients with loss of nerve cells in the brain and spinal cord. Since damaged nerve cells do not regenerate, repair to damage in the brain and spinal cord is severely limited. Attempts to trick the neurons into repair and regrowth have yet to bear fruit. That was when the attempts to transplant healthy neural tissue into damaged areas of the brain were started in an effort to allow the re-establishment of damaged neural circuits. The immunological complications that result, whenever any foreign tissue is transplanted into a human, proved a barrier. The use of fetal tissue is one of the means to minimize the chances of rejection. In the early weeks after conception, fetal cells multiply rapidly and show very little antigenicity because many surface antigens would not yet have developed. These cells are not fully differentiated and adapt easily to the signals received from surrounding tissue in a host. They grow and differentiate in such a manner that they are integrated to form part of the host organ. Fetal cells can also be successfully preserved by cooling and be reanimated. As the technology for developing immortal fetal cell lines for study of gene regulation, pattern formation in embryogenesis, as models of cell interaction and function, for vaccine development and study on cell growth and regulation, cancer and immune response was perfected, hopes for the use of these cells as transplants strengthened. Other potential uses of fetal tissue include treatment of diabetes, genetic retinal abnormalities, optic nerve and spinal cord injury, Alzheimer's disease, aplastic anemia, acute leukemia/lymphoma and liver failure.

### Definitions

#### *Embryonic State*

Between 15 days and 8 weeks postconception of a pregnancy. In the absence of more precise information (i.e. menstrual cycle length), conception is resumed to have taken place two weeks after the beginning of the woman's last menstrual period. The distinction of the 15-day stage as the beginning of the embryonic stage is not arbitrary. The pre-embryo is not isomorphic with the later developmental stages, since cells cannot yet be defined as contributing to the embryo or to the extra embryonic tissue, and complete implantation has not yet been accomplished. At 8 weeks, the rudiments of nearly all the main structures have been laid down giving a general appearance of a mammal-to-be with four limbs and a head.

#### *Fetal Stage*

Subsequent period between 8 weeks and the time the baby is born, at approximately 38 weeks postconception (40 weeks post-last menstrual period).

*Live aborted fetus:* If an aborted fetus is alive, it is a person, no matter how short the period of gestation, and using it for an experiment would, in law, be considered an assault upon it.

*Dead fetus:* An expelled or delivered fetus that exhibits no heart beat or spontaneous breathing. Some organs, tissue and cells remain alive for varying periods after the moment of death of the fetus.

*Neonate Stage*

Newly born live baby of any gestation period up to one and a half months after birth.

**Guidelines for Research on Fetal Tissue or Organs for Transplantation**

1. Every transplantation or research project involving the use of embryonic or fetal tissue must be approved by the Institutional Committee for Stem Cell Research and Therapy (ICSCRT) and ethics committees and referred to National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) for final approval in case of restrictive research as defined in the Stem Cell Research and Therapy Guidelines.
2. All centers doing research on stem cell should be registered with NAC-SCRT.
3. All members of the hospital or research staff-medical and paramedical–directly involved in any of the procedures will be fully informed of the purpose and implications of the research project.
4. The researcher shall not be a party to deliberate conception and/or subsequent abortion for the sake of obtaining tissue or organ for research or saving the life of a family member or for the purpose of commercialization.
5. No research is permitted on the live aborted fetus.
6. Tissue for transplantation or research may be obtained from dead embryos or fetuses, their death resulting from legally induced or spontaneous abortion. Death of an intact embryo or fetus is defined as absence of respiration and heart beat.
7. Voluntary, informed, written consent will be obtained from the mother in two stages—first for the abortion, next for the donation of tissue from the fetus.
8. Termination of pregnancy should not be sought with a view to donate fetal tissue in return for possible financial or therapeutic benefits.
9. The mother's decision to donate fetal tissue is sufficient for the use of the tissue unless the father objects in writing. In cases of incest or rape, the father's objection carries no significance.
10. The mother will not dictate who shall receive the fetal tissue taken for transplantation.
11. Anonymity of donor and recipient will be maintained so that neither party is aware of the identity of the other.
12. The procedure of abortion, or its timing, will not be influenced by the requirements of the transplantation activity. These should solely be based on concern for the safety of the mother.
13. Those participating in termination of pregnancy will not, in any way, be party to the subsequent usage of embryonic or fetal tissue for commercial purposes.
14. The procurement of embryos, fetuses or their tissue for commercial purposes will not involve profit or remuneration.
15. Intact embryos or fetuses will not be kept alive artificially for the purpose of removing usable material.
16. Tissues from aborted fetus can be cultured and banked for use in research on transplantation. If such stored tissue is to be subsequently used for any purpose other than the original objective, a fresh sanction will be obtained from the ICSCRT and ethical committees.

17. Cells obtained from fetuses will not be patented for commercial considerations for their subsequent usage.
18. Use of umbilical cord blood from a live fetus or neonate for transplantation: The fundamental principle in any operation on a live fetus or neonate will be to ensure that no harm will occur to the fetus or neonate. Since the exact timing of the clamping of the umbilical cord has a significant impact on the neonate and early clamping may cause an abrupt surge in arterial pressure resulting in cerebral intraventricular hemorrhage, particularly in premature neonates, normal clamping protocol will be followed when collecting fetal blood for transplantation. There is a risk that the neonate donor may need his or her own cord blood later in life. If the blood has been used for another, he or she might be without blood when it is needed. Parents will be fully informed of the risks of the donation and written consent obtained from them on behalf of the fetus.
19. Use of tissue or organs from dead anencephalic fetus or neonate (fetus or neonate lacking brain development above the level of the brainstem) is permitted. Physicians may provide anencephalic neonates with ventilator assistance and other medical therapies that are necessary to sustain organs till such time as the diagnosis of death is made on the basis of cessation of cardiac function. Retrieval and transplantation of organs of anencephalic fetus are ethically permissible only after such diagnosis of death is made.
20. No transplantation of fetal tissue into man will be permitted unless the following criteria have been met:
    i. There will be a detailed scientific basis for such transplantation.
    ii. Animal experiments must show successful results—eradication of disease, elimination or amelioration of symptoms and signs or successful substitution of deficient chemicals and restoration of normal physiological function by the transplant. These must be documented in one or more indexed journals with good peer review mechanisms.
    iii. All records pertaining to animal experiments must be complete and submitted to specialist and general scientific scrutiny. These records must be preserved for a minimum period of five years after the completion of the study preferably on a permanent basis as far as possible.
    iv. Success in animal experimentation must be shown on a long-term basis. The studies must include investigations on animals receiving the transplants at periodic intervals after the procedure specially with reference to unequivocal demonstration of absence of any transmission of disease through the transplant.
    v. Trials in human patients will commence only on those patients where no other form of treatment is available and where, in the absence of the transplant, the patient is likely to suffer relentless deterioration in his health with fatal termination.
    vi. After obtaining consent, the mother must be screened for transmissible disease. If possible, the material to be transplanted must also be similarly screened.
    vi. Trials in human patients will be carried out only at the institutions having clinical and research facilities needed for such trials, including those that may be required to treat complications that may follow such research.

vii. The research group and the institution(s) in which they work will undertake to conduct free of charge the research on their human participants and also treat completely any complication that may follow their study even if it appears several years after the conclusion of the study.

viii. The research group will provide the human participants a printed document explaining in simple, nontechnical language, the purpose of the study, details of the procedures the human participant is to undergo, complications that may follow these procedures, financial implications, interests of the researchers in the conduct of the study, and a commitment to treat completely and free of cost any complication that may ensue. The human participant must certify in writing that he has studied and understood the contents of this document and that she/he is willing to participate in the study.

ix. Any adverse effects noted will be immediately discussed with members of the ethics committee and the project grounded if these cannot be explained or reasonably corrected in the course of the study.

21. The local ethics committee must ensure report-back measures at every stage of research and confirm that a detailed report on the procedures, findings and conclusions is submitted to an indexed journal for publication even when the results are of a negative nature. The NAC-SCRT should be kept informed.
22. As with therapeutic transplantation, constantly updated local (metropolitan), regional or national lists of available tissues and organs should be maintained to ensure that optimal use is made of all available donations. These lists should be made freely available to all authorized research workers.

## XENOTRANSPLANTATION

### Introduction

Paucity of organs from humans for transplantation into other humans has led to the search for other sources such as animals. Initially the focus was on the great apes, as they appear to be nearest to man in the evolutionary scale. It was soon realized that unbridled use of simians would lead to possible extinction of their species. Attention has thus turned to other animals.

### Definitions

#### *Primates*

The most highly evolved of animals. Includes simians and homo-sapiens.

#### *Simians*

The monkey species, including the great apes.

#### *Species*

Group of individuals sharing similar biological characteristics and who can breed within the group to produce fertile offspring.

#### *Source Animal*

Animal from whom tissues or organs are removed for transplantation in humans. The term 'donor animal' has been discarded as the animals cannot give consent.

*Tissue*

A collection of similar cells, all of which perform the same function. An example is neural tissue within the brain.

*Transgenesis*

The introduction of a foreign gene into an animal or organism. The transferred gene is called transgene.

*Xeno-transplant*

Transplant of cells, tissue or organ from one species to another. This principally concerns transplant from animal to man.

*Zoonoses*

Diseases peculiar to animals in the normal course of events that can, under special circumstances—as after xenotransplant—be transferred to man.

**Ethical Considerations**

*Transmission of Disease from Animal to Man*

There has been considerable apprehension that tissues or organs transplanted from animal to man may convey infection or unwanted genetic abnormalities. This anxiety has prompted most countries, to ban all research on transplanting animal organs to human beings till this issue has been satisfactorily addressed. Measures proposed include the breeding of successive generations of animals and studying them for all known and possible unknown organisms that can cause disease. Only those animals certified free from disease could be considered for transplantation. Our immune responses are likely to reject all foreign tissue and organs transplanted into us. The chances of rejection are minimized, if the source animal is genetically similar to man. This is the reason for considering the great apes as likely source animal. Once the apes were ruled out in order to preserve their species, attention turned to cattle, sheep and pigs. In each of these species, transplant of unaltered tissue or organ will certainly lead to rejection. Pigs are currently the animals of choice as the size of their organs and the anatomical and physiological loads they must carry are similar to those in man. Besides, pigs breed easily and are maintained without much difficulty. Experimental studies have been carried out on kidneys, liver, heart, heart valves and bone marrow, islet cells of the pancreas and nerve cells obtained from pigs with encouraging results. Attempts are on so that pigs be engineered to possess genetic material similar to that in man. This can be achieved by replacing porcine genes by human genes into the cell that will form the pig embryo. Tissues and organs from such transgenic pigs will, it is hoped, stand the scrutiny by the immune systems of the patients into whom they are transplanted and will be left unmolested. However, there are possible problems in using porcine tissue or organs in human transplantation. The average pig survives for only twenty years. Will transplanted tissues function efficiently in man with a life span of three score years and ten, or will they fail after two decades, necessitating further transplants? Equally worrying is the possibility of transferring germs and viruses peculiar to pigs into man through transplanted tissues. Species-specific infective diseases are limited to those species. Under special circumstances—as after transplantation—such organisms may make the leap from one species to another

and cause untold havoc in the new species, which has no immunity against them. Some of the most deadly viruses currently devastating individuals and groups in some African countries are those causing Lassa Fever, the Marburg virus and the Ebola virus. They appear to have spread from bats or other animals to man. The human immunodeficiency virus (HIV) also appears to fall into this category. These questions are still unresolved. Apart from the known bacteria, fungi and viruses, there is concern for those hitherto unknown and undetected, especially so with slow viruses, that produce manifestations of the disease years—often decades—after they gain entry into our systems. Equally disquieting is the fact that once an infective organism makes a jump across species, it may spread like wildfire in the new species—in this case, man.

It is also proposed that extensive research, with long-term follow-up studies be carried out on animal-animal transplants so that we may learn of possible pitfalls and develop measures to avoid them before undertaking the first experiment involving man.

**Guidelines on Xeno-transplantation**

1. Experimental xeno-transplantation must only be permitted between different animal species. Animal-to-man transplants must not be permitted at the present level of knowledge, which may be referred to the Central/National Ethical Committee on Human Research.
2. Institutional scientific and ethics committees must approve of such research studies, with special attention being paid to their relevance, availability of facilities for extensive, sophisticated and long-term studies for transmission of disease through transplantation.
3. An advisory committee consisting of reputed scientists in the field, medical professionals, veterinary experts and microbiologists must oversee all such transplants.
4. Records on all research studies must be detailed, scrupulously maintained and kept available for a long-period of time, perhaps decades.
5. Safeguarding the interest of the pioneer human recipients when such transplants are permitted in future, it is proposed that each and every animal - to – man transplant be very carefully vetted and sanctioned on a case-by-case basis. In each instance, extensive studies on the animals to ensure freedom from infection must be made mandatory. The human recipients of tissues or organs must be carefully followed-up over a long-term.
6. Research involving the *transplantation* of human embryonic cells (*hESc*), human embryonic germ cells (*hEGc*) or human somatic cells (*hSSc*) of a pluripotent or multipotent nature into animals may be done provided that:
   i. The research is designed to reconstitute a specific tissue or organ to derive a preclinical model.
   ii. There is evidence from prior studies that the cells are not likely to contribute to gametes.

These animals transplanted with human stem cells will not be used for reproductive purposes and fall under restricted areas of research as described in the Stem Cell Guidelines for Research and Therapy. Such research after getting approved from IC-SCRT and ethics committee are required to be submitted for clearance from NAC-SCRT before initiation of the research.

## TRANSPLANTATION FOR COSMETIC PURPOSES

1. Research on transplantation for cosmetic purposes (such as the creation of a new ear after transferring tissue from the patient on to a mould which is later implanted into the subcutaneous tissue of a transgenic mouse) will be governed by the same principles as those in using donation of tissue or organ from a live donor.
2. Donation of tissue should be restricted to renewable tissues like skin to an extent where such removal will not greatly alter the normal functions of such tissue.
3. It is imperative that no risk be imposed whilst removing tissue beyond that inherent in surgery. Any manner of experimentation, though it may be intended to improve the survival of the graft, should be prohibited if there is the slightest extra risk to the donor. Examples are pretreatment of the donor with immunosuppressives or anticoagulants.
4. Every such research project should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits and improvement in the success rate of transplantation.
5. The patient must be informed of all possible risks, including those of failure of the transplant in a manner easily understood by him, before his consent is taken.
6. It follows that the donor should be competent to give consent; should be in a position to exercise free power of choice without the slightest element of force, duress, or coercion; and should have sufficient knowledge and comprehension of the participant to be able to make a decision with full understanding of the consequences. Children and mentally incompetent adults so also persons with limited autonomy should not be subjected to such surgery.
7. The experiment should be such as to yield fruitful results for the good of patients who need transplantation without having the donor. The experiment should be undertaken only if there is no other method available of finding the answer to the question raised.
8. The experiment should be so planned and conducted as to avoid all unnecessary risks to the donor, to the tissue to be transplanted, and to the recipient site.
9. Where tissue is to be temporarily transferred to an animal, all necessary precautions should be taken, and adequate facilities should be available, to protect the patient from the most remote possibility of harm.
10. The participants should be at liberty to withdraw from the experiment and to abrogate the consent given earlier, with no requirement to offer any explanation of the reasons for his or her doing so.

## STEM CELL RESEARCH AND THERAPY

The stem cell research holds great promise of improving human health by control of degenerative diseases and restoration of damage to organs by various injuries; but at the same time it also raises several ethical and social issues such as destruction of human embryos to create human embryonic stem (hES) cell lines, potential for introducing commodification in human tissues and organs with inherent barriers of access to socioeconomically deprived and possible use of technology for germ-

line engineering and reproductive cloning. The research in this field, therefore, needs to be regulated to strike a balance.

**Definitions**

*Adult Stem Cell*

A stem cell derived from the tissues or organs of an organism after birth (in contrast to embryonic or fetal stem cells).

*Blastocyst*

A hollow ball of 50 to 100 cells reached after about 5 days of embryonic development. It consists of a sphere made up of an outer layer of cells (the trophoectoderm), a fluid-filled cavity (the blastocel), and a cluster of cells in the interior (the inner cell mass).

*Cell Line*

Cells of common descent continuously cultured in the laboratory is referred to as a cell line.

*Cell Nuclear Replacement (CNR)*

The transfer of an adult cell nucleus into an egg that has had its nucleus removed to asexually create an embryo without the fusion of sperm and egg. It is also known as Somatic Cell Nuclear Transfer (SCNT).

*Clone*

A cell or organism derived from, and genetically identical to another cell or organism.

*Clonal*

Derived from a single cell.

*Cloning*

Creating an organism that is genetically identical to another organism, or a cell that is genetically identical to another cell provided that the so called mother and daughter cells are subsequently separated (see also reproductive and therapeutic cloning).

*Reproductive Cloning*

The embryo developed after Somatic Cell Nuclear Transfer (SCNT) is implanted into the human uterus (of the donor of the ovum or a surrogate recipient) and allowed to develop into a fetus and whole organism. The organism so developed is genetically identical to the donor of the somatic cell nucleus.

*Therapeutic Cloning*

The development of the embryo after Somatic Cell Nuclear Transfer (SCNT) is stopped at the blastocyst stage and embryonic stem cells are derived from the inner cell mass. These stem cells could be differentiated into desired tissue using a cocktail of growth and differentiation factors. The generated tissue/cells could then be transplanted into the original donor of the nucleus avoiding rejection.

*Cord Blood Stem Cell*

Stem cells collected from the umbilical cord at birth that can produce all of the blood cells in the body (hematopoietic).

### Embryo

In humans is the developing stage from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus.

### Early Embryo

The term "early embryo" covers stages of development up to the appearance of primitive streak until 15th day after fertilization which marks the development of fetal body plan.

### Embryonic Germ Cell

Embryonic germ cells are primordial germ cells isolated from the gonadal ridge of 5 to 10 weeks fetus.

### Embryonic Stem Cell

Embryonic stem cells are derived from the inner cell mass up to the stage of blastula. These cells can be cultured indefinitely under *in vitro* conditions that allow proliferation without differentiation, but have the potential of differentiating into any cell of the body.

### Fetal Stem Cell

A stem cell derived from fetal tissue, including placenta. A distinction is drawn between the fetal germ cells, from which the gametes develop, and fetal somatic cells, from which rest of the organism develops.

### Germ Cells

Ova and sperm, and their precursors

### Implantation

The embedding of a blastocyst in the wall of uterus. In humans implantation takes place between 7 to 14 days after fertilization.

### Mesenchymal Stem Cells

Rare stem cells present in human bone marrow and lining of umbilical cord that have been shown to differentiate into a variety of cell types in culture.

### Multipotent

Multipotent stem cells are those which are capable of giving rise to several different types of specialized cells constituting a specific tissue or organ.

### Pluripotent Stem Cell

Has the ability to give rise to various types of cells that develop from the three germ layers (mesoderm, endoderm and ectoderm). Pluripotent stem cell has the potential to generate into every cell type in the body, but cannot develop into a embryo on its own.

### Somatic Cell

Cell of the body other than egg or sperm.

### Somatic Stem Cell

An undifferentiated cell found among differentiated cells in a tissue or organ, which can renew itself and can differentiate to yield the major specialized cell types of the tissue or organ.

