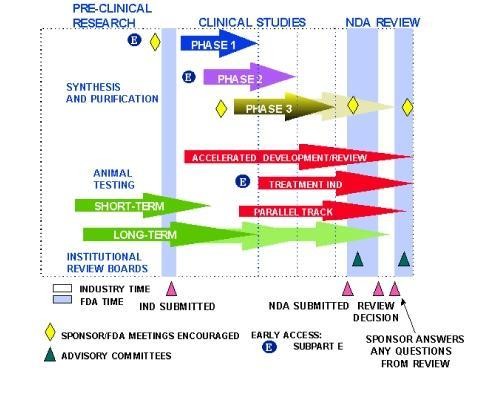
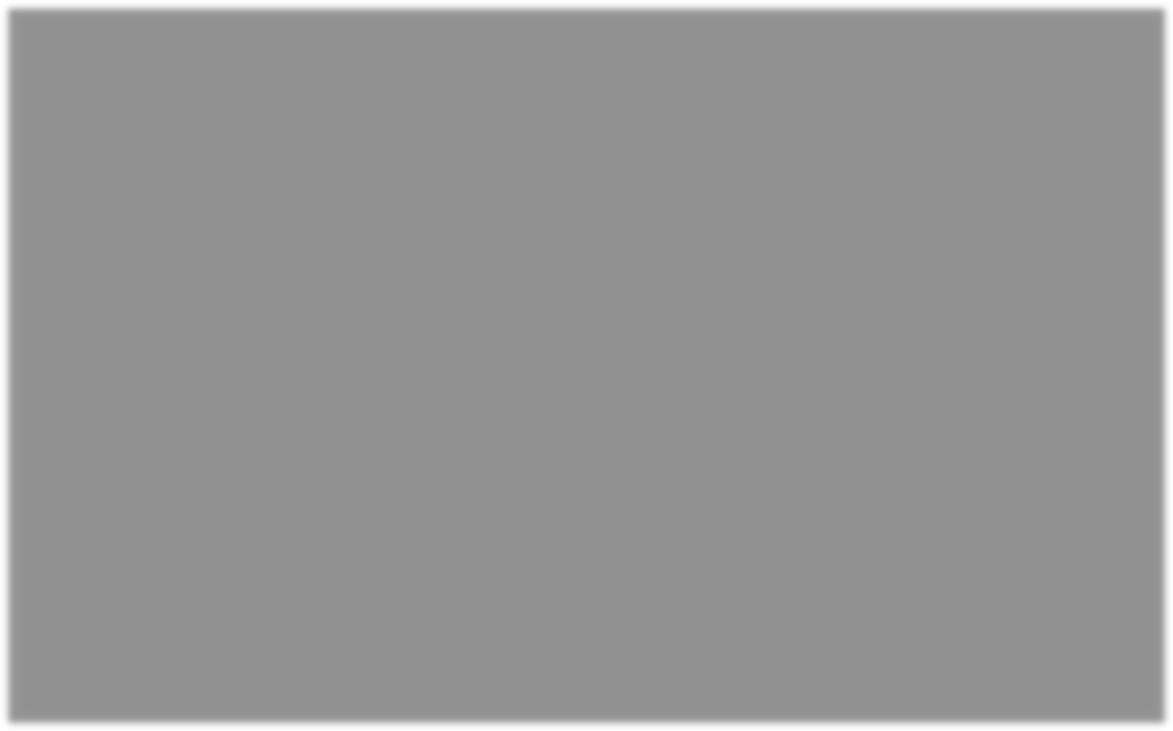
# INDEX

|  |  |  |
| --- | --- | --- |
| SR NO. | TITAL | PAGE NO. |
|  | ABSTRACT | 02 |
|  | INTRODUCTION | 03 |
| 1 | Phase of clinical trials | 03 |
| 2 | Monitoring clinical trial | 8 |
| 3 | Ethical consideration | 8 |
| 4 | Compliance with protocol | 8 |
| 5 | Ethical conduct | 10 |
| 6 | ICH GCP Guidelines | 11 |
| 7 | Evolution of clinical trial in India | 13 |
| 8 | Development methodology | 15 |
| 9 | Role of placebo | 18 |
| 10 | Role of pharmacists in clinical trial | 19 |
| 11 | Conclusion | 20 |
| 12 | Reference | 20 |