*Somatic Cell Nuclear Transfer*

The transfer of a cell nucleus to an egg (or another cell) from which the nucleus has been removed.

*Stem Cells*

Cells capable of self-replication, proliferation and differentiation.

*Supernumerary Embryo or Spare Embryo*

An embryo created by means of *in vitro* fertilization (IVF) for the purpose of assisted reproduction but subsequently not used for it.

*Totipotent*

At two to three days after fertilization, an embryo consists of identical cells, which are *totipotent*. That is to say that each cell could give rise to an embryo on its own producing, for example identical twins or quadruplets. They are totally unspecialized and have the capacity to differentiate into any of the cells, which will constitute the fetus as well as the placenta and membranes around the fetus.

The stem cell guidelines for research have been categorized into mainly three areas, namely, permissible, restrictive and prohibited areas. All centers doing research on stem cell should be registered with NAC-SCRT.

**Permissible Research Areas**

1. *In vitro* studies on established cell lines from any type of stem cell viz. *hES, hEG, hSS* or fetal/adult stem cells may be carried out with notification to IC-SCRT, provided the cell line is registered with the IC-SCRT/NAC-SCRT and GLP is followed.
2. *In vivo* studies with established cell lines from any type of stem cells viz. hES, hEG, hSS, including differentiated derivatives of these cells, *on animals other than primates* with prior approval of IC-SCRT, provided such animals are not allowed to breed. This includes pre-clinical evaluation of efficacy and safety of human stem cell lines.
3. *In vivo* studies on experimental animals (other than primates) using *fetal/adult somatic stem cells* from Bone marrow, peripheral blood, umbilical cord blood, skin, limbal cells, dental cells, bone cells, cartilage cells or any other organ (including placenta), with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines provided in this document.
4. Establishment of new hES cell lines from spare, supernumerary embryos with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines given below. Once the cell line is established, it shall be registered with the IC-SCRT and NAC-SCRT.
5. Establishment of fetal/adult hSS cell lines with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines provided in this document.
6. Establishment of Umbilical Cord stem cell bank with prior approval of the IC-SCRT and IEC provided guidelines given in this document for collection, processing, and storage, etc. of the umbilical cord blood are followed. Appropriate SOP's shall be approved by the IC-SCRT and IEC.

7. Clinical trial with clinical grade stem cells, following ICMR Guidelines for Biomedical Research and GCP guidelines of the GOI, may be carried out with prior approval of IC-SCRT, IEC and DCGI. Clinical grade stem cells are required to be produced under international GMP/GTP conditions. The cells should be well characterized about their stemness and safety as per guidelines given in Annexure II. The headings under which the clinical trial protocols should be written are given in Annexure III. All clinical trials on stem cells shall be registered with NAC-SCRT through IC-SCRT.

**Restricted Areas of Research**

1. Creation of a zygote by IVF, SCNT or any other method with the specific aim of deriving a *hES* cell line for any purpose.
   - Specific justification would be required to consider the request for approval by the NAC-SCRT through IEC and IC-SCRT.
   - It would be required to establish that creation of zygote is critical and essential for the proposed research, and no other alternative will serve the purpose.
   - Informed consent procedure for donation of ova, sperm, somatic cell or other as detailed in these guidelines would need to be followed.
2. Clinical trials sponsored by multinationals, involving stem cell products imported from abroad. Such collaboration shall require prior approval of the NAC-SCRT through IC-SCRT, IEC,DCGI and respective funding agency as per its procedure/Health Ministry's Screening Committee (HMSC).
3. Research involving introduction of hES/hEG/hSS cells into animals, at embryonic or fetal stage of development for studies on pattern of differentiation and integration of human cells into nonhuman animal tissues.
   - If there is a possibility that human cells could contribute in a major way to the development of brain or gonads of the recipient animal, the scientific justification for the experiments must be strong. The animals derived from these experiments shall not be allowed to breed.
   - Such proposals would need approval of the NAC-SCRT through Institutional Animal Ethics Committee (IAEC) and IC-SCRT.
4. Studies on chimeras where stem cells from two or more species are mixed and introduced into animals, including primates, at any stage of development viz. embryonic, fetal or postnatal, for studies on pattern of development and differentiation.
5. Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator.

**Prohibited Areas of Research**

1. Any research related to germ line genetic engineering or reproductive cloning.
2. Any *in vitro* culture of intact human embryo, regardless of the method of its derivation, beyond 14 days or formation of primitive streak, whichever is earlier.
3. Transfer of human blastocysts generated by SCNT or parthenogenetic or androgenetic techniques into a human or nonhuman uterus.
4. Any research involving implantation of human embryo into uterus after *in vitro* manipulation, at any stage of development, in humans or primates.

5. Animals in which any of human stem cells have been introduced at any stage of development should not be allowed to breed.
6. Research involving directed nonautologous donation of any stem cells to a particular individual is also prohibited.

### Research Using Umbilical Cord Blood Stem Cells

Cord blood stem cell banking is permissible. All Cord blood banks have to be registered with the Drug Controller General of India (DCGI) as per the guidelines of blood banks. Purpose of banking should be clearly explained to couples interested in storing cord blood. The ethical issues include concern about ownership and risk of transmission of potential genetic disorders, besides other general issues of confidentiality, justice and beneficence. When it comes to registries and banking, the commercial aspects pose additional problems. The advertising involved in getting and collecting samples, conflict of interest, utility of samples, accessibility and affordability should also be carefully looked into. The following points should be considered while collecting umbilical cord blood as specified in "Ethical Guidelines for Biomedical Research in Human Subjects" 2000 of ICMR:

1. No harm should occur to the fetus or the neonate.
2. Exact timing of the clamping of the umbilical cord should be defined in the clamping protocol.
3. Parents should be informed regarding risks and benefits involved.
4. Free informed consent from parents should be obtained. If there is disagreement between the parents, the mother's wish shall prevail.
5. ID card should be issued for voluntary donation to enable access/benefit in future in case required for self/relative.
6. Standard Operative Procedures for collection, transportation, processing, storage, preservation and clinical use should be laid down with approval of the IC-SCRT and IEC.
7. Detailed protocol for isolation and characterization of mesenchymal and/or stem cells should be approved by IC-SCRT and IEC.
8. Period of preservation for self- use later in life should be prescribed.
9. Detailed protocol for clinical use of stem cells should be in place.
10. Follow-up plans for assessing safety and efficacy of cord blood stem cell therapy should be incorporated.

### Research Using Fetal Stem Cells/Placenta

All proposals involving fetuses or fetal tissue, for research or therapy are permissible. However,

1. Termination of pregnancy should not be sought with a view to donate fetal tissue in return for possible financial or therapeutic benefits.
2. Consent to have a termination of pregnancy and the donation of fetal material for purpose of research or therapy should be taken separately.
3. The medical person responsible for the care of the pregnant woman planning to undergo termination of pregnancy and the person who will be using the fetal material should not be the same. The women shall not have the option to specify the use for a particular person or in a particular way.
4. The identity of the donor and the recipient should be kept confidential.

### Approval for Derivation of a New *hES* Cell Line

Whether new *hES* cell lines are derived from spare embryos or embryos created for the purpose, such research shall consider the following:

1. That the goal of research cannot be achieved in any other way even by research on adult stem cells.
2. There is no existing stem cell line that would be suitable for the purpose.
3. Will increase knowledge about embryo development and causes of miscarriages and birth defects.
4. Increasing the number of ethnically diverse *hES* cell lines.
5. advance knowledge, which can be used for infertility treatment or improving contraception techniques.
6. Increase knowledge about serious diseases and use this knowledge to develop treatments including tissue therapies.
7. Develop methods of therapy for diseased or damaged tissue or organs.
8. Justification for the minimum number of embryos/blastocysts required must be clearly defined.
9. Research teams involved should have appropriate expertise and training in derivation and culture of human/nonhuman ES cells.
   This, however, is not an exhaustive list.

### Responsibility of Investigators and Institutions

1. The investigators and the institutions where the stem cell research is being conducted bear the ultimate responsibility of ensuring that research activities are in accordance with laid down standards and integrity. In particular, scientists whose research involves hES cells should work closely with monitoring/ regulatory bodies, demonstrate respect for autonomy and privacy of those who donate gametes, blastocysts, embryos or somatic cells for SCNT, and be sensitive to public concerns about research that involves human embryos.
2. Each institution should maintain a registry of its investigators who are conducting hES cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding use of hES cells.
3. Each institution shall constitute an IC-SCRT as provided in these guidelines and provide adequate support for its functioning.

### International Collaboration

1. National guidelines of respective countries should be followed.
2. Collaboration will be permitted as per existing procedures of funding agencies (DBT, ICMR, etc.) or the Health Ministry's screening committee, even if no funding is involved after the joint proposal with appropriate MOU is approved by NAC-SCRT.
3. Export of cell lines will be covered under GOI guidelines for Transfer of Biological materials.
4. If there is a conflict between scientific and ethical perspectives of the International collaborator and the domestic side then Indian Ethical Guidelines or law will prevail.

### Commercialization and Patent Issues

Research on stem cells/lines and their applications may have considerable commercial value. Appropriate IPR protection may be considered on merits of each case. If the IPR is commercially exploited, a proportion of benefits shall be ploughed into the community, which has directly or indirectly contributed to the IPR. Community includes all potential beneficiaries such as patient group, research group, etc.

Detailed guidelines have been provided in a separate booklet on 'Stem Cell Research and Therapy' as national guidelines.

## CHAPTER VIII: STATEMENT OF SPECIFIC PRINCIPLES FOR ASSISTED REPRODUCTIVE TECHNOLOGIES

### INTRODUCTION

The special programme by WHO on human reproduction has estimated that there are 60 to 80 million infertile couples worldwide. It has also been variously estimated that between 6 to 10 percent of the couple are infertile. The advent of Assisted Reproductive Technologies (ART) from the late 70s has not only enhanced the possibility of pregnancy but have also made women conceive in situations which would not have been possible decades ago. However, many of these technologies require enormous technical expertise and infrastructure, carry a success rate below 30 percent even in the best of hands, are expensive, and tax the couple's endurance physically, emotionally and economically. In order to ensure quality of care, it is imperative that a proper accreditation procedure is followed in establishment of ART Centers, which should follow standardized protocols and guidelines. National guidelines for Accreditation, Supervision and Regulation of ART Clinics have been formulated by ICMR in 2005 to provide optimum benefit of these newer technologies to appropriate persons by skilled team of experts, at affordable health and economic cost, in all public and private facilities in our country. A national registry pertaining to all centers that are accredited by the licensing authority shall be maintained at ICMR and shall contain records of treatment cycles and outcome. Equally important are issues related to the conduct of research with material obtained as byproducts from the clinical activity. These include the follicular fluid, oocytes, spare embryos, semen samples which can be used by researchers in basic or molecular science.

### DEFINITION

This includes fertilization involving manipulation of gametes outside the human body and the transfer of gametes or embryos into the body.

All protocols used in the laboratory for Assisted Reproduction (AR) procedures must be documented and available as manuals. These manuals should be revised periodically. Log books for the maintenance and periodic overhauling of all equipments should be maintained. The entire procedure from the ovarian stimulation protocol to the oocyte retrieval and oocyte and sperm preparation including evaluation of the morphology of the gametes, their number, timing of

insemination, date of embryo transfer, number of embryos or gametes transferred and the fate of the gametes must be documented. Abnormal pre-embryos such as polyploid embryos should not be transferred. Cryopreserved material must be labeled indexed and stored properly. The laboratory personnel should be well versed with the techniques of cryopreservation.

Batches of culture media must be identified. All agents used in the Laboratory must be entered in a Register and the date of their receipt entered on the box containing them. Asepsis should be maintained at all cost. Each couple undergoing treatment should undergo a minimal screening for HIV and Hepatitis. The laboratory personnel should be adequately protected which include screening and vaccinations. It is essential that all documentation regarding every patient treated in the center is maintained meticulously and all precautions are taken to ensure that confidentiality is maintained.

## GENERAL PRINCIPLES

There is a certain element of risk associated with all AR procedures. It is, therefore, necessary to ascertain the therapeutic and research value of the AR procedure in each case.

### Informed Consent

After duly counseling the couple/oocyte/semen donor, an informed and written consent should be taken from both the spouses as well as the donor, as the case may be.

- They should be explained the various risk factors associated with the procedures in simple language and the words that they can understand. These include risks associated with ovarian hyperstimulation, anaesthestic procedures, and invasive procedures like laparoscopy, aspiration of ovum, etc.
- They should be explained the possibility of multiple pregnancies, ectopic gestation, increased rate of spontaneous abortion, premature births, higher perinatal and infant mortality as well as growth and developmental problems, possible side effects (e.g. of the drug used) and the risks of treatment to the women and the risks associated with multiple pregnancy.
- They should also be explained that:
  i. There is no guarantee on the success/failure of the procedure and the need to reduce the number of viable fetuses, in order to ensure the survival of at least two fetuses.
  ii. There may be possible disruption of the patient's domestic life which the treatment may cause.
  iii. About the possible deterioration of gametes or embryos associated with storage, and possible pain and discomfort.
  iv. About the cost (with suitable break-up) to the patient of the treatment proposed and of an alternative treatment, if any (there must be no other "hidden costs").
  v. About the importance of informing the clinic of the result of the pregnancy in a pre-paid envelope.
  vi. About the advantages and disadvantages of continuing treatment after a certain number of attempts.

- Informed consent should include information regarding use of spare embryos. It should be made clear whether embryos that are not used for transfer could or could not be used for research purposes or implanted in another woman's womb, or "preserved" for use at a later date or destroyed. Investigators should ensure that participants are informed and consent is taken afresh in writing on the above issues at every stage.
- Consent may be withdrawn at any time before implantation.
- Specific consent must be obtained from couples who have their gametes or embryos frozen, with regard to what should be done with them in case of death, or if any of the parties becomes incapable of varying or revoking her or his consent.
- Investigators should clarify the ownership of the embryos that they belong to the genetic mother or the laboratory. Abortions should never be encouraged for research purposes.
- No AR procedure will be done without the consent of the spouse or partner.
- There is no ethical objection at the moment for IVF or any other related procedure for research or for clinical application.

**Selection of Donor**

The semen bank assumes the responsibility in selection of the suitable donor on following terms:

- Complete physical examination of the donor should be done to ascertain the good health of the donors' semen, oocyte or embryo. The donor should be healthy with reasonable expectation of good quality eggs or sperms and preferably with proven fertility record.
- The physical characteristic and mental make-up of the donor should match as closely as possible to that of the spouse of the recipient, specially with reference to color of the skin, eyes and hair, height and build, religious and ethnic background, the educational level and ABO blood type.
- Blood group of the proposed donor and donee should be tested with respect to Rh compatibility.
- No person suffering from any sexually transmitted disease (e.g. syphilis, gonorrhea, chlamydia, herpes, HIV, etc.), infectious disease (e.g. hepatitis B and C, HIV) or genetically transmissible disease should be used as donor. Sexually transmitted diseases should be ruled out within a week of obtaining the seminal fluid.
- It is essential that donated semen is cryopreserved and used only after 6 months as this would enable the center to retest the donor after 6 months for HIV and eliminate the potential risk of HIV transmission in the 'window' period of HIV infection.
- Identity of the donor as well as the recipient should be protected from each other. However, all the records of the donor must be preserved for at least 10 years in order to trace her/him in case of any eventuality and should be confidential.
- Confidentiality of the entire procedure and its outcome is advisable and therefore, no relative should be accepted as a donor in order to avoid identification and claims of parenthood and inheritance rights.
- Any information about clients and donors must be kept confidential. No information about the treatment of couples provided under a treatment

agreement may be disclosed to anyone other than the accreditation authority or persons covered by the license, except with the consent of the person(s) to whom the information relates, or in a medical emergency concerning the patient, or a court order. It is this person(s)' right to decide what information will be passed on and to whom.

- Written consent of the donor should be taken towards unrestricted use of sperms or oocytes for AR, as well as an undertaking from him/her that he/she will not attempt to seek the identity of the recipient. In case the donor is married, the written consent of the spouse should be taken, if possible.
- It is also desirable to restrict the use of semen from the same donor to a maximum of 10 pregnancies to avoid the possibility of an incestuous relationship occurring among the offsprings at a later date.
- In case of the oocyte donor, incurring any health problems related to the process of donation, the costs of the subsequent health care should be borne by the potential recipient couple irrespective of whether they receive oocyte donation as planned or not.
- In case of unused surplus/spare embryos, consent of the concerned couple should be obtained to cryopreserve such embryos for donation to other needy couples. Such embryo donations should be kept anonymous. The ownership rights of such embryos rest with the couple concerned.

**Gametes and Embryos**

Respect for embryo can be shown by:

1. Accepting limits on what can be done in embryo research.
2. Committing to an interdisciplinary process of peer group review of planned research.
3. Carrying out an informed consent process for gamete and embryo donors.

Further, respect for the embryo's moral status can be shown by careful regulation of conditions of research, safeguards against commercial exploitation of embryo research, and limiting the time within which research can be done on embryo up to *14 days' growth*, i.e. when the *primitive streak* appears. This restriction is in keeping with the policy in several nations that permit research with embryos. At this time, the development of nervous system begins and the embryo begins to become a distinct individual.

With regard to use of gametes or embryo:

- No woman shall be treated with gametes or embryos derived from gametes of more than one man or woman.
- No ART clinic shall mix semen from two individuals before use.
- No ART clinic shall provide a couple with embryo of desired sex.
- No gametes shall be stored for more than 10 years.
- An embryo shall be stored for not more than five years.
- Sale, transfer or use outside India is prohibited.
- The donor shall relinquish all parental rights over the child which may be conceived from her or his gamete.

Women have a special position as care givers for children with disabilities. Since the bulk of care falls upon the women, she should make the final decision among reproductive options, without coercion from her partner, her doctor, or the law. The choice is more than the absence of legal prohibition or coercion and should

include the economic and social ability to act upon a decision, including disability. There should be a positive right to affordable genetic services, safe abortion and medically indicated care for children with disabilities.

### Cloning (through nuclear transplantation or embryo splitting)

The possibility of human cloning cannot be rejected since sheep and mice have already been cloned. However, since its safety, success, utility and ethical acceptability is not yet established, *research on cloning* with intent to produce an identical human being, as of today, is prohibited.

## SPECIFIC PRINCIPLES

### Legitimacy of the Child born through ART

A child born through AR is presumed to be the legitimate child of the couple having been born within the wedlock and with consent of both the spouses with all the attendant rights of parentage, support and inheritance. Sperm/oocyte donor should have no parental right or duties in relation to the child and their anonymity should be protected.

### IVF-ET *(in-vitro* fertilization and embryo-transfer) and Surrogate Motherhood

There are no medico-legal problems posed by IVF-ET with egg and sperm of married couple. Donation of either egg or sperm is governed on the same lines as those for Artificial Insemination Donor with the married partner as the natural or biological mother. IVF-ET with donated egg or sperm or womb leasing will create two to three sets of parents, genetic/biological and natural. Following consensus has emerged universally with respect to surrogate motherhood:

1. Surrogacy is an arrangement in which a woman agrees to carry a pregnancy that is genetically unrelated to her and her husband, with the intention to carry it to term and hand over the child to the genetic parents with whom she enters into a contract for surrogacy.
2. It should be resorted to only when it is coupled with authorized adoption wherever applicable.
3. The intending parents should have a preferential right to adopt the child subject to six week's postpartum delay for necessary maternal consent.
4. Surrogacy should be resorted to only if medically certified as the only solution to infertility or any other medical bar on pregnancy by the intending mother.
5. A qualified consultant should supervise to enforce adequate genetic screening.
6. Abortion under the Abortion Law on the medical ground should be inviolate right of the surrogate and the genetic parents have no claim over the amounts already paid.
7. The contract for surrogacy is legally enforceable. It shall provide for all expenses related to medical management during pregnancy, delivery, and immediate postpartum period till adoption and should be borne by the intending couple. Monetary compensation for agreeing to be the surrogate may also be specified in the agreement.
8. Information about the surrogate shall be kept confidential except with the consent of the person whom the information relates to or by court order.

9. ART clinics shall not provide surrogate mothers or information on potential surrogate mothers to couples or individuals.

### Preservation, Utilization and Destruction of Embryos

Research is prohibited on embryos *of more than 14 days after fertilization* excluding the period during which the embryo was frozen with maximum storage period of 10 years and a 5 yearly review of semen and embryo deposits as practiced in other countries, e.g. UK.

### Spare Embryos

Embryo-splitting may be resorted to in selected cases for overcoming the paucity of suitable embryos during ART in a couple. Child born of cryopreserved embryos after divorce is deemed to be illegitimate if existing law does not permit it.

### Right of Children/Parents

- A child born through ART shall be presumed to be the legitimate child of the couple, having been born in wedlock and with the consent of both the spouses.
- Therefore, the child shall have a legal right to parental support, inheritance, and all other privileges of a child born to a couple through sexual intercourse.
- Children born through use of donor gametes and their social/adopted parents have the right to know the medical or genetic information about the genetic parents that may be relevant to the child's health.
- The child's has a right to seek information on genetic parent(s) or surrogate mother (including a copy of the DNA fingerprint, if available) on reaching 18 years, except for information on the personal identity of the gamete donor or the surrogate mother unless when required in threatening medical conditions.
- The couple is not obliged to provide the information to the child on their own when she/he reaches the age of 18, but no attempt must be made by the couple to hide this information from the child should an occasion arise when this issue becomes important for the child.

  Pre-conceptual or pre-implantation sex selection is prohibited except for detecting *specific sex-linked genetic disorders.*

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# WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects

*Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:*
*29th WMA General Assembly, Tokyo, Japan, October 1975*
*35th WMA General Assembly, Venice, Italy, October 1983*
*41st WMA General Assembly, Hong Kong, September 1989*
*48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996*
*52nd WMA General Assembly, Edinburgh, Scotland, October 2000*
*53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)*
*55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)*
*59th WMA General Assembly, Seoul, October 2008*

## INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures

and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

## BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, based on a thorough knowledge of the scientific literature, other relevant sources of information and adequate laboratory, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee,

especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although, it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be

expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations, the research may be done only after consideration and approval of a Research Ethics Committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers, all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

## ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and where appropriate, made publicly available.

# International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

**ICH Harmonised Tripartite Guideline**

**Guideline for Good Clinical Practice**
**E6(R1)**

Current *Step 4* version

dated 10 June 1996

*(including the Post Step 4 corrections)*

*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.*

**E6(R1)**
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**Guideline for Good Clinical Practice**
**ICH Harmonised Tripartite Guideline**

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting
on 1 May 1996, this guideline is recommended for
adoption to the three regulatory parties to ICH
*(This document includes the Post Step 4 corrections agreed by the Steering Committee on 10 June 1996)*

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# Guideline for Good Clinical Practice

## INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

### 1 Glossary

#### *1.1 Adverse Drug Reaction (ADR)*

In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

#### *1.2 Adverse Event (AE)*

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

*1.3 Amendment (to the protocol)*

See Protocol Amendment.

*1.4 Applicable Regulatory Requirement(s)*

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

*1.5 Approval (in relation to Institutional Review Boards)*

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

*1.6 Audit*

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

*1.7 Audit Certificate*

A declaration of confirmation by the auditor that an audit has taken place.

*1.8 Audit Report*

A written evaluation by the sponsor's auditor of the results of the audit.

*1.9 Audit Trail*

Documentation that allows reconstruction of the course of events.

*1.10 Blinding/Masking*

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

*1.11 Case Report Form (CRF)*

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

*1.12 Clinical Trial/Study*

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

### 1.13 Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

### 1.14 Comparator (Product)

An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

### 1.15 Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

### 1.16 Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

### 1.17 Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

### 1.18 Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

### 1.19 Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

### 1.20 Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

### 1.21 Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g. domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

### 1.22 Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, X-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

*1.23 Essential Documents*

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

*1.24 Good Clinical Practice (GCP)*

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

*1.25 Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)*

An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

*1.26 Impartial Witness*

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

*1.27 Independent Ethics Committee (IEC)*

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and nonmedical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

*1.28 Informed Consent*

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

*1.29 Inspection*

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

*1.30 Institution (medical)*

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

*1.31 Institutional Review Board (IRB)*

An independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

*1.32 Interim Clinical Trial/Study Report*

A report of intermediate results and their evaluation-based on analyses performed during the course of a trial.

*1.33 Investigational Product*

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

*1.34 Investigator*

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

*1.35 Investigator/Institution*

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

*1.36 Investigator's Brochure*

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure).

*1.37 Legally Acceptable Representative*

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

*1.38 Monitoring*

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

*1.39 Monitoring Report*

A written report from the monitor to the sponsor after each site visit and/or other trialrelated communication according to the sponsor's SOPs.

*1.40 Multicentre Trial*

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

*1.41 Nonclinical Study*

Biomedical studies not performed on human subjects.

*1.42 Opinion (in relation to Independent Ethics Committee)*

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

*1.43 Original Medical Record*

See Source Documents.

*1.44 Protocol*

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

*1.45 Protocol Amendment*

A written description of a change(s) to or formal clarification of a protocol.

*1.46 Quality Assurance (QA)*

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

*1.47 Quality Control (QC)*

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

*1.48 Randomization*

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

*1.49 Regulatory Authorities*

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

*1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)*

Any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
  or
- Is a congenital anomaly/birth defect
  (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

*1.51 Source Data*

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

*1.52 Source Documents*

Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

*1.53 Sponsor*

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

*1.54 Sponsor-Investigator*

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g. it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

*1.55 Standard Operating Procedures (SOPs)*

Detailed, written instructions to achieve uniformity of the performance of a specific function.

*1.56 Subinvestigator*

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g. associates, residents, research fellows). See also Investigator.

*1.57 Subject/Trial Subject*

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

*1.58 Subject Identification Code*

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

*1.59 Trial Site*

The location(s) where trial-related activities are actually conducted.

*1.60 Unexpected Adverse Drug Reaction*

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

*1.61 Vulnerable Subjects*

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

*1.62 Well-being (of the trial subjects)*

The physical and mental integrity of the subjects participating in a clinical trial.

**2 The Principles of ICH GCP**

2.1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
2.8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
2.9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
2.10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
2.11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
2.12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
2.13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

## 3 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

### *3.1 Responsibilities*

3.1.1. An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.
3.1.2. The IRB/IEC should obtain the following documents: trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfill its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion
- modifications required prior to its approval/favourable opinion
- disapproval/negative opinion
- termination/suspension of any prior approval/favourable opinion

3.1.3. The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.
3.1.4. The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.
3.1.5. The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the

additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6. When a nontherapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7. Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

3.1.8. The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9. The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

*3.2 Composition, Functions and Operations*

3.2.1. The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a nonscientific area.

c. At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter. A list of IRB/IEC members and their qualifications should be maintained.

3.2.2. The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3. An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4. Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5. The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6. An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

*3.3 Procedures*

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1. Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2. Scheduling, notifying its members of, and conducting its meetings.

3.3.3. Conducting initial and continuing review of trials.

3.3.4. Determining the frequency of continuing review, as appropriate.

3.3.5. Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6. Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7. Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8. Specifying that the investigator should promptly report to the IRB/IEC:
   a. Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).
   b. Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).
   c. All adverse drug reactions (ADRs) that are both serious and unexpected.
   d. New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9. Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:
   a. Its trial-related decisions/opinions.
   b. The reasons for its decisions/opinions.
   c. Procedures for appeal of its decisions/opinions.

*3.4 Records*

The IRB/IEC should retain all relevant records (e.g. written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

**4 Investigator**

*4.1 Investigator's Qualifications and Agreements*

4.1.1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through

up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

*4.2 Adequate Resources*

4.2.1. The investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

*4.3 Medical Care of Trial Subjects*

4.3.1. A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

*4.4 Communication with IRB/IEC*

4.4.1. Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements), and any other written information to be provided to subjects.

4.4.2. As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3. During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

*4.5 Compliance with Protocol*

4.5.1. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s)).

4.5.3. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

a. To the IRB/IEC for review and approval/favourable opinion
b. To the sponsor for agreement and, if required
c. To the regulatory authority(ies).

*4.6 Investigational Product(s)*

4.6.1. Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately

that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4. The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5. The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

*4.7 Randomization Procedures and Unblinding*

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g. accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

*4.8 Informed Consent of Trial Subjects*

4.8.1. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner, if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.

4.8.6. The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a. That the trial involves research.
b. The purpose of the trial.
c. The trial treatment(s) and the probability for random assignment to each treatment.
d. The trial procedures to be followed, including all invasive procedures.
e. The subject's responsibilities.
f. Those aspects of the trial that are experimental.
g. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
h. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
i. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
j. The compensation and/or treatment available to the subject in the event of trial-related injury.
k. The anticipated prorated payment, if any, to the subject for participating in the trial.

l. The anticipated expenses, if any, to the subject for participating in the trial.

m. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

o. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

p. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

s. The expected duration of the subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

4.8.11. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12. When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g. minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13. Except as described in 4.8.14, a nontherapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14. Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

a. The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.

b. The foreseeable risks to the subjects are low.
c. The negative impact on the subject's well-being is minimized and low.
d. The trial is not prohibited by law.
e. The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

*4.9 Records and Reports*

4.9.1. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical

development of the investigational product. These documents should be retained for a longer-period however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7. Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

*4.10 Progress Reports*

4.10.1. The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2. The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

*4.11 Safety Reporting*

4.11.1. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3. For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g. autopsy reports and terminal medical reports).

*4.12 Premature Termination or Suspension of a Trial*

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2. If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3. If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

*4.13 Final Report(s) by Investigator*

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

**5 Sponsor**

*5.1 Quality Assurance and Quality Control*

5.1.1. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2. The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4. Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

*5.2 Contract Research Organization (CRO)*

5.2.1. A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2. Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3. Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4. All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

*5.3 Medical Expertise*

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

*5.4 Trial Design*

5.4.1. The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2. For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

*5.5 Trial Management, Data Handling, and Record Keeping*

5.5.1. The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2. The sponsor may consider establishing an independent datamonitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3. When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

a. Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

b. Maintains SOPs for using these systems.

c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).

d. Maintain a security system that prevents unauthorized access to the data.

e. Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

f. Maintain adequate backup of the data.

g. Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

5.5.4. If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5. The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6. The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7. The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the

country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8. If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9. If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10. Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11. The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer-period however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12. The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

*5.6 Investigator Selection*

5.6.1. The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2. Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3. The sponsor should obtain the investigator's/institution's agreement:

a. To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1).

b. To comply with procedures for data recording/reporting.

c. To permit monitoring, auditing and inspection (see 4.1.4).

d. To retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

*5.7 Allocation of Responsibilities*

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

*5.8 Compensation to Subjects and Investigators*

5.8.1. If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2. The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3. When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

*5.9 Financing*

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

*5.10 Notification/Submission to Regulatory Authority(ies)*

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

*5.11 Confirmation of Review by IRB/IEC*

5.11.1. The sponsor should obtain from the investigator/institution:

a. The name and address of the investigator's/institution's IRB/IEC.

b. A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

c. Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2. If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3. The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

*5.12 Information on Investigational Product(s)*

5.12.1. When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2. The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

*5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)*

5.13.1. The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2. The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3. The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4. In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5. If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

*5.14 Supplying and Handling Investigational Product(s)*

5.14.1. The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2. The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation [e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies)].

5.14.3. The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4. The sponsor should:

a. Ensure timely delivery of investigational product(s) to the investigator(s).

b. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).

c. Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

d. Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5. The sponsor should:

a. Take steps to ensure that the investigational product(s) are stable over the period of use.

b. Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

*5.15 Record Access*

5.15.1. The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2. The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

*5.16 Safety Information*

5.16.1. The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2. The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

*5.17 Adverse Drug Reaction Reporting*

5.17.1. The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2. Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3. The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

*5.18 Monitoring*

5.18.1. Purpose

The purposes of trial monitoring are to verify that:

a. The rights and well-being of human subjects are protected.
b. The reported trial data are accurate, complete, and verifiable from source documents.
c. The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2. Selection and Qualifications of Monitors

a. Monitors should be appointed by the sponsor.
b. Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.
c. Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3. Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4. Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a. Acting as the main line of communication between the sponsor and the investigator.
b. Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
c. Verifying, for the investigational product(s):
    i. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
    ii. That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

iii. That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
iv. That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
v. That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

d. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
e. Verifying that written informed consent was obtained before each subject's participation in the trial.
f. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
g. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
h. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
i. Verifying that the investigator is enroling only eligible subjects.
j. Reporting the subject recruitment rate.
k. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
l. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
m. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:
    i The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
    ii. Any dose and/or therapy modifications are well-documented for each of the trial subjects.
    iii. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
    iv. Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
    v. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.
n. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

o. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).
p. Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).
q. Communicating deviations from the protocol, SOP's, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5. Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6. Monitoring Report

a. The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.
b. Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.
c. Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.
d. The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

### *5.19 Audit*

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1. Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2. Selection and Qualification of Auditors

a. The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.
b. The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3. Auditing Procedures

a. The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.
b. The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

c. The observations and findings of the auditor(s) should be documented.
d. To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP noncompliance exists, or in the course of legal proceedings.
e. When required by applicable law or regulation, the sponsor should provide an audit certificate.

*5.20 Noncompliance*

5.20.1. Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2. If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

*5.21 Premature Termination or Suspension of a Trial*

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

*5.22 Clinical Trial/Study Reports*

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases).

*5.23 Multicentre Trials*

For multicentre trials, the sponsor should ensure that:

5.23.1. All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2. The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3. The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4. All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.
5.23.5. Communication between investigators is facilitated.

## 6 Clinical Trial Protocol and Protocol Amendment(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

### *6.1 General Information*

6.1.1. Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
6.1.2. Name and address of the sponsor and monitor (if other than the sponsor).
6.1.3. Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
6.1.4. Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
6.1.5. Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
6.1.6. Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
6.1.7. Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

### *6.2 Background Information*

6.2.1. Name and description of the investigational product(s).
6.2.2. A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
6.2.3. Summary of the known and potential risks and benefits, if any, to human subjects.
6.2.4. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
6.2.5. A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
6.2.6. Description of the population to be studied.
6.2.7. References to literature and data that are relevant to the trial, and that provide background for the trial.

### *6.3 Trial Objectives and Purpose*

A detailed description of the objectives and the purpose of the trial.

### *6.4 Trial Design*

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2. A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3. A description of the measures taken to minimize/avoid bias, including:
   a. Randomization.
   b. Blinding.

6.4.4. A description of the trial treatment(s) the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6. A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8. Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9. The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

### *6.5 Selection and Withdrawal of Subjects*

6.5.1. Subject inclusion criteria.

6.5.2. Subject exclusion criteria.

6.5.3. Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
   a. When and how to withdraw subjects from the trial/investigational product treatment.
   b. The type and timing of the data to be collected for withdrawn subjects.
   c. Whether and how subjects are to be replaced.
   d. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

### *6.6 Treatment of Subjects*

6.6.1. The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3. Procedures for monitoring subject compliance.

### *6.7 Assessment of Efficacy*

6.7.1. Specification of the efficacy parameters.

6.7.2. Methods and timing for assessing, recording, and analysing of efficacy parameters.

### *6.8 Assessment of Safety*

6.8.1. Specification of safety parameters.

6.8.2. The methods and timing for assessing, recording, and analysing safety parameters.
6.8.3. Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
6.8.4. The type and duration of the follow-up of subjects after adverse events.

*6.9 Statistics*

6.9.1. A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).
6.9.2. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
6.9.3. The level of significance to be used.
6.9.4. Criteria for the termination of the trial.
6.9.5. Procedure for accounting for missing, unused, and spurious data.
6.9.6. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
6.9.7. The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

*6.10 Direct Access to Source Data/Documents*

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

*6.11 Quality Control and Quality Assurance*

*6.12 Ethics*

Description of ethical considerations relating to the trial.

*6.13 Data Handling and Record Keeping*

*6.14 Financing and Insurance*

Financing and insurance, if not addressed in a separate agreement.

*6.15 Publication Policy*

Publication policy, if not addressed in a separate agreement.

*6.16 Supplements*

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports).

**7 Investigator's Brochure**

*7.1 Introduction*

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s)

in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e. a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

### *7.2 General Considerations*

The IB should include:

7.2.1. Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e. research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference

to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2. Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

### *7.3 Contents of the Investigator's Brochure*

The IB should contain the following sections, each with literature references where appropriate:

7.3.1. Table of Contents

An example of the Table of Contents is given in Appendix 2.

7.3.2. Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3. Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4. Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified, if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5. Nonclinical Studies

*Introduction*: The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g. milligram/kilogram (mg/kg))

- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response.

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

a. *Nonclinical Pharmacology*: A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g. special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

b. *Pharmacokinetics and Product Metabolism in Animals*: A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

c. *Toxicology*: A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:
   - Single dose
   - Repeated dose
   - Carcinogenicity
   - Special studies (e.g. irritancy and sensitisation)
   - Reproductive toxicity
   - Genotoxicity (mutagenicity).

6. Effects in Humans

*Introduction*: A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including

information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

a. Pharmacokinetics and Product Metabolism in Humans
   - A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
   - Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
   - Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
   - Population subgroups (e.g. gender, age, and impaired organ function).
   - Interactions (e.g. product-product interactions and effects of food).
   - Other pharmacokinetic data (e.g. results of population studies performed within clinical trial(s).

b. Safety and Efficacy

   A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

   The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

c. Marketing Experience

   The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g. formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7. Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources

on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

### 7.4 APPENDIX 1

Title Page *(Example)*
Sponsor's Name
Product:
Research Number:
Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)

**Investigator's Brochure**

Edition Number:
Release Date:

Replaces Previous Edition Number:
Date:

### APPENDIX 2

**Table of Contents of Investigator's Brochure *(Example)***

- Confidentiality Statement (optional)
- Signature Page (optional)

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies

5.1. Nonclinical Pharmacology
5.2. Pharmacokinetics and Product Metabolism in Animals
5.3. Toxicology

6. Effects in Humans
6.1. Pharmacokinetics and Product Metabolism in Humans
6.2. Safety and Efficacy
6.3. Marketing Experience
7. Summary of Data and Guidance for the Investigator

NB: References on 1. Publications
2. Reports
These references should be found at the end of each chapter
Appendices (if any).