# Abstract:-

Preclinical studies using animals to study the potential of a therapeutic drug or Strategy are important steps before translation to clinical trials. However, evidence has shown that poor quality in the design and conduct of these studies has Not only impeded clinical translation but also led to significant waste of valuable Research resources. It is clear that experimental biases are related to the poor Quality seen with preclinical studies. In this chapter, we will focus on hypothesis Testing type of preclinical studies and explain general concepts and principles in relation to the design of in vivo experiments, provide definitions of experimental biases and how to avoid them, and discuss major sources contributing to experimental biases and how to mitigate these sources. We will also explore the differences between confirmatory and exploratory studies, and discuss available guidelines on preclinical studies and how to use them. This chapter, together with relevant information in other chapters in the handbook, provides a powerful tool to enhance scientific rigour for preclinical studies without restricting creativity conditions.



# INTRODUCTION

A clinical trial is a research study that tests a new medical Treatment or a new way of using an existing treatment to See if it will be a better way to prevent and screen for Diagnose or treat a disease (1). For any new drug to enter in Clinical trial, it must pass preclinical studies. Preclinical Studies involve in vitro (i.e. test-tube or Laboratory) Studies and trials on animal populations. Wide range of Dosages of the study drug is given to animal subjects or to An in-vitro substrate in order to obtain preliminary Efficacy, toxicity and pharmacokinetic information.(2)

# . PHASES OF CLINICAL TRIAL

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies(3).

# Pre-clinical studies

Pre-clinical studies involve in vitro (i.e., test tube or laboratory) studies and trials on animal populations. Wideranging dosages of the study drug are given to the animal

subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information and to assist pharmaceutical companies in deciding whether it is worthwhile to go ahead with further testing.

# Phase 0

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration’s (FDA) 2006 Guidance on Exploratory InvInvestigations New Drug (IND) Studies Phase 0 trials are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies. 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 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).

# Phase I

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally 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. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have end-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIV drug trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. Pay ranges from a small amount of money for a short period of residence, to a larger amount of up to approx £4000 depending on length of participation.There are different kinds of Phase I trials:

# SAD

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. If they do not exhibit any adverse side 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 pre-calculated 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 (MTD).

# MAD

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug.

# Phase II

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects. Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements (how much drug should be given), whereas Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)). Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

# Phase III

Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency . While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory

agencies (FDA (USA), TGA (Australia), EMEA (European Union), .Once a drug has proved satisfactory after Phase III trials, 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 different countries . Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.

# Phase IV

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I- III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx)(2).

# INVESTIGATIONAL NEW DRUG (IND) / CLINICAL TRIAL EXCEPTION (CTX) / CLINICAL TRIAL AUTHORIZATION (CTA) APPLICATION

INDs (in the U.S.), CTXs (in the U.K.) and CTAs (in Australia) are examples of requests submitted to appropriate regulatory authorities for permission to conduct investigational research. This research can include testing of a new dosage form or new use of a drug already approved to be marketed. In addition to obtaining permission from appropriate regulatory authorities, an Institutional or Independent Review Board (IRB) OR Ethical Advisory Board must approve the protocol for testing as well as the

informed consent documents that volunteers sign prior to participate in a clinical study. An IRB is an independent committee of physicians, community advocates and others that ensures a clinical trial is ethical and the rights of study participants are protected.

# NEW DRUG APPLICATION (NDA) / MARKETING AUTHORIZATION APPLICATION (MAA)

NDAs (in the U.S.) and MAAs (in the U.K.) are examples of applications to market a new drug. Such application document safety and efficacy of the investigational drug and contain all the information collected during the drug development process. At the conclusion of successful preclinical and clinical testing, this series of documents is submitted to the FDA in the U.S. or to the applicable regulatory authorities ion other countries. The application must present substantial evidence that the drug will have the effect it is represented to have when people use it or under the conditions for which it is prescribed recommended or suggested in the labeling. Obtaining approval to market a new drug frequently takes between

# NEW DRUG APPLICATION (NDA) / MARKETING AUTHORIZATION APPLICATION (MAA*)*

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# 1.2.TYPES OF CINICAL TRIAL:

1. **Treatment trials**

Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

# Prevention trials

Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

# 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

Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness(2).