## 8 Essential Documents For The Conduct Of A Clinical Trial

### *8.1 Introduction*

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

### *8.2 Before the Clinical Phase of the Trial Commences*

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

| 8.2 | *Title of document* | *Purpose* | *Located in files of* | |
|---|---|---|---|---|
| | | | *Investigator/ institution* | *Sponsor* |
| 8.2.1 | Investigator's brochure | To document that relevant and current scientific information about the investigational product has been provided to the investigator | × | × |
| 8.2.2 | Signed protocol and amendments, if any, and sample case report form (CRF) | To document investigator and sponsor agreement to the protocol/amendment(s) and CRF | × | × |
| 8.2.3 | Information given to trial subject<br>- Informed consent form (including all applicable translations) | To document the informed consent | × | × |
| | - Any other written information | To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent | × | × |
| | - Advertisement for subject recruitment (if used) | To document that recruitment measures are appropriate and not coercive | × | |
| 8.2.4 | Financial aspects of the trial | To document the financial agreement between the investigator/ institution and the sponsor for the trial | × | × |
| 8.2.5 | Insurance statement(where required) | To document that compensation to subject(s) for trial-related injury will be available | × | × |
| 8.2.6 | Signed agreement between involved parties, e.g. | To document agreements | × | × |
| | - Investigator/institution and sponsor | | × | × |
| | - Investigator/institution and CRO | | | (where required) |
| | - sponsor and CRO | | | |
| | - investigator/institution and authority (ies) (where required) | | | |
| 8.2.7 | Dated, documented approval/ favourable opinion of institutional | To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the | × | × |

| | *Title of document* | *Purpose* | *Located in files of* *Investigator/ institution* | *Sponsor* |
|---|---|---|---|---|
| | review board (IRB) /independent ethics committee (IEC) of the following:<br>- protocol and any amendments<br>- CRF (if applicable)<br>- informed consent form(s)<br>- any other written information to be provided to the subject(s)<br>- advertisement for subject recruitment (if used)<br>- subject compensation (if any)<br>- any other documents given approval/ favourable opinion | version number and date of the document(s) | | |
| 8.2.8 | Institutional review board/independent ethics committee composition | To document that the IRB/IEC is constituted in agreement with GCP | × | × (where required) |
| 8.2.9 | Regulatory authority (IES) authorisation/approval/notification of protocol (where required) | To document appropriate authorisation/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s) | × (where required) | × (where required) |
| 8.2.10 | Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s) | To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects | × | × |
| 8.2.11 | Normal value(s)/range(s) for medical/ laboratory/technical procedure(s) and/ or test(s) included in the protocol | To document normal values and/or ranges of the tests | × | × |
| 8.2.12 | Medical/laboratory/technical procedures/tests<br>- Certification or<br>- Accreditation or | To document competence of facility to perform required test(s) , and support reliability of results | × (where required) | × |

*Contd...*

| | *Title of document* | *Purpose* | *Located in files of* *Investigator/ institution* | *Sponsor* |
|---|---|---|---|---|
| | - Established quality control and/or external quality assessment or<br>- Other validation (where required) | | | |
| 8.2.13 | Sample of label(s) attached to investigational product container(s) | To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects | | × |
| 8.2.14 | Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or investigator's brochure) | To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials | × | × |
| 8.2.15 | Shipping records for investigational product(s) and trial-related materials | To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability | × | × |
| 8.2.16 | Certificate(s) of analysis of investigational product(s) shipped | To document identity, purity, and strength of investigational product(s) to be used in the trial | | × |
| 8.2.17 | Decoding procedures for blinded trials | To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment | × | × (third party if applicable) |
| 8.2.18 | Master randomisation list | To document method for randomisation of trial population | | × (third party if applicable) |
| 8.2.19 | Pre-trial monitoring report | To document that the site is suitable for the trial (may be combined with 8.2.20) | | × |
| 8.2.20 | Trial initiation monitoring report | To document that trial procedures were reviewed with the investigator and the investigator's trial staff ( may be combined with 8.2.19) | × | × |

*During the Clinical Conduct of the Trial*

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

| | *Title of document* | *Purpose* | *Located in files of* Investigator/ institution | Sponsor |
|---|---|---|---|---|
| 8.3.1 | Investigator's brochure updates | To document that investigator is informed in a timely manner of relevant information as it becomes available | × | × |
| 8.3.2 | Any revision to:<br>- Protocol/amendment(s) and CRF<br>- Informed consent form<br>- Any other written information provided to subjects<br>- Advertisement for subject recruitment (if used) | To document revisions of these trial related documents that take effect during trial | × | × |
| 8.3.3 | Dated, documented approval/ favourable opinion of institutional review board (IRB)/independent ethics committee (IEC) of the following:<br>- Protocol amendment(s)<br>- Revision(s) of:<br>- Informed consent form<br>- Any other written information to be provided to the subject<br>- Advertisement for subject recruitment (if used)<br>- Any other documents given approval/ favourable opinion<br>- Continuing review of trial (where required) | To document that the amendment(s) and/or revision(s) have been subject to irb/iec review and were given approval/ favourable opinion. To identify the version number and date of the document(s). | × | × |

*Contd...*

| | *Title of document* | *Purpose* | *Located in files of* *Investigator/ institution* | *Sponsor* |
|---|---|---|---|---|
| 8.3.4 | Regulatory authority(ies) authorisations /approvals/notifications where required for:<br>- Protocol amendment(s) and other documents | To document compliance with applicable regulatory requirements | × (where required) | × |
| 8.3.5 | Curriculum vitae for new investigator(s) and/or sub-investigator(s) | (see 8.2.10) | × | × |
| 8.3.6 | Updates to normal value(s)/range(s) for medical/ laboratory/ technical procedure(s)/test(s) included in the protocol | To document normal values and ranges that are revised during the trial (see 8.2.11) | × | × |
| 8.3.7 | Updates of medical/laboratory/ technical procedures/tests<br>- Certification or<br>- Accreditation or<br>- Established quality control and/or external quality assessment or<br>- Other validation (where required) | To document that tests remain adequate throughout the trial period (see 8.2.12) | × (where required) | × |
| 8.3.8 | Documentation of investigational product(s) and trial-related materials shipment | (see 8.2.15.) | × | × |
| 8.3.9 | Certificate(s) of analysis for new batches of investigational products | (see 8.2.16) | | × |
| 8.3.10 | Monitoring visit reports | To document site visits by, and findings of, the monitor | | × |
| 8.3.11 | Relevant communications other than site visits<br>- Letters<br>- Meeting notes<br>- Notes of telephone calls | To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (ae) reporting | × | × |

*Contd...*

| | *Title of document* | *Purpose* | *Located in files of* | |
|---|---|---|---|---|
| | | | *Investigator/ institution* | *Sponsor* |
| 8.3.12 | Signed informed consent forms | To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3) | × | |
| 8.3.13 | Source documents | To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject | × | |
| 8.3.14 | Signed, dated and completed case report forms ( CRF) | To document that the investigator or authorised member of the investigator's staff confirms the observations recorded | × (copy) | × (original) |
| 8.3.15 | Documentation of CRF Corrections | To document all changes/additions or corrections made to CRF after initial data were recorded | × (copy) | × (original) |
| 8.3.16 | Notification by originating investigator to sponsor of serious adverse events and related reports | Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11 | × | × |
| 8.3.17 | Notification by sponsor and/or investigator, where applicable, to regulatory authority(IES) and IRB(s)/ IEC(s) of unexpected serious adverse drug reactions and of other safety information | Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2 | × (where required) | × |
| 8.3.18 | Notification by sponsor to investigators of safety information | Notification by sponsor to investigators of safety information in accordance with 5.16.2 | × | × |
| 8.3.19 | Interim or annual reports to IRB/IEC and authority (IES) | Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(IES) in accordance with 5.17.3 | × | × (where required) |
| 8.3.20 | Subject screening log | To document identification of subjects who entered pre-trial screening | × | × (where required) |

*Contd...*

| | *Title of document* | *Purpose* | *Located in files of* *Investigator/ institution* | | *Sponsor* |
|---|---|---|---|---|---|
| 8.3.21 | Subject identification code list | To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject | × | | |
| 8.3.22 | Subject enrolment log | To document chronological enrolment of subjects by trial number | × | | |
| 8.3.23 | Investigational products accountability at the site | To document that investigational product(s) have been used according to the protocol | × | | × |
| 8.3.24 | Signature sheet | To document signatures and initials of all persons authorised to make entries and/or corrections on CRFS | × | | × |
| 8.3.25 | Record of retained body fluids/ tissue samples (if any) | To document location and identification of retained samples if assays need to be repeated | × | | × |

### *After Completion or Termination of the Trial*

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

| | *Title of document* | *Purpose* | *Located in files of* | |
|---|---|---|---|---|
| | | | *Investigator/ institution* | *Sponsor* |
| 8.4.1 | Investigational product(s) accountability at site | To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor | × | × |
| 8.4.2 | Documentation of investigational product destruction | To document destruction of unused investigational products by sponsor or at site | × (if destroyed at site) | × |
| 8.4.3 | Completed subject identification code list | To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time | × | |
| 8.4.4 | Audit certificate (if available) | To document that audit was performed | | × |
| 8.4.5 | Final trial close-out monitoring report | To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files | | × |
| 8.4.6 | Treatment allocation and decoding documentation | Returned to sponsor to document any decoding that may have occurred | | × |
| 8.4.7 | Final report by investigator to IRB/IEC where required, and where applicable, to the regulatory authority(ies) | To document completion of the trial | × | |
| 8.4.8 | Clinical study report | To document results and interpretation of trial | × (if applicable) | × |

# Statistical Principles for Clinical Trials
## ICH Topic E 9 (CPMP/ICH/363/96) EMEA Document

### 1 INTRODUCTION

#### 1.1 Background and Purpose

The efficacy and safety of medicinal products should be demonstrated by clinical trials which follow the guidance in 'Good Clinical Practice: Consolidated Guideline' (ICH E6) adopted by the ICH, 1 May 1996. The role of statistics in clinical trial design and analysis is acknowledged as essential in that ICH guideline. The proliferation of statistical research in the area of clinical trials coupled with the critical role of clinical research in the drug approval process and health care in general necessitate a succinct document on statistical issues related to clinical trials. This guidance is written primarily to attempt to harmonise the principles of statistical methodology applied to clinical trials for marketing applications submitted in Europe, Japan and the United States.

As a starting point, this guideline utilised the CPMP' (Committee for Proprietary Medicinal Products) Note for Guidance entitled 'Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations for Medicinal Products' (December, 1994). It was also influenced by 'Guidelines on the Statistical Analysis of Clinical Studies' (March, 1992) from the Japanese Ministry of Health and Welfare and the U.S. Food and Drug Administration document entitled 'Guideline for the Format and Content of the Clinical and Statistical Sections of a New Drug Application' (July, 1988) . Some topics related to statistical principles and methodology are also embedded within other ICH guidelines, particularly those listed below. The specific guidance that contains related text will be identified in various sections of this document.

- E1A: The Extent of Population Exposure to Assess Clinical Safety
- E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- E2B: Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
- E2C: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
- E3: Structure and Content of Clinical Study Reports
- E4: Dose-Response Information to Support Drug Registration
- E5: Ethnic Factors in the Acceptability of Foreign Clinical Data
- E6: Good Clinical Practice: Consolidated Guideline
- E7: Studies in Support of Special Populations: Geriatrics
- E8: General Considerations for Clinical Trials
- E10: Choice of Control Group in Clinical Trials

M1: Standardisation of Medical Terminology for Regulatory Purposes
M3: Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

This guidance is intended to give direction to sponsors in the design, conduct, analysis, and evaluation of clinical trials of an investigational product in the context of its overall clinical development. The document will also assist scientific experts charged with preparing application summaries or assessing evidence of efficacy and safety, principally from clinical trials in later phases of development.

### 1.2 Scope and Direction

The focus of this guidance is on statistical principles. It does not address the use of specific statistical procedures or methods. Specific procedural steps to ensure that principles are implemented properly are the responsibility of the sponsor. Integration of data across clinical trials is discussed, but is not a primary focus of this guidance. Selected principles and procedures related to data management or clinical trial monitoring activities are covered in other ICH guidelines and are not addressed here.

This guidance should be of interest to individuals from a broad range of scientific disciplines. However, it is assumed that the actual responsibility for all statistical work associated with clinical trials will lie with an appropriately qualified and experienced statistician, as indicated in ICH E6. The role and responsibility of the trial statistician (see Glossary), in collaboration with other clinical trial professionals, is to ensure that statistical principles are applied appropriately in clinical trials supporting drug development. Thus, the trial statistician should have a combination of education/training and sufficient experience to implement the principles articulated in this guidance.

For each clinical trial contributing to a marketing application, all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins. The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial. The protocol and subsequent amendments should be approved by the responsible personnel, including the trial statistician. The trial statistician should ensure that the protocol and any amendments cover all relevant statistical issues clearly and accurately, using technical terminology as appropriate.

The principles outlined in this guidance are primarily relevant to clinical trials conducted in the later phases of development, many of which are confirmatory trials of efficacy. In addition to efficacy, confirmatory trials may have as their primary variable a safety variable (e.g. an adverse event, a clinical laboratory variable or an electrocardiographic measure), a pharmacodynamic or a pharmacokinetic variable (as in a confirmatory bioequivalence trial). Furthermore, some confirmatory findings may be derived from data integrated across trials, and selected principles in this guidance are applicable in this situation. Finally, although the early phases of drug development consist mainly of clinical trials that are exploratory in nature, statistical principles are also relevant to these clinical trials. Hence, the substance of this document should be applied as far as possible to all phases of clinical development.

Many of the principles delineated in this guidance deal with minimising bias (see Glossary) and maximising precision. As used in this guidance, the term 'bias' describes the systematic tendency of any factors associated with the design, conduct, analysis and interpretation of the results of clinical trials to make the estimate of a treatment effect (see Glossary) deviate from its true value. It is important to identify potential sources of bias as completely as possible so that attempts to limit such bias may be made. The presence of bias may seriously compromise the ability to draw valid conclusions from clinical trials.

Some sources of bias arise from the design of the trial, for example an assignment of treatments such that subjects at lower risk are systematically assigned to one treatment. Other sources of bias arise during the conduct and analysis of a clinical trial. For example, protocol violations and exclusion of subjects from analysis based upon knowledge of subject outcomes are possible sources of bias that may affect the accurate assessment of the treatment effect. Because bias can occur in subtle or unknown ways and its effect is not measurable directly, it is important to evaluate the robustness of the results and primary conclusions of the trial. Robustness is a concept that refers to the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis. Robustness implies that the treatment effect and primary conclusions of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches. The interpretation of statistical measures of uncertainty of the treatment effect and treatment comparisons should involve consideration of the potential contribution of bias to the p-value, confidence interval, or inference.

Because the predominant approaches to the design and analysis of clinical trials have been based on frequentist statistical methods, the guidance largely refers to the use of frequentist methods (see Glossary) when discussing hypothesis testing and/or confidence intervals. This should not be taken to imply that other approaches are not appropriate: the use of Bayesian (see Glossary) and other approaches may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust.

## 2 CONSIDERATIONS FOR OVERALL CLINICAL DEVELOPMENT

### 2.1 Trial Context

#### *2.1.1 Development Plan*

The broad aim of the process of clinical development of a new drug is to find out whether there is a dose range and schedule at which the drug can be shown to be simultaneously safe and effective, to the extent that the risk-benefit relationship is acceptable. The particular subjects who may benefit from the drug, and the specific indications for its use, also need to be defined.

Satisfying these broad aims usually requires an ordered programme of clinical trials, each with its own specific objectives (see ICH E8). This should be specified in a clinical plan, or a series of plans, with appropriate decision points and flexibility to allow modification as knowledge accumulates. A marketing application should clearly describe the main content of such plans, and the contribution made by each trial. Interpretation and assessment of the evidence from the total programme of

trials involves synthesis of the evidence from the individual trials (see Section 7.2). This is facilitated by ensuring that common standards are adopted for a number of features of the trials such as dictionaries of medical terms, definition and timing of the main measurements, handling of protocol deviations and so on. A statistical summary, overview or meta-analysis (see Glossary) may be informative when medical questions are addressed in more than one trial. Where possible this should be envisaged in the plan so that the relevant trials are clearly identified and any necessary common features of their designs are specified in advance. Other major statistical issues (if any) that are expected to affect a number of trials in a common plan should be addressed in that plan.

### *2.1.2 Confirmatory Trial*

A confirmatory trial is an adequately controlled trial in which the hypotheses are stated in advance and evaluated. As a rule, confirmatory trials are necessary to provide firm evidence of efficacy or safety. In such trials the key hypothesis of interest follows directly from the trial's primary objective, is always pre-defined, and is the hypothesis that is subsequently tested when the trial is complete. In a confirmatory trial it is equally important to estimate with due precision the size of the effects attributable to the treatment of interest and to relate these effects to their clinical significance.

Confirmatory trials are intended to provide firm evidence in support of claims and hence adherence to protocols and standard operating procedures is particularly important; unavoidable changes should be explained and documented, and their effect examined. A justification of the design of each such trial, and of other important statistical aspects such as the principal features of the planned analysis, should be set out in the protocol. Each trial should address only a limited number of questions.

Firm evidence in support of claims requires that the results of the confirmatory trials demonstrate that the investigational product under test has clinical benefits. The confirmatory trials should therefore be sufficient to answer each key clinical question relevant to the efficacy or safety claim clearly and definitively. In addition, it is important that the basis for generalisation (see Glossary) to the intended patient population is understood and explained; this may also influence the number and type (e.g. specialist or general practitioner) of centres and/or trials needed. The results of the confirmatory trial(s) should be robust. In some circumstances the weight of evidence from a single confirmatory trial may be sufficient.

### *2.1.3 Exploratory Trial*

The rationale and design of confirmatory trials nearly always rests on earlier clinical work carried out in a series of exploratory studies. Like all clinical trials, these exploratory studies should have clear and precise objectives. However, in contrast to confirmatory trials, their objectives may not always lead to simple tests of pre-defined hypotheses. In addition, exploratory trials may sometimes require a more flexible approach to design so that changes can be made in response to accumulating results. Their analysis may entail data exploration; tests of hypothesis may be carried out, but the choice of hypothesis may be data dependent. Such trials cannot be the basis of the formal proof of efficacy, although they may contribute to the total body of relevant evidence.

Any individual trial may have both confirmatory and exploratory aspects. For example, in most confirmatory trials the data are also subjected to exploratory

analyses which serve as a basis for explaining or supporting their findings and for suggesting further hypotheses for later research. The protocol should make a clear distinction between the aspects of a trial which will be used for confirmatory proof and the aspects which will provide data for exploratory analysis.

## 2.2 Scope of Trials

### *2.2.1 Population*

In the earlier phases of drug development the choice of subjects for a clinical trial may be heavily influenced by the wish to maximise the chance of observing specific clinical effects of interest, and hence they may come from a very narrow subgroup of the total patient population for which the drug may eventually be indicated. However by the time the confirmatory trials are undertaken, the subjects in the trials should more closely mirror the target population. Hence, in these trials it is generally helpful to relax the inclusion and exclusion criteria as much as possible within the target population, while maintaining sufficient homogeneity to permit precise estimation of treatment effects. No individual clinical trial can be expected to be totally representative of future users, because of the possible influences of geographical location, the time when it is conducted, the medical practices of the particular investigator(s) and clinics, and so on. However the influence of such factors should be reduced wherever possible, and subsequently discussed during the interpretation of the trial results.