# 2. MONITORING CLINICAL TRIALS:

The purposes of trial monitoring are to verify that:

1. The rights and well being of human subjects are protected.
2. The reported trial data are protected.
3. The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

# ETHICAL CONSIDERATION

An Independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non- medical 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 favorable opinion on, the trial protocol, the suitability of the investigators 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.

# COMPLIANCE WITH PROTOCOL

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 were 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. The investigator should not implement in deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval

/ favorable opinion from the IRB / IES of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subject, or when the change(s) involves only logistical or administrative aspect of the trial (e.g. change in monitor (s), change of telephone no.(s). Investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.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/ favorable 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.

1. To the IRB/IEC for review and approval/favorable opinion.
2. To the sponsor for agreement.
3. To the regulatory authority (IES).

# PLANS OF CLINICAL TRIALS

Trials may be open, blind or double-blind.

# Open trials

In an open trial, the researcher knows the full details of the treatment and so does the patient. These trials are open to challenge for bias, and they do nothing to reduce the placebo effect. However, sometimes they are unavoidable, as placebo treatments are not always possible (see Blinding). Usually this kind of study design is used in bioequivalence studies

# Blind trials

* 1. **Single-blind trial**

In a single-blind trial, the researcher knows the details of the treatment but the patient does not. Because the patient does not know which treatment is being administered (the new treatment or another treatment) there might be no placebo effect. In practice, since the researcher knows, it is possible for him to treat the patient differently or to subconsciously hint to the patient important treatment-related details, thus influencing the outcome of the study.

# Double-blind trial

In a double-blind trial, one researcher allocates a series of numbers to 'new treatment' or 'old treatment'. The second researcher is told the numbers, but not what they have been allocated to. Since the second researcher does not know, he cannot possibly tell the patient, directly or otherwise, and cannot give in to patient pressure to give him the new treatment. In this system, there is also often a more realistic distribution of sexes and ages of patients. Therefore double-blind (or randomized) trials are preferred, as they tend to give the most accurate results.

# Triple-blind trial

Some randomized controlled trials are considered triple-blinded, although the meaning of this may vary according to the exact study design. The common meaning is that the subject, researcher and person administering the treatment (often a pharmacist) are blinded to what is being given. Alternately, it may mean that the patient, researcher and statistician are blinded. The team monitoring the response may be unaware of the intervention being given in the control and study groups. These additional precautions are often in place with the more commonly accepted term "double blind trials", and thus the term "triple-blinded" is infrequently used. However, it connotes an additional layer of security to prevent undue influence of study results by anyone directly involved with the study(6)

# 5.ETHICAL CONDUCT

Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. The local ethics committee has discretion on how it will supervise nonintervention studies (observational studies or those using already collected data). In the U.S., this body is called the Institutional Review Board (IRB). Most Ribs are located at the local

investigator's hospital or institution, but some sponsors allow the use of a central (independent/for profit) IRB for investigators who work at smaller institutions.To be ethical, researchers must obtain the full and informe consent of participating human subjects. (One of the Rib’s main functions is ensuring that potential patients are adequately informed about the clinical trial.) If the patient is unable to consent for him/herself, researchers can seek consent from the patient's legally authorized representative. .In some U.S. locations, the local IRB must certify researchers and their staff before they can conduct clinical trials. They must understand the federal patient privacy (HIPAA) law and good clinical practice. International Conference of Harmonization Guidelines for Good Clinical Practice (ICH GCP) is a set of standards used internationally for the conduct of clinical trials. The guidelines aim to ensure that the "rights, safety and well being of trial subjects are protected". The declaration of Helsinki of the World Medical Association (1964) codifies recommendation for guidance of doctors in clinical research(7).

# 6 ICH GCP GU5IDELINES

The principals of ICH GCP --

1. Clinical trial should be conducted in accordance with the ethical principals that have their origin in the declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement.
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.
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.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) independent ethics committee (IEC) approval / favorable opinion.
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.

1. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks.
2. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
3. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
4. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement.
5. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approval protocol.
6. Systems with procedures that assure the quality of every aspect of the trial should be implanted(5).

# INTERNATIONAL CONFERENCE ON HARMONIZATION GUIDELINES

In Recognition of the international market place for pharmaceutical and in an effort to achieve global efficiency for both regulatory agencies and the pharmaceutical industry, the FDA, counterpart agencies of the European Union and Japan and geographic representatives of the pharmaceutical industry formed a tripartite organization in 1991 to discuss, identify, and address relevant regulatory issues.This organization, named the international conference on Harmonization of Pharmaceuticals for Human Use (ICH) has worked toward harmonizing, or bringing together, regulatory requirements with the long-range goal of establishing a uniform set of standards for drug registration within these geographic areas. With ICH success, duplicative technical requirements for registering Pharmaceuticals would be eliminated, new drug approvals would occur more rapidly, patients’ access to new medicines would be enhanced worldwide, the quality, safety, and efficacy of imported products would be improved, and there would be an increase in information transfer between participating countries.The ICH’s work

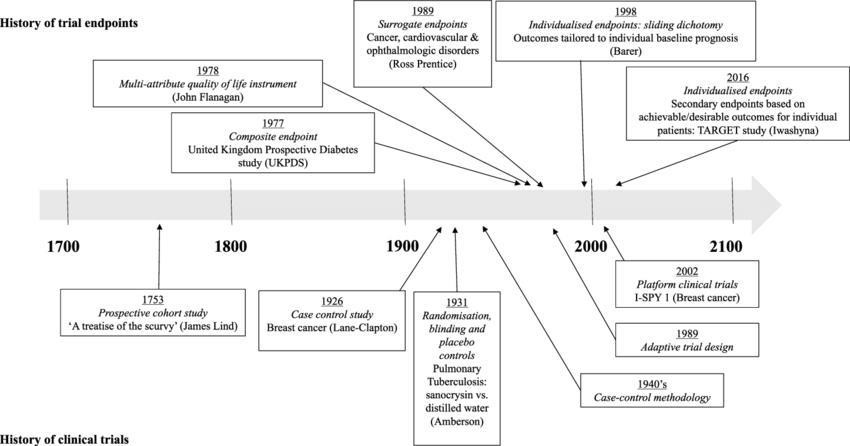
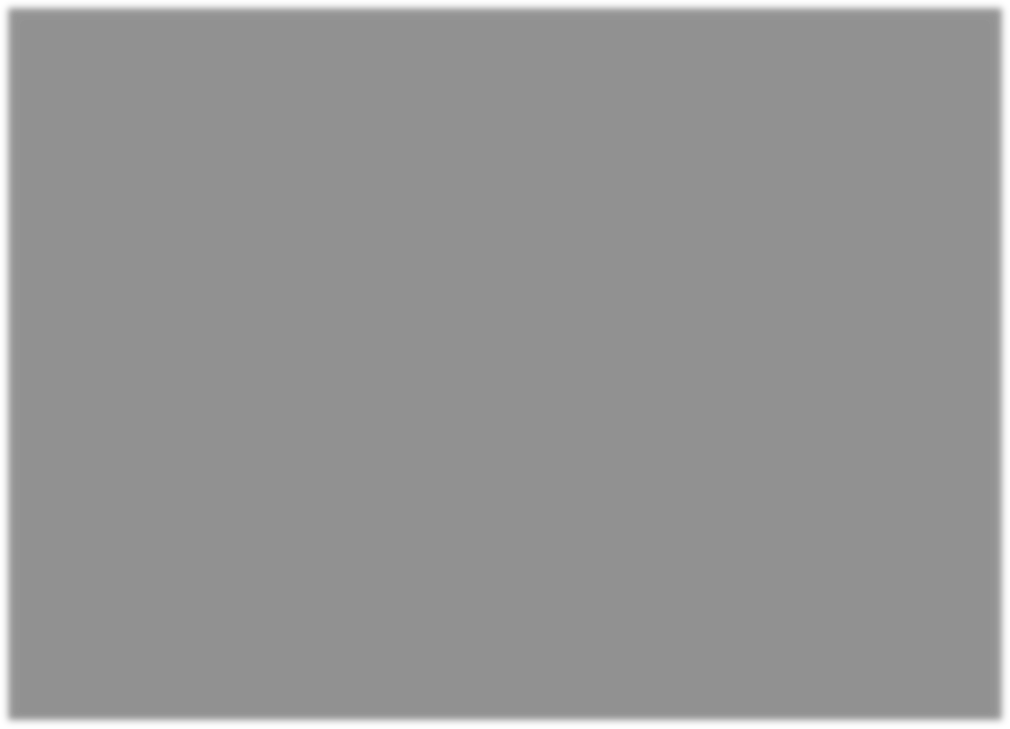
toward uniform standards is focused on three general areas, quality, safety and efficacy. The quality topic includes stability, light stability, analytical validation, impurities, and biotechnology.The safety topics include carcinogenicity, genotoxicity, toxicokinetics, reproduction toxicity and single and repeat-dose toxicity.The efficacy topics include population exposure, managing clinical trials, clinical study reports, dose response, ethic factors, good clinical practices, and geriatrics. For each topic, relevant regulations are identified, addressed and consensus guidelines developed.The intension is that these guidelines will be incorporated in to domestic regulations. In the United states the resulting guidelines are published in the Federal Register as notices, with accompanying statements indicating that the guideline should be “Useful” or “considered” by applicants conducting required studies or submitting registration applications. Examples of specific ICH developed guidelines:

1. Stability testing of new drug substances and products
2. Validation of analytical procedures for Pharmaceuticals
3. Impurities in new drug substances and products
4. General consideration for clinical trail

# Evolution of Clinical Trials in India

India has recently been recognized as an attractive country for clinical trials. But the country’s journey in clinical research field has a long history. India has a rich heritage of traditional medicine – Ayurveda. The classic ayurvedic texts contain detailed observations on diseases and in-depth guidance on remedies. It is likely that these descriptions are based on direct observations made by the ancient ayurveda experts. However, there is no recorded documentation in the ancient texts of any clinical experiments. Hence, one has to fall back on current history of medical research in India. The major historic milestones of the Indian Council of Medical Research reflect, in many ways, the growth and development of medical research in the country over the last nine decades. First meeting of the Governing Body of the Indian Research Fund Association (IRFA) was held on November 15, 1911 at the Plague Laboratory, Bombay, under the Chairmanship of Sir Harcourt Butler.11 At the 2nd meeting of the Governing Body in 1912, a historic decision was taken to start a journal for Indian Medical research. Between 1918- 20, several projects on beriberi, malaria, kala azar and indigenous drugs were initiated. In 1945, a Clinical Research Unit - the first

research unit of IRFA attached to a medical institution- was established at the Indian Cancer Research Centre, Bombay. In 1949, IRFA was redesignated as the Indian Council of Medical Research. Over next 60 years, ICMR established many national research centers in the fields of nutrition, tuberculosis, leprosy, viral disease, cholera, enteric disease, reproductive disorders, toxicology, cancer, traditional medicine, gas



disaster, genetics, AIDS etc. The Central Ethical Committee of ICMR on Human Research constituted under the Chairmanship of Hon’ble Justice (Retired) M.N. Venkatachaliah held its first meeting on September 10, 1996. Several subcommittees were constituted to consider ethical issues in specific areas e.g., Epidemiological Research; Clinical Evaluation of Products to be used on Humans; Organ Transplantation; Human Genetics*,* etc. The committee released Ethical Guidelines for Biomedical Research on Human Participants in 2000 which were revised in 2006. 9 Schedule Y of Drugs and Cosmetics Act came into force in 1988 and established the regulatory guidelines for clinical trial (CT) permission. The schedule did force the industry to conduct Phase III clinical trials for registration of a new drug and supported growth of a predominantly generic Indian pharmaceutical industry. However, this schedule only permitted clinical trials at a phase lower than its global status. This phase lag obstructed integration of India in global clinical development.

The next major step has been revision of Schedule Y in Jan 2005.12 As compared to Schedule Y 1988, which had narrow and restrictive definitions of clinical trial phases, the amended Schedule Y 2005 provided pragmatic definitions for Phase I to IV. 12 The definitions and guidelines for clinical trial phases are broad and rational. The earlier restrictions on number patients and centers in early phases stipulated in Schedule Y 1988 were removed allowing the sponsor company freedom to decide these in relation to protocol requirements. The phase lag requirements gave way to acceptance of concurrent Phase II-III as part of global clinical trials. Schedule Y 2005 legalized Indian GCP guidelines of 2001. This schedule stipulated GCP responsibilities of ethics committee (EC), investigator and sponsor and suggested formats for critical documents

e.g. consent, report, EC approval, reporting of serious adverse event. These amendments in Schedule Y have been a major step forward in direction of GCP compliant trials and have provided the much-needed regulatory support to GCP guidelines. Since the Scurvy trial, clinical trials have evolved into a standardized procedure, focusing on scientific assessment of efficacy and guarding the patient safety.As the discipline of drug development is enriched by novel therapies and technologies, there will always be a continuing need to balance medical progress and patient safety. As the scientific advances continue to occur, there will be new ethical and regulatory challenges requiring dynamic updates in ethical and legal fram**(3,8)**