### *2.2.2 Primary and Secondary Variables*

The primary variable ('target' variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. There should generally be only one primary variable. This will usually be an efficacy variable, because the primary objective of most confirmatory trials is to provide strong scientific evidence regarding efficacy. Safety/tolerability may sometimes be the primary variable, and will always be an important consideration. Measurements relating to quality of life and health economics are further potential primary variables. The selection of the primary variable should reflect the accepted norms and standards in the relevant field of research. The use of a reliable and validated variable with which experience has been gained either in earlier studies or in published literature is recommended. There should be sufficient evidence that the primary variable can provide a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria. The primary variable should generally be the one used when estimating the sample size (see section 3.5).

In many cases, the approach to assessing subject outcome may not be straightforward and should be carefully defined. For example, it is inadequate to specify mortality as a primary variable without further clarification; mortality may be assessed by comparing proportions alive at fixed points in time, or by comparing overall distributions of survival times over a specified interval. Another common example is a recurring event; the measure of treatment effect may again be a simple dichotomous variable (any occurrence during a specified interval), time to first occurrence, rate of occurrence (events per time units of observation), etc. The assessment of functional status over time in studying treatment for chronic disease

presents other challenges in selection of the primary variable. There are many possible approaches, such as comparisons of the assessments done at the beginning and end of the interval of observation, comparisons of slopes calculated from all assessments throughout the interval, comparisons of the proportions of subjects exceeding or declining beyond a specified threshold, or comparisons based on methods for repeated measures data. To avoid multiplicity concerns arising from post hoc definitions, it is critical to specify in the protocol the precise definition of the primary variable as it will be used in the statistical analysis. In addition, the clinical relevance of the specific primary variable selected and the validity of the associated measurement procedures will generally need to be addressed and justified in the protocol.

The primary variable should be specified in the protocol, along with the rationale for its selection. Redefinition of the primary variable after unblinding will almost always be unacceptable, since the biases this introduces are difficult to assess. When the clinical effect defined by the primary objective is to be measured in more than one way, the protocol should identify one of the measurements as the primary variable on the basis of clinical relevance, importance, objectivity, and/or other relevant characteristics, whenever such selection is feasible.

Secondary variables are either supportive measurements related to the primary objective or measurements of effects related to the secondary objectives. Their pre-definition in the protocol is also important, as well as an explanation of their relative importance and roles in interpretation of trial results. The number of secondary variables should be limited and should be related to the limited number of questions to be answered in the trial.

### *2.2.3 Composite Variables*

If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or 'composite' variable, using a pre-defined algorithm. Indeed, the primary variable sometimes arises as a combination of multiple clinical measurements (e.g. the rating scales used in arthritis, psychiatric disorders and elsewhere). This approach addresses the multiplicity problem without requiring adjustment to the type I error. The method of combining the multiple measurements should be specified in the protocol, and an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit. When a composite variable is used as a primary variable, the components of this variable may sometimes be analysed separately, where clinically meaningful and validated. When a rating scale is used as a primary variable, it is especially important to address such factors as content validity (see Glossary), inter- and intra-rater reliability (see Glossary) and responsiveness for detecting changes in the severity of disease.

### *2.2.4 Global Assessment Variables*

In some cases, 'global assessment' variables (see Glossary) are developed to measure the overall safety, overall efficacy, and/or overall usefulness of a treatment. This type of variable integrates objective variables and the investigator's overall impression about the state or change in the state of the subject, and is usually a scale of ordered categorical ratings. Global assessments of overall efficacy are well established in some therapeutic areas, such as neurology and psychiatry.

Global assessment variables generally have a subjective component. When a global assessment variable is used as a primary or secondary variable, fuller details of the scale should be included in the protocol with respect to:

1. The relevance of the scale to the primary objective of the trial;
2. The basis for the validity and reliability of the scale;
3. How to utilise the data collected on an individual subject to assign him/her to a unique category of the scale;
4. How to assign subjects with missing data to a unique category of the scale, or otherwise evaluate them.

If objective variables are considered by the investigator when making a global assessment, then those objective variables should be considered as additional primary, or at least important secondary, variables.

Global assessment of usefulness integrates components of both benefit and risk and reflects the decision making process of the treating physician, who must weigh benefit and risk in making product use decisions. A problem with global usefulness variables is that their use could in some cases lead to the result of two products being declared equivalent despite having very different profiles of beneficial and adverse effects. For example, judging the global usefulness of a treatment as equivalent or superior to an alternative may mask the fact that it has little or no efficacy but fewer adverse effects. Therefore it is not advisable to use a global usefulness variable as a primary variable. If global usefulness is specified as primary, it is important to consider specific efficacy and safety outcomes separately as additional primary variables.

### *2.2.5 Multiple Primary Variables*

It may sometimes be desirable to use more than one primary variable, each of which (or a subset of which) could be sufficient to cover the range of effects of the therapies. The planned manner of interpretation of this type of evidence should be carefully spelled out. It should be clear whether an impact on any of the variables, some minimum number of them, or all of them, would be considered necessary to achieve the trial objectives. The primary hypothesis or hypotheses and parameters of interest (e.g. mean, percentage, distribution) should be clearly stated with respect to the primary variables identified, and the approach to statistical inference described. The effect on the type I error should be explained because of the potential for multiplicity problems (see Section 5.6); the method of controlling type I error should be given in the protocol. The extent of intercorrelation among the proposed primary variables may be considered in evaluating the impact on type I error. If the purpose of the trial is to demonstrate effects on all of the designated primary variables, then there is no need for adjustment of the type I error, but the impact on type II error and sample size should be carefully considered.

### *2.2.6 Surrogate Variables*

When direct assessment of the clinical benefit to the subject through observing actual clinical efficacy is not practical, indirect criteria (surrogate variables - see Glossary) may be considered. Commonly accepted surrogate variables are used in a number of indications where they are believed to be reliable predictors of clinical benefit. There are two principal concerns with the introduction of any proposed surrogate variable. First, it may not be a true predictor of the clinical outcome of interest. For example it may measure treatment activity associated with one specific

pharmacological mechanism, but may not provide full information on the range of actions and ultimate effects of the treatment, whether positive or negative. There have been many instances where treatments showing a highly positive effect on a proposed surrogate have ultimately been shown to be detrimental to the subjects' clinical outcome; conversely, there are cases of treatments conferring clinical benefit without measurable impact on proposed surrogates. Secondly, proposed surrogate variables may not yield a quantitative measure of clinical benefit that can be weighed directly against adverse effects. Statistical criteria for validating surrogate variables have been proposed but the experience with their use is relatively limited. In practice, the strength of the evidence for surrogacy depends upon (i) the biological plausibility of the relationship, (ii) the demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome and (iii) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome. Relationships between clinical and surrogate variables for one product do not necessarily apply to a product with a different mode of action for treating the same disease.

#### *2.2.7 Categorised Variables*

Dichotomisation or other categorisation of continuous or ordinal variables may sometimes be desirable. Criteria of 'success' and 'response' are common examples of dichotomies which require precise specification in terms of, for example, a minimum percentage improvement (relative to baseline) in a continuous variable, or a ranking categorised as at or above some threshold level (e.g. 'good') on an ordinal rating scale. The reduction of diastolic blood pressure below 90mmHg is a common dichotomisation. Categorisations are most useful when they have clear clinical relevance. The criteria for categorisation should be pre-defined and specified in the protocol, as knowledge of trial results could easily bias the choice of such criteria. Because categorisation normally implies a loss of information, a consequence will be a loss of power in the analysis; this should be accounted for in the sample size calculation.

### 2.3 Design Techniques to Avoid Bias

The most important design techniques for avoiding bias in clinical trials are blinding and randomisation, and these should be normal features of most controlled clinical trials intended to be included in a marketing application. Most such trials follow a double-blind approach in which treatments are pre-packed in accordance with a suitable randomisation schedule, and supplied to the trial centre(s) labelled only with the subject number and the treatment period so that no one involved in the conduct of the trial is aware of the specific treatment allocated to any particular subject, not even as a code letter. This approach will be assumed in Section 2.3.1 and most of Section 2.3.2, exceptions being considered at the end.

Bias can also be reduced at the design stage by specifying procedures in the protocol aimed at minimising any anticipated irregularities in trial conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems, and also to handle the problems that do occur in the analysis of data.

### 2.3.1 Blinding

Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed.

A double-blind trial is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. This includes anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. This level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded. If any of the sponsor staff who are not involved in the treatment or clinical evaluation of the subjects are required to be unblinded to the treatment code (e.g. bioanalytical scientists, auditors, those involved in serious adverse event reporting), the sponsor should have adequate standard operating procedures to guard against inappropriate dissemination of treatment codes. In a single-blind trial the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa. In an open-label trial the identity of treatment is known to all. The double-blind trial is the optimal approach. This requires that the treatments to be applied during the trial cannot be distinguished (appearance, taste, etc.) either before or during administration, and that the blind is maintained appropriately during the whole trial.

Difficulties in achieving the double-blind ideal can arise: the treatments may be of a completely different nature, for example, surgery and drug therapy; two drugs may have different formulations and, although they could be made indistinguishable by the use of capsules, changing the formulation might also change the pharmacokinetic and/or pharmacodynamic properties and hence require that bioequivalence of the formulations be established; the daily pattern of administration of two treatments may differ. One way of achieving double-blind conditions under these circumstances is to use a 'double-dummy' (see Glossary) technique. This technique may sometimes force an administration scheme that is sufficiently unusual to influence adversely the motivation and compliance of the subjects. Ethical difficulties may also interfere with its use when, for example, it entails dummy operative procedures. Nevertheless, extensive efforts should be made to overcome these difficulties.

The double-blind nature of some clinical trials may be partially compromised by apparent treatment induced effects. In such cases, blinding may be improved by blinding investigators and relevant sponsor staff to certain test results (e.g. selected clinical laboratory measures). Similar approaches (see below) to minimising bias in open-label trials should be considered in trials where unique or specific treatment effects may lead to unblinding individual patients.

If a double -blind trial is not feasible, then the single-blind option should be considered. In some cases only an open-label trial is practically or ethically possible. Single-blind and open-label trials provide additional flexibility, but it is particularly important that the investigator's knowledge of the next treatment should not

influence the decision to enter the subject; this decision should precede knowledge of the randomised treatment. For these trials, consideration should be given to the use of a centralised randomisation method, such as telephone randomisation, to administer the assignment of randomised treatment. In addition, clinical assessments should be made by medical staff who are not involved in treating the subjects and who remain blind to treatment. In single-blind or open-label trials every effort should be made to minimise the various known sources of bias and primary variables should be as objective as possible. The reasons for the degree of blinding adopted should be explained in the protocol, together with steps taken to minimise bias by other means. For example, the sponsor should have adequate standard operating procedures to ensure that access to the treatment code is appropriately restricted during the process of cleaning the database prior to its release for analysis.

Breaking the blind (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the subject's physician for the subject's care. Any intentional or unintentional breaking of the blind should be reported and explained at the end of the trial, irrespective of the reason for its occurrence. The procedure and timing for revealing the treatment assignments should be documented.

In this document, the blind review (see Glossary) of data refers to the checking of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind.

### *2.3.2 Randomisation*

Randomisation introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

The randomisation schedule of a clinical trial documents the random allocation of treatments to subjects. In the simplest situation it is a sequential list of treatments (or treatment sequences in a crossover trial) or corresponding codes by subject number. The logistics of some trials, such as those with a screening phase, may make matters more complicated, but the unique pre-planned assignment of treatment, or treatment sequence, to subject should be clear. Different trial designs will require different procedures for generating randomisation schedules. The randomisation schedule should be reproducible (if the need arises).

Although unrestricted randomisation is an acceptable approach, some advantages can generally be gained by randomising subjects in blocks. This helps to increase the comparability of the treatment groups, particularly when subject characteristics may change over time, as a result, for example, of changes in recruitment policy. It also provides a better guarantee that the treatment groups will be of nearly equal size. In crossover trials it provides the means of obtaining balanced designs with their greater efficiency and easier interpretation. Care should be taken to choose block lengths that are sufficiently short to limit possible imbalance, but that are long enough to avoid predictability towards the end of the sequence in a block. Investigators and other relevant staff should generally be blind to the

block length; the use of two or more block lengths, randomly selected for each block, can achieve the same purpose. (Theoretically, in a double-blind trial predictability does not matter, but the pharmacological effects of drugs may provide the opportunity for intelligent guesswork.)

In multicentre trials (see Glossary) the randomisation procedures should be organised centrally. It is advisable to have a separate random scheme for each centre, i.e. to stratify by centre or to allocate several whole blocks to each centre. More generally, stratification by important prognostic factors measured at baseline (e.g. severity of disease, age, sex, etc.) may sometimes be valuable in order to promote balanced allocation within strata; this has greater potential benefit in small trials. The use of more than two or three stratification factors is rarely necessary, is less successful at achieving balance and is logistically troublesome. The use of a dynamic allocation procedure (see below) may help to achieve balance across a number of stratification factors simultaneously provided the rest of the trial procedures can be adjusted to accommodate an approach of this type. Factors on which randomisation has been stratified should be accounted for later in the analysis.

The next subject to be randomised into a trial should always receive the treatment corresponding to the next free number in the appropriate randomisation schedule (in the respective stratum, if randomisation is stratified). The appropriate number and associated treatment for the next subject should only be allocated when entry of that subject to the randomised part of the trial has been confirmed. Details of the randomisation that facilitate predictability (e.g. block length) should not be contained in the trial protocol. The randomisation schedule itself should be filed securely by the sponsor or an independent party in a manner that ensures that blindness is properly maintained throughout the trial. Access to the randomisation schedule during the trial should take into account the possibility that, in an emergency, the blind may have to be broken for any subject. The procedure to be followed, the necessary documentation, and the subsequent treatment and assessment of the subject should all be described in the protocol.

Dynamic allocation is an alternative procedure in which the allocation of treatment to a subject is influenced by the current balance of allocated treatments and, in a stratified trial, by the stratum to which the subject belongs and the balance within that stratum. Deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation. Every effort should be made to retain the double-blind status of the trial. For example, knowledge of the treatment code may be restricted to a central trial office from where the dynamic allocation is controlled, generally through telephone contact. This in turn permits additional checks of eligibility criteria and establishes entry into the trial, features that can be valuable in certain types of multicentre trial. The usual system of pre-packing and labelling drug supplies for double-blind trials can then be followed, but the order of their use is no longer sequential. It is desirable to use appropriate computer algorithms to keep personnel at the central trial office blind to the treatment code. The complexity of the logistics and potential impact on the analysis should be carefully evaluated when considering dynamic allocation.

## 3. TRIAL DESIGN CONSIDERATIONS

### 3.1 Design Configuration

#### *3.1.1 Parallel Group Design*

The most common clinical trial design for confirmatory trials is the parallel group design in which subjects are randomised to one of two or more arms, each arm being allocated a different treatment. These treatments will include the investigational product at one or more doses, and one or more control treatments, such as placebo and/or an active comparator. The assumptions underlying this design are less complex than for most other designs. However, as with other designs, there may be additional features of the trial that complicate the analysis and interpretation (e.g. covariates, repeated measurements over time, interactions between design factors, protocol violations, dropouts (see Glossary) and withdrawals).

#### *3.1.2 Crossover Design*

In the crossover design, each subject is randomised to a sequence of two or more treatments, and hence acts as his own control for treatment comparisons. This simple manoeuvre is attractive primarily because it reduces the number of subjects and usually the number of assessments needed to achieve a specific power, sometimes to a marked extent. In the simplest 2×2 crossover design each subject receives each of two treatments in randomised order in two successive treatment periods, often separated by a washout period. The most common extension of this entails comparing n(>2) treatments in n periods, each subject receiving all n treatments. Numerous variations exist, such as designs in which each subject receives a subset of n(>2) treatments, or ones in which treatments are repeated within a subject.

Crossover designs have a number of problems that can invalidate their results. The chief difficulty concerns carryover, that is, the residual influence of treatments in subsequent treatment periods. In an additive model the effect of unequal carryover will be to bias direct treatment comparisons. In the 2×2 design the carryover effect cannot be statistically distinguished from the interaction between treatment and period and the test for either of these effects lacks power because the corresponding contrast is 'between subject'. This problem is less acute in higher order designs, but cannot be entirely dismissed.

When the crossover design is used it is therefore important to avoid carryover. This is best done by selective and careful use of the design on the basis of adequate knowledge of both the disease area and the new medication. The disease under study should be chronic and stable. The relevant effects of the medication should develop fully within the treatment period. The washout periods should be sufficiently long for complete reversibility of drug effect. The fact that these conditions are likely to be met should be established in advance of the trial by means of prior information and data.

There are additional problems that need careful attention in crossover trials. The most notable of these are the complications of analysis and interpretation arising from the loss of subjects. Also, the potential for carryover leads to difficulties in assigning adverse events which occur in later treatment periods to the appropriate treatment. These, and other issues, are described in ICH E4. The crossover design

should generally be restricted to situations where losses of subjects from the trial are expected to be small.

A common, and generally satisfactory, use of the 2×2 crossover design is to demonstrate the bioequivalence of two formulations of the same medication. In this particular application in healthy volunteers, carryover effects on the relevant pharmacokinetic variable are most unlikely to occur if the wash-out time between the two periods is sufficiently long. However it is still important to check this assumption during analysis on the basis of the data obtained, for example by demonstrating that no drug is detectable at the start of each period.

### *3.1.3 Factorial Designs*

In a factorial design two or more treatments are evaluated simultaneously through the use of varying combinations of the treatments. The simplest example is the 2×2 factorial design in which subjects are randomly allocated to one of the four possible combinations of two treatments, A and B say. These are: A alone; B alone; both A and B; neither A nor B. In many cases this design is used for the specific purpose of examining the interaction of A and B. The statistical test of interaction may lack power to detect an interaction if the sample size was calculated based on the test for main effects. This consideration is important when this design is used for examining the joint effects of A and B, in particular, if the treatments are likely to be used together.

Another important use of the factorial design is to establish the dose-response characteristics of the simultaneous use of treatments C and D, especially when the efficacy of each monotherapy has been established at some dose in prior trials. A number, m, of doses of C is selected, usually including a zero dose (placebo), and a similar number, n, of doses of D. The full design then consists of m×n treatment groups, each receiving a different combination of doses of C and D. The resulting estimate of the response surface may then be used to help to identify an appropriate combination of doses of C and D for clinical use (see ICH E4).

In some cases, the 2×2 design may be used to make efficient use of clinical trial subjects by evaluating the efficacy of the two treatments with the same number of subjects as would be required to evaluate the efficacy of either one alone. This strategy has proved to be particularly valuable for very large mortality trials. The efficiency and validity of this approach depends upon the absence of interaction between treatments A and B so that the effects of A and B on the primary efficacy variables follow an additive model, and hence the effect of A is virtually identical whether or not it is additional to the effect of B. As for the crossover trial, evidence that this condition is likely to be met should be established in advance of the trial by means of prior information and data.