# DEVELOPMENT METHODOLOGY

This section covers issues and considerations relating to the development plan and to its individual component studies.

Important considerations for determining the nature of non-clinical studies and their timing with respect to clinical trials include:

1. and total exposure proposed in individual patients
2. characteristics of the drug (e.g. long half life, biotechnology products)
3. disease or condition targeted for treatment
4. use in special populations (e.g. women of childbearing potential)
5. route of administration

The need for non-clinical information including toxicology, pharmacology and pharmacokinetics to support clinical trials is addressed in the ICH M3 and S6 documents.

# 1 Safety Studies

For the first studies in humans, the dose that is administered should be determined by careful examination of the prerequisite non-clinical pharmacokinetic, pharmacological and toxicological evaluations (see ICH M3). Early non-clinical studies should provide

# 2.sufficient

information to support selection of the initial human dose and safe duration of exposure, and to provide information about physiological and toxicological effects of a new drug.

Pharmacological and Pharmacokinetic Studies The basis and direction of the clinical exploration and development rests on the non-clinical pharmacokinetic and pharmacology profile, which includes information such as:

1. Pharmacological basis of principal effects (mechanism of action).
2. Dose-response or concentration-response relationships and duration of action
3. Study of the potential clinical routes of administration
4. Systemic general pharmacology, including pharmacological effects on major organ systems and physiological responses
5. Studies of absorption, distribution, metabolism and excretion

Quality of Investigational Medicinal Products Formulations used in clinical trials should be well characterised, including information on bioavailability wherever feasible. The formulation should be appropriate for the stage of drug development. Ideally, the supply of a formulation will be adequate to allow testing in a series of studies that examine a range of doses. During drug development different formulations of a drug may be tested. Links between formulations, established by bioequivalence studies or other means are important in interpreting clinical study results across the development program.

# Phases of Clinical Development

Clinical drug development is often described as consisting of four temporal phases (I - IV). It is important to recognise that the phase of development provides an inadequate

basisfor classification of clinical trials because one type of trial may occur in several phases A classification system using study objectives as discussed in section 2.2 is preferable. It is important to appreciate that the phase concept is a description, not a set of requirements. It is also important to realise that the temporal phases do not imply a fixed order of studies since for some drugs in a development plan the typical sequence will not be appropriate or necessary. For example, although human pharmacology studies are typically conducted during Phase I, many such studies are conducted at each of the other three stages, but nonetheless sometimes labelled as Phase I studies. demonstrates this close but variable correlation between the two classification systems. The distribution of the points of the graph shows that the types of study are not synonymous with the phases of development.

Drug development is ideally a logical, step-wise procedure in which information from small early studies is used to support and plan later larger, more definitive studies. To develop new drugs efficiently, it is essential to identify characteristics of the investigational medicine in the early stages of development and to plan an appropriate development based on this profile. Initial trials provide an early evaluation of short- term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials. Later confirmatory studies are generally larger and longer and include a more diverse patient population. Dose-response information should be obtained at all stages of development, from early tolerance studies, to studies of short-term pharmacodynamic effect, to large efficacy studies (see ICH E4). Throughout development, new data may suggest the need for additional studies that are typically part of an earlier phase. For example, blood level data in a late trial may suggest a need for a drug-drug interaction study, or adverse effects may suggest the need for further dose finding and/or additional non-clinical studies. In addition, to support a new marketing

Phase I (Most typical kind of study: Human Pharmacology)

Phase I starts with the initial administration of an investigational new drug into humans. Although human pharmacology studies are typically identified with Phase I, they may also be indicated at other points in the development sequence. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or certain types of patients, e.g. patients with mild

hypertension. Drugs with significant potential toxicity, e.g. cytotoxic drugs, are usually studied in patients. Studies in this phase can be open, baseline controlled or may use randomisation and blinding, to improve the validity of observations. Studies conducted in Phase I typically involve one or a combination of the following aspects:

# a) Estimation of Initial Safety and Tolerability

The initial and subsequent administration of an investigational new drug into humans is usually intended to determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be Pharmacokinel.