## 3.2 Multicentre Trials

Multicentre trials are carried out for two main reasons. Firstly, a multicentre trial is an accepted way of evaluating a new medication more efficiently; under some circumstances, it may present the only practical means of accruing sufficient subjects to satisfy the trial objective within a reasonable time-frame. Multicentre trials of this nature may, in principle, be carried out at any stage of clinical development. They may have several centres with a large number of subjects per centre or, in the case of a rare disease, they may have a large number of centres with very few subjects per centre.

Secondly, a trial may be designed as a multicentre (and multi -investigator) trial primarily to provide a better basis for the subsequent generalisation of its findings. This arises from the possibility of recruiting the subjects from a wider population and of administering the medication in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. In this case the involvement of a number of investigators also gives the potential for a wider range of clinical judgement concerning the value of the medication. Such a trial would be a confirmatory trial in the later phases of drug development and would be likely to involve a large number of investigators and centres. It might sometimes be conducted in a number of different countries in order to facilitate generalisability (see Glossary) even further.

If a multicentre trial is to be meaningfully interpreted and extrapolated, then the manner in which the protocol is implemented should be clear and similar at all centres. Furthermore the usual sample size and power calculations depend upon the assumption that the differences between the compared treatments in the centres are unbiased estimates of the same quantity. It is important to design the common protocol and to conduct the trial with this background in mind. Procedures should be standardised as completely as possible. Variation of evaluation criteria and schemes can be reduced by investigator meetings, by the training of personnel in advance of the trial and by careful monitoring during the trial. Good design should generally aim to achieve the same distribution of subjects to treatments within each centre and good management should maintain this design objective. Trials that avoid excessive variation in the numbers of subjects per centre and trials that avoid a few very small centres have advantages if it is later found necessary to take into account the heterogeneity of the treatment effect from centre to centre, because they reduce the differences between different weighted estimates of the treatment effect. (This point does not apply to trials in which all centres are very small and in which centre does not feature in the analysis.) Failure to take these precautions, combined with doubts about the homogeneity of the results may, in severe cases, reduce the value of a multicentre trial to such a degree that it cannot be regarded as giving convincing evidence for the sponsor's claims.

In the simplest multicentre trial, each investigator will be responsible for the subjects recruited at one hospital, so that 'centre' is identified uniquely by either investigator or hospital. In many trials, however, the situation is more complex. One investigator may recruit subjects from several hospitals; one investigator may represent a team of clinicians (subinvestigators) who all recruit subjects from their own clinics at one hospital or at several associated hospitals. Whenever there is room for doubt about the definition of centre in a statistical model, the statistical section of the protocol (see Section 5.1) should clearly define the term (e.g. by investigator, location or region) in the context of the particular trial. In most instances centres can be satisfactorily defined through the investigators and ICH E6 provides relevant guidance in this respect. In cases of doubt the aim should be to define centres so as to achieve homogeneity in the important factors affecting the measurements of the primary variables and the influence of the treatments. Any rules for combining centres in the analysis should be justified and specified prospectively in the protocol where possible, but in any case decisions concerning this approach should always be taken blind to treatment, for example at the time of the blind review.

The statistical model to be adopted for the estimation and testing of treatment effects should be described in the protocol. The main treatment effect may be investigated first using a model which allows for centre differences, but does not include a term for treatment-by-centre interaction. If the treatment effect is homogeneous across centres, the routine inclusion of interaction terms in the model reduces the efficiency of the test for the main effects. In the presence of true heterogeneity of treatment effects, the interpretation of the main treatment effect is controversial.

In some trials, for example some large mortality trials with very few subjects per centre, there may be no reason to expect the centres to have any influence on the primary or secondary variables because they are unlikely to represent influences of clinical importance. In other trials it may be recognised from the start that the limited numbers of subjects per centre will make it impracticable to include the centre effects in the statistical model. In these cases it is not appropriate to include a term for centre in the model, and it is not necessary to stratify the randomisation by centre in this situation.

If positive treatment effects are found in a trial with appreciable numbers of subjects per centre, there should generally be an exploration of the heterogeneity of treatment effects across centres, as this may affect the generalisability of the conclusions. Marked heterogeneity may be identified by graphical display of the results of individual centres or by analytical methods, such as a significance test of the treatment-by-centre interaction. When using such a statistical significance test, it is important to recognise that this generally has low power in a trial designed to detect the main effect of treatment.

If heterogeneity of treatment effects is found, this should be interpreted with care and vigorous attempts should be made to find an explanation in terms of other features of trial management or subject characteristics. Such an explanation will usually suggest appropriate further analysis and interpretation. In the absence of an explanation, heterogeneity of treatment effect as evidenced, for example, by marked quantitative interactions (see Glossary) implies that alternative estimates of the treatment effect may be required, giving different weights to the centres, in order to substantiate the robustness of the estimates of treatment effect. It is even more important to understand the basis of any heterogeneity characterised by marked qualitative interactions (see Glossary), and failure to find an explanation may necessitate further clinical trials before the treatment effect can be reliably predicted.

Up to this point the discussion of multicentre trials has been based on the use of fixed effect models. Mixed models may also be used to explore the heterogeneity of the treatment effect. These models consider centre and treatment-by-centre effects to be random, and are especially relevant when the number of sites is large.

## 3.3 Type of Comparison

### *3.3.1 Trials to Show Superiority*

Scientifically, efficacy is most convincingly established by demonstrating superiority to placebo in a placebo- controlled trial, by showing superiority to an active control treatment or by demonstrating a dose-response relationship. This type of trial is referred to as a 'superiority' trial (see Glossary). Generally in this guidance superiority trials are assumed, unless it is explicitly stated otherwise.

For serious illnesses, when a therapeutic treatment which has been shown to be efficacious by superiority trial(s) exists, a placebo-controlled trial may be considered unethical. In that case the scientifically sound use of an active treatment as a control should be considered. The appropriateness of placebo control vs. active control should be considered on a trial by trial basis.

### 3.3.2 Trials to Show Equivalence or Non-inferiority

In some cases, an investigational product is compared to a reference treatment without the objective of showing superiority. This type of trial is divided into two major categories according to its objective; one is an 'equivalence' trial (see Glossary) and the other is a 'non-inferiority' trial (see Glossary).

Bioequivalence trials fall into the former category. In some situations, clinical equivalence trials are also undertaken for other regulatory reasons such as demonstrating the clinical equivalence of a generic product to the marketed product when the compound is not absorbed and therefore not present in the blood stream.

Many active control trials are designed to show that the efficacy of an investigational product is no worse than that of the active comparator, and hence fall into the latter category. Another possibility is a trial in which multiple doses of the investigational drug are compared with the recommended dose or multiple doses of the standard drug. The purpose of this design is simultaneously to show a dose-response relationship for the investigational product and to compare the investigational product with the active control.

Active control equivalence or non- inferiority trials may also incorporate a placebo, thus pursuing multiple goals in one trial; for example, they may establish superiority to placebo and hence validate the trial design and simultaneously evaluate the degree of similarity of efficacy and safety to the active comparator. There are well known difficulties associated with the use of the active control equivalence (or non-inferiority) trials that do not incorporate a placebo or do not use multiple doses of the new drug. These relate to the implicit lack of any measure of internal validity (in contrast to superiority trials), thus making external validation necessary. The equivalence (or non-inferiority) trial is not conservative in nature, so that many flaws in the design or conduct of the trial will tend to bias the results towards a conclusion of equivalence. For these reasons, the design features of such trials should receive special attention and their conduct needs special care. For example, it is especially important to minimise the incidence of violations of the entry criteria, non-compliance, withdrawals, losses to follow-up, missing data and other deviations from the protocol, and also to minimise their impact on the subsequent analyses.

Active comparators should be chosen with care. An example of a suitable active comparator would be a widely used therapy whose efficacy in the relevant indication has been clearly established and quantified in well-designed and well-documented superiority trial(s) and which can be reliably expected to exhibit similar efficacy in the contemplated active control trial. To this end, the new trial should have the same important design features (primary variables, the dose of the active comparator, eligibility criteria, etc.) as the previously conducted superiority trials in which the active comparator clearly demonstrated clinically relevant efficacy, taking into account advances in medical or statistical practice relevant to the new trial.

It is vital that the protocol of a trial designed to demonstrate equivalence or non- inferiority contain a clear statement that this is its explicit intention. An equivalence margin should be specified in the protocol; this margin is the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator. For the active control equivalence trial, both the upper and the lower equivalence margins are needed, while only the lower margin is needed for the active control non-inferiority trial. The choice of equivalence margins should be justified clinically.

Statistical analysis is generally based on the use of confidence intervals (see Section 5.5). For equivalence trials, two-sided confidence intervals should be used. Equivalence is inferred when the entire confidence interval falls within the equivalence margins. Operationally, this is equivalent to the method of using two simultaneous one-sided tests to test the (composite) null hypothesis that the treatment difference is outside the equivalence margins versus the (composite) alternative hypothesis that the treatment difference is within the margins. Because the two null hypotheses are disjoint, type I error is appropriately controlled. For non -inferiority trials a one-sided interval should be used. The confidence interval approach has a one-sided hypothesis test counterpart for testing the null hypothesis that the treatment difference (investigational product minus control) is equal to the lower equivalence margin versus the alternative that the treatment difference is greater than the lower equivalence margin. The choice of type I error should be a consideration separate from the use of a one-sided or two- sided procedure. Sample size calculations should be based on these methods (see Section 3.5).

Concluding equivalence or non-inferiority based on observing a non-significant test result of the null hypothesis that there is no difference between the investigational product and the active comparator is inappropriate.

There are also special issues in the choice of analysis sets. Subjects who withdraw or dropout of the treatment group or the comparator group will tend to have a lack of response, and hence the results of using the full analysis set (see Glossary) may be biased toward demonstrating equivalence (see Section 5.2.3).

### *3.3.3 Trials to Show Dose-response Relationship*

How response is related to the dose of a new investigational product is a question to which answers may be obtained in all phases of development, and by a variety of approaches (see ICH E4). Dose -response trials may serve a number of objectives, amongst which the following are of particular importance: the confirmation of efficacy; the investigation of the shape and location of the dose-response curve; the estimation of an appropriate starting dose; the identification of optimal strategies for individual dose adjustments; the determination of a maximal dose beyond which additional benefit would be unlikely to occur. These objectives should be addressed using the data collected at a number of doses under investigation, including a placebo (zero dose) wherever appropriate. For this purpose the application of procedures to estimate the relationship between dose and response, including the construction of confidence intervals and the use of graphical methods, is as important as the use of statistical tests. The hypothesis tests that are used may need to be tailored to the natural ordering of doses or to particular questions regarding the shape of the dose -response curve (e.g. monotonicity). The details of the planned statistical procedures should be given in the protocol.

### 3.4 Group Sequential Designs

Group sequential designs are used to facilitate the conduct of interim analysis (see Section 4.5 and Glossary). While group sequential designs are not the only acceptable types of designs permitting interim analysis, they are the most commonly applied because it is more practicable to assess grouped subject outcomes at periodic intervals during the trial than on a continuous basis as data from each subject become available. The statistical methods should be fully specified in advance of the availability of information on treatment outcomes and subject treatment assignments (i.e. blind breaking, see Section 4.5). An Independent Data Monitoring Committee (see Glossary) may be used to review or to conduct the interim analysis of data arising from a group sequential design (see Section 4.6). While the design has been most widely and successfully used in large, long-term trials of mortality or major non-fatal endpoints, its use is growing in other circumstances. In particular, it is recognised that safety must be monitored in all trials and therefore the need for formal procedures to cover early stopping for safety reasons should always be considered.

### 3.5 Sample Size

The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed. This number is usually determined by the primary objective of the trial. If the sample size is determined on some other basis, then this should be made clear and justified. For example, a trial sized on the basis of safety questions or requirements or important secondary objectives may need larger numbers of subjects than a trial sized on the basis of the primary efficacy question (see, for example, ICH E1a).

Using the usual method for determining the appropriate sample size, the following items should be specified: a primary variable, the test statistic, the null hypothesis, the alternative ('working') hypothesis at the chosen dose(s) (embodying consideration of the treatment difference to be detected or rejected at the dose and in the subject population selected), the probability of erroneously rejecting the null hypothesis (the type I error), and the probability of erroneously failing to reject the null hypothesis (the type II error), as well as the approach to dealing with treatment withdrawals and protocol violations. In some instances, the event rate is of primary interest for evaluating power, and assumptions should be made to extrapolate from the required number of events to the eventual sample size for the trial.

The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculations (such as variances, mean values, response rates, event rates, difference to be detected). The basis of these estimates should also be given. It is important to investigate the sensitivity of the sample size estimate to a variety of deviations from these assumptions and this may be facilitated by providing a range of sample sizes appropriate for a reasonable range of deviations from assumptions. In confirmatory trials, assumptions should normally be based on published data or on the results of earlier trials. The treatment difference to be detected may be based on a judgement concerning the minimal effect which has clinical relevance in the management of patients or on a judgement concerning the anticipated effect of the new treatment, where this is larger. Conventionally the probability of type I error is set at 5% or less or as dictated by any adjustments made necessary for multiplicity considerations; the precise choice may be influenced by the prior plausibility of the

hypothesis under test and the desired impact of the results. The probability of type II error is conventionally set at 10 to 20%; it is in the sponsor's interest to keep this figure as low as feasible especially in the case of trials that are difficult or impossible to repeat. Alternative values to the conventional levels of type I and type II error may be acceptable or even preferable in some cases.

Sample size calculations should refer to the number of subjects required for the primary analysis. If this is the 'full analysis set', estimates of the effect size may need to be reduced compared to the per protocol set (see Glossary). This is to allow for the dilution of the treatment effect arising from the inclusion of data from patients who have withdrawn from treatment or whose compliance is poor. The assumptions about variability may also need to be revised.

The sample size of an equivalence trial or a non-inferiority trial (see Section 3.3.2) should normally be based on the objective of obtaining a confidence interval for the treatment difference that shows that the treatments differ at most by a clinically acceptable difference. When the power of an equivalence trial is assessed at a true difference of zero, then the sample size necessary to achieve this power is underestimated if the true difference is not zero. When the power of a non - inferiority trial is assessed at a zero difference, then the sample size needed to achieve that power will be underestimated if the effect of the investigational product is less than that of the active control. The choice of a 'clinically acceptable' difference needs justification with respect to its meaning for future patients, and may be smaller than the 'clinically relevant' difference referred to above in the context of superiority trials designed to establish that a difference exists.

The exact sample size in a group sequential trial cannot be fixed in advance because it depends upon the play of chance in combination with the chosen stopping guideline and the true treatment difference. The design of the stopping guideline should take into account the consequent distribution of the sample size, usually embodied in the expected and maximum sample sizes.

When event rates are lower than anticipated or variability is larger than expected, methods for sample size re-estimation are available without unblinding data or making treatment comparisons (see Section 4.4).

### 3.6 Data Capture and Processing

The collection of data and transfer of data from the investigator to the sponsor can take place through a variety of media, including paper case record forms, remote site monitoring systems, medical computer systems and electronic transfer. Whatever data capture instrument is used, the form and content of the information collected should be in full accordance with the protocol and should be established in advance of the conduct of the clinical trial. It should focus on the data necessary to implement the planned analysis, including the context information (such as timing assessments relative to dosing) necessary to confirm protocol compliance or identify important protocol deviations. 'Missing values' should be distinguishable from the 'value zero' or 'characteristic absent'.

The process of data capture through to database finalisation should be carried out in accordance with GCP (see ICH E6, Section 5). Specifically, timely and reliable processes for recording data and rectifying errors and omissions are necessary to ensure delivery of a quality database and the achievement of the trial objectives through the implementation of the planned analysis.

## 4 TRIAL CONDUCT CONSIDERATIONS

### 4.1 Trial Monitoring and Interim Analysis

Careful conduct of a clinical trial according to the protocol has a major impact on the credibility of the results (see ICH E6). Careful monitoring can ensure that difficulties are noticed early and their occurrence or recurrence minimised.

There are two distinct types of monitoring that generally characterise confirmatory clinical trials sponsored by the pharmaceutical industry. One type of monitoring concerns the oversight of the quality of the trial, while the other type involves breaking the blind to make treatment comparisons (i.e. interim analysis). Both types of trial monitoring, in addition to entailing different staff responsibilities, involve access to different types of trial data and information, and thus different principles apply for the control of potential statistical and operational bias.

For the purpose of overseeing the quality of the trial the checks involved in trial monitoring may include whether the protocol is being followed, the acceptability of data being accrued, the success of planned accrual targets, the appropriateness of the design assumptions, success in keeping patients in the trials, etc. (see Sections 4.2 to 4.4). This type of monitoring does not require access to information on comparative treatment effects, nor unblinding of data and therefore has no impact on type I error. The monitoring of a trial for this purpose is the responsibility of the sponsor (see ICH E6) and can be carried out by the sponsor or an independent group selected by the sponsor. The period for this type of monitoring usually starts with the selection of the trial sites and ends with the collection and cleaning of the last subject's data.

The other type of trial monitoring (interim analysis) involves the accruing of comparative treatment results. Interim analysis requires unblinded (i.e. key breaking) access to treatment group assignment (actual treatment assignment or identification of group assignment) and comparative treatment group summary information. This necessitates that the protocol (or appropriate amendments prior to a first analysis) contains statistical plans for the interim analysis to prevent certain types of bias. This is discussed in Sections 4.5 and 4.6.

### 4.2 Changes in Inclusion and Exclusion Criteria

Inclusion and exclusion criteria should remain constant, as specified in the protocol, throughout the period of subject recruitment. Changes may occasionally be appropriate, for example, in long term trials, where growing medical knowledge either from outside the trial or from interim analyses may suggest a change of entry criteria. Changes may also result from the discovery by monitoring staff that regular violations of the entry criteria are occurring, or that seriously low recruitment rates are due to over -restrictive criteria. Changes should be made without breaking the blind and should always be described by a protocol amendment which should cover any statistical consequences, such as sample size adjustments arising from different event rates, or modifications to the planned analysis, such as stratifying the analysis according to modified inclusion/exclusion criteria.

### 4.3 Accrual Rates

In trials with a long time -scale for the accrual of subjects, the rate of accrual should be monitored and, if it falls appreciably below the projected level, the reasons

should be identified and remedial actions taken in order to protect the power of the trial and alleviate concerns about selective entry and other aspects of quality. In a multicentre trial these considerations apply to the individual centres.

### 4.4 Sample Size Adjustment

In long term trials there will usually be an opportunity to check the assumptions which underlay the original design and sample size calculations. This may be particularly important if the trial specifications have been made on preliminary and/or uncertain information. An interim check conducted on the blinded data may reveal that overall response variances, event rates or survival experience are not as anticipated. A revised sample size may then be calculated using suitably modified assumptions, and should be justified and documented in a protocol amendment and in the clinical study report. The steps taken to preserve blindness and the consequences, if any, for the type I error and the width of confidence intervals should be explained. The potential need for re-estimation of the sample size should be envisaged in the protocol whenever possible (see Section 3.5).

### 4.5 Interim Analysis and Early Stopping

An interim analysis is any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a trial. Because the number, methods and consequences of these comparisons affect the interpretation of the trial, all interim analyses should be carefully planned in advance and described in the protocol. Special circumstances may dictate the need for an interim analysis that was not defined at the start of a trial. In these cases, a protocol amendment describing the interim analysis should be completed prior to unblinded access to treatment comparison data. When an interim analysis is planned with the intention of deciding whether or not to terminate a trial, this is usually accomplished by the use of a group sequential design which employs statistical monitoring schemes as guidelines (see Section 3.4). The goal of such an interim analysis is to stop the trial early if the superiority of the treatment under study is clearly established, if the demonstration of a relevant treatment difference has become unlikely or if unacceptable adverse effects are apparent. Generally, boundaries for monitoring efficacy require more evidence to terminate a trial early (i.e. they are more conservative) than boundaries for monitoring safety. When the trial design and monitoring objective involve multiple endpoints then this aspect of multiplicity may also need to be taken into account.

The protocol should describe the schedule of interim analyses, or at least the considerations which will govern its generation, for example if flexible alpha spending function approaches are to be employed; further details may be given in a protocol amendment before the time of the first interim analysis. The stopping guidelines and their properties should be clearly described in the protocol or amendments. The potential effects of early stopping on the analysis of other important variables should also be considered. This material should be written or approved by the Data Monitoring Committee (see Section 4.6), when the trial has one. Deviations from the planned procedure always bear the potential of invalidating the trial results. If it becomes necessary to make changes to the trial, any consequent changes to the statistical procedures should be specified in an amendment to the protocol at the earliest opportunity, especially discussing the impact on any analysis

and inferences that such changes may cause. The procedures selected should always ensure that the overall probability of type I error is controlled.

The execution of an interim analysis should be a completely confidential process because unblinded data and results are potentially involved. All staff involved in the conduct of the trial should remain blind to the results of such analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons. This principle may be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the interim analysis. Investigators should only be informed about the decision to continue or to discontinue the trial, or to implement modifications to trial procedures.

Most clinical trials intended to support the efficacy and safety of an investigational product should proceed to full completion of planned sample size accrual; trials should be stopped early only for ethical reasons or if the power is no longer acceptable. However, it is recognised that drug development plans involve the need for sponsor access to comparative treatment data for a variety of reasons, such as planning other trials. It is also recognised that only a subset of trials will involve the study of serious life-threatening outcomes or mortality which may need sequential monitoring of accruing comparative treatment effects for ethical reasons. In either of these situations, plans for interim statistical analysis should be in place in the protocol or in protocol amendments prior to the unblinded access to comparative treatment data in order to deal with the potential statistical and operational bias that may be introduced.

For many clinical trials of investigational products, especially those that have major public health significance, the responsibility for monitoring comparisons of efficacy and/or safety outcomes should be assigned to an external independent group, often called an Independent Data Monitoring Committee (IDMC), a Data and Safety Monitoring Board or a Data Monitoring Committee whose responsibilities should be clearly described.

When a sponsor assumes the role of monitoring efficacy or safety comparisons and therefore has access to unblinded comparative information, particular care should be taken to protect the integrity of the trial and to manage and limit appropriately the sharing of information. The sponsor should assure and document that the internal monitoring committee has complied with written standard operating procedures and that minutes of decision making meetings including records of interim results are maintained.

Any interim analysis that is not planned appropriately (with or without the consequences of stopping the trial early) may flaw the results of a trial and possibly weaken confidence in the conclusions drawn. Therefore, such analyses should be avoided. If unplanned interim analysis is conducted, the clinical study report should explain why it was necessary, the degree to which blindness had to be broken, provide an assessment of the potential magnitude of bias introduced, and the impact on the interpretation of the results.

4.6 Role of Independent Data Monitoring Committee (IDMC) (see Sections 1.25 and 5.52 of ICH E6)

An IDMC may be established by the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial. The IDMC should have

written operating procedures and maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. The independence of the IDMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. The IDMC is a separate entity from an Institutional Review Board (IRB) or an Independent Ethics Committee (IEC), and its composition should include clinical trial scientists knowledgeable in the appropriate disciplines including statistics.

When there are sponsor representatives on the IDMC, their role should be clearly defined in the operating procedures of the committee (for example, covering whether or not they can vote on key issues). Since these sponsor staff would have access to unblinded information, the procedures should also address the control of dissemination of interim trial results within the sponsor organisation.

## 5 DATA ANALYSIS CONSIDERATIONS

### 5.1 Pre-specification of the Analysis

When designing a clinical trial the principal features of the eventual statistical analysis of the data should be described in the statistical section of the protocol. This section should include all the principal features of the proposed confirmatory analysis of the primary variable(s) and the way in which anticipated analysis problems will be handled. In case of exploratory trials this section could describe more general principles and directions.

The statistical analysis plan (see Glossary) may be written as a separate document to be completed after finalising the protocol. In this document, a more technical and detailed elaboration of the principal features stated in the protocol may be included (see Section 7.1). The plan may include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The plan should be reviewed and possibly updated as a result of the blind review of the data (see Section 7.1 for definition) and should be finalised before breaking the blind. Formal records should be kept of when the statistical analysis plan was finalised as well as when the blind was subsequently broken.

If the blind review suggests changes to the principal features stated in the protocol, these should be documented in a protocol amendment. Otherwise, it will suffice to update the statistical analysis plan with the considerations suggested from the blind review. Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.

In the statistical section of the clinical study report the statistical methodology should be clearly described including when in the clinical trial process methodology decisions were made (see ICH E3).

### 5.2 Analysis Sets

The set of subjects whose data are to be included in the main analyses should be defined in the statistical section of the protocol. In addition, documentation for all subjects for whom trial procedures (e.g. run-in period) were initiated may be useful. The content of this subject documentation depends on detailed features of the particular trial, but at least demographic and baseline data on disease status should be collected whenever possible.

If all subjects randomised into a clinical trial satisfied all entry criteria, followed all trial procedures perfectly with no losses to follow-up, and provided complete data records, then the set of subjects to be included in the analysis would be self-evident. The design and conduct of a trial should aim to approach this ideal as closely as possible, but, in practice, it is doubtful if it can ever be fully achieved. Hence, the statistical section of the protocol should address anticipated problems prospectively in terms of how these affect the subjects and data to be analysed. The protocol should also specify procedures aimed at minimising any anticipated irregularities in study conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems, and also to handle the problems that do occur in the analysis of data. Possible amendments to the way in which the analysis will deal with protocol violations should be identified during the blind review. It is desirable to identify any important protocol violation with respect to the time when it occurred, its cause and influence on the trial result. The frequency and type of protocol violations, missing values, and other problems should be documented in the clinical study report and their potential influence on the trial results should be described (see ICH E3).

Decisions concerning the analysis set should be guided by the following principles : 1) to minimise bias, and 2) to avoid inflation of type I error.

### *5.2.1 Full Analysis Set*

The intention-to-treat (see Glossary) principle implies that the primary analysis should include all randomised subjects. Compliance with this principle would necessitate complete follow-up of all randomised subjects for study outcomes. In practice this ideal may be difficult to achieve, for reasons to be described. In this document the term 'full analysis set' is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects. Preservation of the initial randomisation in analysis is important in preventing bias and in providing a secure foundation for statistical tests. In many clinical trials the use of the full analysis set provides a conservative strategy. Under many circumstances it may also provide estimates of treatment effects which are more likely to mirror those observed in subsequent practice.

There are a limited number of circumstances that might lead to excluding randomised subjects from the full analysis set including the failure to satisfy major entry criteria (eligibility violations), the failure to take at least one dose of trial medication and the lack of any data post randomisation. Such exclusions should always be justified. Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:

(i) The entry criterion was measured prior to randomisation;
(ii) The detection of the relevant eligibility violations can be made completely objectively;
(iii) All subjects receive equal scrutiny for eligibility violations; (This may be difficult to ensure in an open-label study, or even in a double-blind study if the data are unblinded prior to this scrutiny, emphasising the importance of the blind review.)
(iv) All detected violations of the particular entry criterion are excluded.

In some situations, it may be reasonable to eliminate from the set of all randomised subjects any subject who took no trial medication. The intention-to-treat principle would be preserved despite the exclusion of these patients provided, for example, that the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment. In other situations it may be necessary to eliminate from the set of all randomised subjects any subject without data post randomisation. No analysis is complete unless the potential biases arising from these specific exclusions, or any others, are addressed.

When the full analysis set of subjects is used, violations of the protocol that occur after randomisation may have an impact on the data and conclusions, particularly if their occurrence is related to treatment assignment. In most respects it is appropriate to include the data from such subjects in the analysis, consistent with the intention-to- treat principle. Special problems arise in connection with subjects withdrawn from treatment after receiving one or more doses who provide no data after this point, and subjects otherwise lost to follow-up, because failure to include these subjects in the full analysis set may seriously undermine the approach. Measurements of primary variables made at the time of the loss to follow-up of a subject for any reason, or subsequently collected in accordance with the intended schedule of assessments in the protocol, are valuable in this context; subsequent collection is especially important in studies where the primary variable is mortality or serious morbidity. The intention to collect data in this way should be described in the protocol. Imputation techniques, ranging from the carrying forward of the last observation to the use of complex mathematical models, may also be used in an attempt to compensate for missing data. Other methods employed to ensure the availability of measurements of primary variables for every subject in the full analysis set may require some assumptions about the subjects' outcomes or a simpler choice of outcome (e.g. success / failure). The use of any of these strategies should be described and justified in the statistical section of the protocol and the assumptions underlying any mathematical models employed should be clearly explained. It is also important to demonstrate the robustness of the corresponding results of analysis especially when the strategy in question could itself lead to biased estimates of treatment effects.

Because of the unpredictability of some problems, it may sometimes be preferable to defer detailed consideration of the manner of dealing with irregularities until the blind review of the data at the end of the trial, and, if so, this should be stated in the protocol.

### *5.2.2 Per Protocol Set*

The 'per protocol' set of subjects, sometimes described as the 'valid cases', the 'efficacy' sample or the 'evaluable subjects' sample, defines a subset of the subjects in the full analysis set who are more compliant with the protocol and is characterised by criteria such as the following:

(i) The completion of a certain pre-specified minimal exposure to the treatment regimen;
(ii) The availability of measurements of the primary variable(s);
(iii) The absence of any major protocol violations including the violation of entry criteria.

The precise reasons for excluding subjects from the per protocol set should be fully defined and documented before breaking the blind in a manner appropriate to the circumstances of the specific trial.

The use of the per protocol set may maximise the opportunity for a new treatment to show additional efficacy in the analysis, and most closely reflects the scientific model underlying the protocol. However, the corresponding test of the hypothesis and estimate of the treatment effect may or may not be conservative depending on the trial; the bias, which may be severe, arises from the fact that adherence to the study protocol may be related to treatment and outcome.

The problems that lead to the exclusion of subjects to create the per protocol set, and other protocol violations, should be fully identified and summarised. Relevant protocol violations may include errors in treatment assignment, the use of excluded medication, poor compliance, loss to follow-up and missing data. It is good practice to assess the pattern of such problems among the treatment groups with respect to frequency and time to occurrence.

### *5.2.3 Roles of the Different Analysis Sets*

In general, it is advantageous to demonstrate a lack of sensitivity of the principal trial results to alternative choices of the set of subjects analysed. In confirmatory trials it is usually appropriate to plan to conduct both an analysis of the full analysis set and a per protocol analysis, so that any differences between them can be the subject of explicit discussion and interpretation. In some cases, it may be desirable to plan further exploration of the sensitivity of conclusions to the choice of the set of subjects analysed. When the full analysis set and the per protocol set lead to essentially the same conclusions, confidence in the trial results is increased, bearing in mind, however, that the need to exclude a substantial proportion of subjects from the per protocol analysis throws some doubt on the overall validity of the trial.

The full analysis set and the per protocol set play different roles in superiority trials (which seek to show the investigational product to be superior), and in equivalence or non-inferiority trials (which seek to show the investigational product to be comparable, see section 3.3.2). In superiority trials the full analysis set is used in the primary analysis (apart from exceptional circumstances) because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis, since the non-compliers included in the full analysis set will generally diminish the estimated treatment effect. However, in an equivalence or non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully.

## 5.3 Missing Values and Outliers

Missing values represent a potential source of bias in a clinical trial. Hence, every effort should be undertaken to fulfil all the requirements of the protocol concerning the collection and management of data. In reality, however, there will almost always be some missing data. A trial may be regarded as valid, nonetheless, provided the methods of dealing with missing values are sensible, and particularly if those methods are pre-defined in the protocol. Definition of methods may be refined by updating this aspect in the statistical analysis plan during the blind review. Unfortunately, no universally applicable methods of handling missing values can be recommended. An investigation should be made concerning the sensitivity of the results of analysis to the method of handling missing values, especially if the number of missing values is substantial.

A similar approach should be adopted to exploring the influence of outliers, the statistical definition of which is, to some extent, arbitrary. Clear identification of a particular value as an outlier is most convincing when justified medically as well as statistically, and the medical context will then often define the appropriate action. Any outlier procedure set out in the protocol or the statistical analysis plan should be such as not to favour any treatment group a priori. Once again, this aspect of the analysis can be usefully updated during blind review. If no procedure for dealing with outliers was foreseen in the trial protocol, one analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect should be performed and differences between their results discussed.

### 5.4 Data Transformation

The decision to transform key variables prior to analysis is best made during the design of the trial on the basis of similar data from earlier clinical trials. Transformations (e.g. square root, logarithm) should be specified in the protocol and a rationale provided, especially for the primary variable(s). The general principles guiding the use of transformations to ensure that the assumptions underlying the statistical methods are met are to be found in standard texts; conventions for particular variables have been developed in a number of specific clinical areas. The decision on whether and how to transform a variable should be influenced by the preference for a scale which facilitates clinical interpretation.

Similar considerations apply to other derived variables, such as the use of change from baseline, percentage change from baseline, the 'area under the curve' of repeated measures, or the ratio of two different variables. Subsequent clinical interpretation should be carefully considered, and the derivation should be justified in the protocol. Closely related points are made in Section 2.2.2.

### 5.5 Estimation, Confidence Intervals and Hypothesis Testing

The statistical section of the protocol should specify the hypotheses that are to be tested and/or the treatment effects which are to be estimated in order to satisfy the primary objectives of the trial. The statistical methods to be used to accomplish these tasks should be described for the primary (and preferably the secondary) variables, and the underlying statistical model should be made clear. Estimates of treatment effects should be accompanied by confidence intervals, whenever possible, and the way in which these will be calculated should be identified. A description should be given of any intentions to use baseline data to improve precision or to adjust estimates for potential baseline differences, for example by means of analysis of covariance.

It is important to clarify whether one- or two -sided tests of statistical significance will be used, and in particular to justify prospectively the use of one-sided tests. If hypothesis tests are not considered appropriate, then the alternative process for arriving at statistical conclusions should be given. The issue of one-sided or two-sided approaches to inference is controversial and a diversity of views can be found in the statistical literature. The approach of setting Type I errors for one-sided tests at half the conventional Type I error used in two-sided tests is preferable in regulatory settings. This promotes consistency with the two-sided confidence intervals that are generally appropriate for estimating the possible size of the difference between two treatments.

The particular statistical model chosen should reflect the current state of medical and statistical knowledge about the variables to be analysed as well as the statistical design of the trial. All effects to be fitted in the analysis (for example in analysis of variance models) should be fully specified, and the manner, if any, in which this set of effects might be modified in response to preliminary results should be explained. The same considerations apply to the set of covariates fitted in an analysis of covariance. (See also Section 5.7.). In the choice of statistical methods due attention should be paid to the statistical distribution of both primary and secondary variables. When making this choice (for example between parametric and non-parametric methods) it is important to bear in mind the need to provide statistical estimates of the size of treatment effects together with confidence intervals (in addition to significance tests).

The primary analysis of the primary variable should be clearly distinguished from supporting analyses of the primary or secondary variables. Within the statistical section of the protocol or the statistical analysis plan there should also be an outline of the way in which data other than the primary and secondary variables will be summarised and reported. This should include a reference to any approaches adopted for the purpose of achieving consistency of analysis across a range of trials, for example for safety data.

Modelling approaches that incorporate information on known pharmacological parameters, the extent of protocol compliance for individual subjects or other biologically based data may provide valuable insights into actual or potential efficacy, especially with regard to estimation of treatment effects. The assumptions underlying such models should always be clearly identified, and the limitations of any conclusions should be carefully described.

### 5.6 Adjustment of Significance and Confidence Levels

When multiplicity is present, the usual frequentist approach to the analysis of clinical trial data may necessitate an adjustment to the Type I error. Multiplicity may arise, for example, from multiple primary variables (see Section 2.2.2), multiple comparisons of treatments, repeated evaluation over time and/or interim analyses (see Section 4.5). Methods to avoid or reduce multiplicity are sometimes preferable when available, such as the identification of the key primary variable (multiple variables), the choice of a critical treatment contrast (multiple comparisons), the use of a summary measure such as 'area under the curve' (repeated measures). In confirmatory analyses, any aspects of multiplicity which remain after steps of this kind have been taken should be identified in the protocol; adjustment should always be considered and the details of any adjustment procedure or an explanation of why adjustment is not thought to be necessary should be set out in the analysis plan.

### 5.7 Subgroups, Interactions and Covariates

The primary variable(s) is often systematically related to other influences apart from treatment. For example, there may be relationships to covariates such as age and sex, or there may be differences between specific subgroups of subjects such as those treated at the different centres of a multicentre trial. In some instances an adjustment for the influence of covariates or for subgroup effects is an integral part of the planned analysis and hence should be set out in the protocol. Pre-trial

deliberations should identify those covariates and factors expected to have an important influence on the primary variable(s), and should consider how to account for these in the analysis in order to improve precision and to compensate for any lack of balance between treatment groups. If one or more factors are used to stratify the design, it is appropriate to account for those factors in the analysis. When the potential value of an adjustment is in doubt, it is often advisable to nominate the unadjusted analysis as the one for primary attention, the adjusted analysis being supportive. Special attention should be paid to centre effects and to the role of baseline measurements of the primary variable. It is not advisable to adjust the main analyses for covariates measured after randomisation because they may be affected by the treatments.

The treatment effect itself may also vary with subgroup or covariate - for example, the effect may decrease with age or may be larger in a particular diagnostic category of subjects. In some cases such interactions are anticipated or are of particular prior interest (e.g. geriatrics), and hence a subgroup analysis, or a statistical model including interactions, is part of the planned confirmatory analysis. In most cases, however, subgroup or interaction analyses are exploratory and should be clearly identified as such; they should explore the uniformity of any treatment effects found overall. In general, such analyses should proceed first through the addition of interaction terms to the statistical model in question, complemented by additional exploratory analysis within relevant subgroups of subjects, or within strata defined by the covariates. When exploratory, these analyses should be interpreted cautiously; any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted.

### 5.8 Integrity of Data and Computer Software Validity

The credibility of the numerical results of the analysis depends on the quality and validity of the methods and software (both internally and externally written) used both for data management (data entry, storage, verification, correction and retrieval) and also for processing the data statistically. Data management activities should therefore be based on thorough and effective standard operating procedures. The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available.

## 6 EVALUATION OF SAFETY AND TOLERABILITY

### 6.1 Scope of Evaluation

In all clinical trials evaluation of safety and tolerability (see Glossary) constitutes an important element. In early phases this evaluation is mostly of an exploratory nature, and is only sensitive to frank expressions of toxicity, whereas in later phases the establishment of the safety and tolerability profile of a drug can be characterised more fully in larger samples of subjects. Later phase controlled trials represent an important means of exploring in an unbiased manner any new potential adverse effects, even if such trials generally lack power in this respect.

Certain trials may be designed with the purpose of making specific claims about superiority or equivalence with regard to safety and tolerability compared

to another drug or to another dose of the investigational drug. Such specific claims should be supported by relevant evidence from confirmatory trials, similar to that necessary for corresponding efficacy claims.

### 6.2 Choice of Variables and Data Collection

In any clinical trial the methods and measurements chosen to evaluate the safety and tolerability of a drug will depend on a number of factors, including knowledge of the adverse effects of closely related drugs, information from non-clinical and earlier clinical trials and possible consequences of the pharmacodynamic/pharmacokinetic properties of the particular drug, the mode of administration, the type of subjects to be studied, and the duration of the trial. Laboratory tests concerning clinical chemistry and haematology, vital signs, and clinical adverse events (diseases, signs and symptoms) usually form the main body of the safety and tolerability data. The occurrence of serious adverse events and treatment discontinuations due to adverse events are particularly important to register (see ICH E2A and ICH E3).

Furthermore, it is recommended that a consistent methodology be used for the data collection and evaluation throughout a clinical trial program in order to facilitate the combining of data from different trials. The use of a common adverse event dictionary is particularly important. This dictionary has a structure which gives the possibility to summarise the adverse event data on three different levels; system-organ class, preferred term or included term (see Glossary). The preferred term is the level on which adverse events usually are summarised, and preferred terms belonging to the same system-organ class could then be brought together in the descriptive presentation of data (see ICH M1).

### 6.3 Set of Subjects to be Evaluated and Presentation of Data

For the overall safety and tolerability assessment, the set of subjects to be summarised is usually defined as those subjects who received at least one dose of the investigational drug. Safety and tolerability variables should be collected as comprehensively as possible from these subjects, including type of adverse event, severity, onset and duration (see ICH E2B). Additional safety and tolerability evaluations may be needed in specific subpopulations, such as females, the elderly (see ICH E7), the severely ill, or those who have a common concomitant treatment. These evaluations may need to address more specific issues (see ICH E3).

All safety and tolerability variables will need attention during evaluation, and the broad approach should be indicated in the protocol. All adverse events should be reported, whether or not they are considered to be related to treatment. All available data in the study population should be accounted for in the evaluation. Definitions of measurement units and reference ranges of laboratory variables should be made with care; if different units or different reference ranges appear in the same trial (e.g. if more than one laboratory is involved), then measurements should be appropriately standardised to allow a unified evaluation. Use of a toxicity grading scale should be prespecified and justified.

The incidence of a certain adverse event is usually expressed in the form of a proportion relating number of subjects experiencing events to number of subjects at risk. However, it is not always self-evident how to assess incidence. For example, depending on the situation the number of exposed subjects or the extent of exposure

(in person -years) could be considered for the denominator. Whether the purpose of the calculation is to estimate a risk or to make a comparison between treatment groups it is important that the definition is given in the protocol. This is especially important if long-term treatment is planned and a substantial proportion of treatment withdrawals or deaths are expected. For such situations survival analysis methods should be considered and cumulative adverse event rates calculated in order to avoid the risk of underestimation.

In situations when there is a substantial background noise of signs and symptoms (e.g. in psychiatric trials) one should consider ways of accounting for this in the estimation of risk for different adverse events. One such method is to make use of the 'treatment emergent' (see Glossary) concept in which adverse events are recorded only if they emerge or worsen relative to pretreatment baseline.

Other methods to reduce the effect of the background noise may also be appropriate such as ignoring adverse events of mild severity or requiring that an event should have been observed at repeated visits to qualify for inclusion in the numerator. Such methods should be explained and justified in the protocol.

### 6.4 Statistical Evaluation

The investigation of safety and tolerability is a multidimensional problem. Although some specific adverse effects can usually be anticipated and specifically monitored for any drug, the range of possible adverse effects is very large, and new and unforeseeable effects are always possible. Further, an adverse event experienced after a protocol violation, such as use of an excluded medication, may introduce a bias. This background underlies the statistical difficulties associated with the analytical evaluation of safety and tolerability of drugs, and means that conclusive information from confirmatory clinical trials is the exception rather than the rule.

In most trials the safety and tolerability implications are best addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals wherever this aids interpretation. It is also valuable to make use of graphical presentations in which patterns of adverse events are displayed both within treatment groups and within subjects.

The calculation of p-values is sometimes useful either as an aid to evaluating a specific difference of interest, or as a 'flagging' device applied to a large number of safety and tolerability variables to highlight differences worth further attention. This is particularly useful for laboratory data, which otherwise can be difficult to summarise appropriately. It is recommended that laboratory data be subjected to both a quantitative analysis, e.g. evaluation of treatment means, and a qualitative analysis where counting of numbers above or below certain thresholds are calculated.

If hypothesis tests are used, statistical adjustments for multiplicity to quantify the type I error are appropriate, but the type II error is usually of more concern. Care should be taken when interpreting putative statistically significant findings when there is no multiplicity adjustment.

In the majority of trials investigators are seeking to establish that there are no clinically unacceptable differences in safety and tolerability compared with either a comparator drug or a placebo. As is the case for non- inferiority or equivalence evaluation of efficacy the use of confidence intervals is preferred to hypothesis testing in this situation. In this way, the considerable imprecision often arising from low frequencies of occurrence is clearly demonstrated.

### 6.5 Integrated Summary

The safety and tolerability properties of a drug are commonly summarised across trials continuously during an investigational product's development and in particular at the time of a marketing application. The usefulness of this summary, however, is dependent on adequate and well-controlled individual trials with high data quality.

The overall usefulness of a drug is always a question of balance between risk and benefit and in a single trial such a perspective could also be considered, even if the assessment of risk/benefit usually is performed in the summary of the entire clinical trial program. (See Section 7.2.2)

For more details on the reporting of safety and tolerability, see Chapter 12 of ICH E3.

## 7 REPORTING

### 7.1 Evaluation and Reporting

As stated in the Introduction, the structure and content of clinical study reports is the subject of ICH E3. That ICH guidance fully covers the reporting of statistical work, appropriately integrated with clinical and other material. The current section is therefore relatively brief.

During the planning phase of a trial the principal features of the analysis should have been specified in the protocol as described in Section 5. When the conduct of the trial is over and the data are assembled and available for preliminary inspection, it is valuable to carry out the blind review of the planned analysis also described in Section 5. This pre-analysis review, blinded to treatment, should cover decisions concerning, for example, the exclusion of subjects or data from the analysis sets; possible transformations may also be checked, and outliers defined; important covariates identified in other recent research may be added to the model; the use of parametric or non-parametric methods may be reconsidered. Decisions made at this time should be described in the report, and should be distinguished from those made after the statistician has had access to the treatment codes, as blind decisions will generally introduce less potential for bias. Statisticians or other staff involved in unblinded interim analysis should not participate in the blind review or in making modifications to the statistical analysis plan. When the blinding is compromised by the possibility that treatment induced effects may be apparent in the data, special care will be needed for the blind review.

Many of the more detailed aspects of presentation and tabulation should be finalised at or about the time of the blind review so that by the time of the actual analysis full plans exist for all its aspects including subject selection, data selection and modification, data summary and tabulation, estimation and hypothesis testing. Once data validation is complete, the analysis should proceed according to the pre-defined plans; the more these plans are adhered to, the greater the credibility of the results. Particular attention should be paid to any differences between the planned analysis and the actual analysis as described in the protocol, protocol amendments or the updated statistical analysis plan based on a blind review of data. A careful explanation should be provided for deviations from the planned analysis.

All subjects who entered the trial should be accounted for in the report, whether or not they are included in the analysis. All reasons for exclusion from analysis

should be documented; for any subject included in the full analysis set but not in the per protocol set, the reasons for exclusion from the latter should also be documented. Similarly, for all subjects included in an analysis set, the measurements of all important variables should be accounted for at all relevant time-points.

The effect of all losses of subjects or data, withdrawals from treatment and major protocol violations on the main analyses of the primary variable(s) should be considered carefully. Subjects lost to follow up, withdrawn from treatment, or with a severe protocol violation should be identified, and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

Descriptive statistics form an indispensable part of reports. Suitable tables and/or graphical presentations should illustrate clearly the important features of the primary and secondary variables and of key prognostic and demographic variables. The results of the main analyses relating to the objectives of the trial should be the subject of particularly careful descriptive presentation. When reporting the results of significance tests, precise p-values (e.g.'p=0.034') should be reported rather than making exclusive reference to critical values.

Although the primary goal of the analysis of a clinical trial should be to answer the questions posed by its main objectives, new questions based on the observed data may well emerge during the unblinded analysis. Additional and perhaps complex statistical analysis may be the consequence. This additional work should be strictly distinguished in the report from work which was planned in the protocol.

The play of chance may lead to unforeseen imbalances between the treatment groups in terms of baseline measurements not pre-defined as covariates in the planned analysis but having some prognostic importance nevertheless. This is best dealt with by showing that an additional analysis which accounts for these imbalances reaches essentially the same conclusions as the planned analysis. If this is not the case, the effect of the imbalances on the conclusions should be discussed.

In general, sparing use should be made of unplanned analyses. Such analyses are often carried out when it is thought that the treatment effect may vary according to some other factor or factors. An attempt may then be made to identify subgroups of subjects for whom the effect is particularly beneficial. The potential dangers of over-interpretation of unplanned subgroup analyses are well known (see also Section 5.7), and should be carefully avoided. Although similar problems of interpretation arise if a treatment appears to have no benefit, or an adverse effect, in a subgroup of subjects, such possibilities should be properly assessed and should therefore be reported.

Finally statistical judgement should be brought to bear on the analysis, interpretation and presentation of the results of a clinical trial. To this end the trial statistician should be a member of the team responsible for the clinical study report, and should approve the clinical report.

### 7.2 Summarising the Clinical Database

An overall summary and synthesis of the evidence on safety and efficacy from all the reported clinical trials is required for a marketing application (Expert report in EU, integrated summary reports in USA, Gaiyo in Japan). This may be accompanied, when appropriate, by a statistical combination of results.

Within the summary a number of areas of specific statistical interest arise: describing the demography and clinical features of the population treated during the course of the clinical trial programme; addressing the key questions of efficacy by considering the results of the relevant (usually controlled) trials and highlighting the degree to which they reinforce or contradict each other; summarising the safety information available from the combined database of all the trials whose results contribute to the marketing application and identifying potential safety issues. During the design of a clinical programme careful attention should be paid to the uniform definition and collection of measurements which will facilitate subsequent interpretation of the series of trials, particularly if they are likely to be combined across trials. A common dictionary for recording the details of medication, medical history and adverse events should be selected and used. A common definition of the primary and secondary variables is nearly always worthwhile, and essential for meta-analysis. The manner of measuring key efficacy variables, the timing of assessments relative to randomisation/entry, the handling of protocol violators and deviators and perhaps the definition of prognostic factors, should all be kept compatible unless there are valid reasons not to do so.

Any statistical procedures used to combine data across trials should be described in detail. Attention should be paid to the possibility of bias associated with the selection of trials, to the homogeneity of their results, and to the proper modelling of the various sources of variation. The sensitivity of conclusions to the assumptions and selections made should be explored.

### *7.2.1 Efficacy Data*

Individual clinical trials should always be large enough to satisfy their objectives. Additional valuable information may also be gained by summarising a series of clinical trials which address essentially identical key efficacy questions. The main results of such a set of trials should be presented in an identical form to permit comparison, usually in tables or graphs which focus on estimates plus confidence limits. The use of meta-analytic techniques to combine these estimates is often a useful addition, because it allows a more precise overall estimate of the size of the treatment effects to be generated, and provides a complete and concise summary of the results of the trials. Under exceptional circumstances a meta analytic approach may also be the most appropriate way, or the only way, of providing sufficient overall evidence of efficacy via an overall hypothesis test. When used for this purpose the meta-analysis should have its own prospectively written protocol.

### *7.2.2 Safety Data*

In summarising safety data it is important to examine the safety database thoroughly for any indications of potential toxicity, and to follow up any indications by looking for an associated supportive pattern of observations. The combination of the safety data from all human exposure to the drug provides an important source of information, because its larger sample size provides the best chance of detecting the rarer adverse events and, perhaps, of estimating their approximate incidence. However, incidence data from this database are difficult to evaluate because of the lack of a comparator group, and data from comparative trials are especially valuable in overcoming this difficulty. The results from trials which use a common comparator (placebo or specific active comparator) should be combined and presented separately for each comparator providing sufficient data.

All indications of potential toxicity arising from exploration of the data should be reported. The evaluation of the reality of these potential adverse effects should take account of the issue of multiplicity arising from the numerous comparisons made. The evaluation should also make appropriate use of survival analysis methods to exploit the potential relationship of the incidence of adverse events to duration of exposure and/or follow-up. The risks associated with identified adverse effects should be appropriately quantified to allow a proper assessment of the risk/benefit relationship.

## GLOSSARY

### Bayesian Approaches

Approaches to data analysis that provide a posterior probability distribution for some parameter (e.g. treatment effect), derived from the observed data and a prior probability distribution for the parameter. The posterior distribution is then used as the basis for statistical inference.

### Bias (Statistical & Operational)

The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value. Bias introduced through deviations in conduct is referred to as 'operational' bias. The other sources of bias listed above are referred to as 'statistical'.

### Blind Review

The checking and assessment of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind, for the purpose of finalising the planned analysis.

### Content Validity

The extent to which a variable (e.g. a rating scale) measures what it is supposed to measure.

### Double-Dummy

A technique for retaining the blind when administering supplies in a clinical trial, when the two treatments cannot be made identical. Supplies are prepared for Treatment A (active and indistinguishable placebo) and for Treatment B (active and indistinguishable placebo). Subjects then take two sets of treatment; either A (active) and B (placebo), or A (placebo) and B (active).

### Dropout

A subject in a clinical trial who for any reason fails to continue in the trial until the last visit required of him/her by the study protocol.

**Equivalence Trial**

A trial with the primary objective of showing that the response to two or more treatments differs by an amount which is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.
Frequentist Methods

Statistical methods, such as significance tests and confidence intervals, which can be interpreted in terms of the frequency of certain outcomes occurring in hypothetical repeated realisations of the same experimental situation.

**Full Analysis Set**

The set of subjects that is as close as possible to the ideal implied by the intention-to-treat principle. It is derived from the set of all randomised subjects by minimal and justified elimination of subjects.

**Generalisability, Generalisation**

The extent to which the findings of a clinical trial can be reliably extrapolated from the subjects who participated in the trial to a broader patient population and a broader range of clinical settings.

**Global Assessment Variable**

A single variable, usually a scale of ordered categorical ratings, which integrates objective variables and the investigator's overall impression about the state or change in state of a subject.

**Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)**

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

**Intention-To-Treat Principle**

The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment.

**Interaction (Qualitative and Quantitative)**

The situation in which a treatment contrast (e.g. difference between investigational product and control) is dependent on another factor (e.g. centre). A quantitative interaction refers to the case where the magnitude of the contrast differs at the different levels of the factor, whereas for a qualitative interaction the direction of the contrast differs for at least one level of the factor.

**Inter-Rater Reliability**

The property of yielding equivalent results when used by different raters on different occasions.

**Intra-Rater Reliability**

The property of yielding equivalent results when used by the same rater on different occasions.

**Interim Analysis**

Any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to the formal completion of a trial.

**Meta-Analysis**

The formal evaluation of the quantitative evidence from two or more trials bearing on the same question. This most commonly involves the statistical combination of summary statistics from the various trials, but the term is sometimes also used to refer to the combination of the raw data.

**Multicentre Trial**

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

**Non-Inferiority Trial**

A trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparative agent (active or placebo control).

**Preferred and Included Terms**

In a hierarchical medical dictionary, for example MedDRA, the included term is the lowest level of dictionary term to which the investigator description is coded. The preferred term is the level of grouping of included terms typically used in reporting frequency of occurrence. For example, the investigator text "Pain in the left arm" might be coded to the included term "Joint pain", which is reported at the preferred term level as "Arthralgia".

**Per Protocol Set (Valid Cases, Efficacy Sample, Evaluable Subjects Sample)**

The set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations.

**Safety and Tolerability**

The safety of a medical product concerns the medical risk to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and haematology), vital signs, clinical adverse events (diseases, signs and symptoms),

and other special safety tests (e.g. ECGs, ophthalmology). The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject.

### Statistical Analysis Plan

A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

### Superiority Trial

A trial with the primary objective of showing that the response to the investigational product is superior to a comparative agent (active or placebo control).

### Surrogate Variable

A variable that provides an indirect measurement of effect in situations where direct measurement of clinical effect is not feasible or practical.

### Treatment Effect

An effect attributed to a treatment in a clinical trial. In most clinical trials the treatment effect of interest is a comparison (or contrast) of two or more treatments.

### Treatment Emergent

An event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.

### Trial Statistician

A statistician who has a combination of education/training and experience sufficient to implement the principles in this guidance and who is responsible for the statistical aspects of the trial.

# Index

# Drug Discovery and Clinical Research

***Salient Features***

- A unique and excellent text
- Presents recent advances in the field of drug discovery and clinical research
- Deals with drug discovery and development, clinical development, bioethics, medical devices, pharmacovigilance, data management, safety monitoring, patient recruitment, etc.
- Overviews phases and steps of preclinical and clinical trials in drug discovery and research
- Includes annexures, flow charts, figures, tables, boxes, color plates, etc. for easy comprehension of the subject
- Useful for medical, pharmacy and clinical research students, teachers, professionals in pharmaceutical industry, biophysicists, statisticians, drug regulatory officials and researchers.

**SK Gupta** is currently Dean and Director General, Institute of Clinical Research (India), which is one of the Premier and Pioneering Institutes in the country. He was formerly Head of the Department of Pharmacology at All India Institute of Medical Sciences, New Delhi and is the founder of WHO National Pharmacovigilance center at AIIMS. In recognition of his outstanding contributions in the field, he has been expert-member of a number of committees of DST, DBT, CSIR, ICMR and Ministry of Health and Family Welfare, Government of India and was member of governing body of the Central Council of Research in Ayurveda. He has been conferred with prestigious Fellowships of International Society of Eye Research, USA, International Academy of Cardiovascular Sciences, Canada and Fellow of the Romanian Society of Sciences. He has been visiting Professor to several prestigious universities in UK, USA, Germany and Japan. He has been recipient of prestigious awards and was recently conferred the 'Distinguished Services Award in Cardiovascular Science, Medicine and Surgery' by International Academy of Cardiovascular Sciences, Canada. He has several patents to his credit and one of his ophthalmic formulations is being commercialized. He has been the President of the Indian Pharmacological Society and is currently President of International Academy of Cardiovascular Sciences and Member, Executive Committee of the International Society of Heart Research. He has published more than 350 research papers and edited eight books and have guided more than 150 postgraduate students. He is Elected Fellow of the Indian Pharmacological Society. He is considered as "Father of Clinical Research Education in India".

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