# c) Assessment of Pharmacodynamics

Depending on the drug and the endpoint studied, pharmacodynamic studies and studies relating drug blood levels to response (PK/PD studies) may be conducted in healthy volunteer subjects or in patients with the target disease. In patients, if there is an appropriate measure, pharmacodynamic data can provide early estimates of activity and potential efficacy and may guide the dosage and dose regimen in later studies.

# 9.ROLE OF PLACEBO

Placebo is a Latin term which means “ I may please you.” The placebo effect is an effect attributable to a medicament as a procedure, and is not due to any specific pharmacodynamic property of the substance for the condition being treated. Placebo effect may be defined as “ how the patients perception of treatment influences his / her response.” Placebos are used, During the clinical trial, to eliminate the possibility that the benefit of the drug is solely due to chance; and as therapeutic agents that work psychologically .A placebo preparation is usually an inert substance like starch or lactose. However occasionally it may be a drug that is active but in a different situation. In fact, even when an active drug is used, its placebo effect often comforts the patient much before the drug is effective. It is well known that the patient as well as his relatives get some immediate relief as soon as the doctor’s medicine is administered, irrespective of its drug content. Placebos can often produce relief of subjective symptoms associated with psychological disturbances. This includes relief from anxiety, headache, pain, insomnia and breathlessness. Objective responses such as increase or decrease in Europhiles and eosinophils may sometimes be seen with placebos. When administered for its therapeutic effects, the placebo preparation, must appear to be

relevant to the illness, must be harmless, Should preferably conform to the patient’s expectations and To be effective, the ‘potency ‘ of the preparation must be shown by some signs such as strong taste, a colorful capsule or a tablet of odd shape and sometimes even by obvious but harmless side effect like colored urine. During clinical trials, placebos are used to eliminate the effect of bias of the physician and the patient, particularly in evaluating a new drug claimed to be effective in conditions like bronchial asthma, angina pectoris, pain and psychiatric disorders. In such cases the placebo should be indistinguishable from the active medicament in physical prosperities like color, smell, taste and form.

# Placebo effect may be modified by:

1. Personality of the physician.
2. Personality of the patient.
3. Form of administration**(9)**

# ROLE OF PHARMACISTS IN CLINICAL TRIALS

Pharmacists have an active role to play in research and clinical trials first of all, we provide the necessary facilities required for proper storage of the investigational medicinal products (IMPs), either in the fridge or atcontrolled room temperature. Regular temperature monitoring is ensured and recorded. It is also the pharmacist’s duty to ensure there is constant supply of IMPs at all times, and that they are dispensed to patients accordingly.

Patients are counselled on the correct use of the IMPs in addition to any written information that is provided, such as, Informed Consent Form or the Patient Information Leaflet. IMPs returns from patients are counted and documented to determine compliance to the treatment. For inject able IMPs, pharmacists will also ensure that they are prepared in accordance to the specifications stipulated in the trial, and that they are administered appropriately.Besides managing clinical trials, oncology pharmacists often run research projects that are aimed at improving outcomes in patients who receive medications, such as chemotherapy or other supportive drugs like anti-emetics, blood growth factor injections, etc.Drug Utilization Evaluations (DUEs) are research projects that are commonly conducted by pharmacists. These projects aim to facilitate rational use of drugs within our patients. Essentially, providing insights on

how drugs are used in patients and observing prescribing patterns by our physicians. DUEs are sometimes considered as drug audits because pharmacists are ensuring the use of medication is appropriate. In addition, pharmacists also conduct observational surveys that are aimed at investigating patients’ or physicians’ perspectives and attitudes towards medications. Results obtained from surveys are used to improve the services that we provide to our patients. Currently, NCC’s oncology pharmacy is conducting two surveys. They are aimed at investigating patients’ use of complementary and alternative medications and on patients’ perspective on safe handling of oral anti-cancer drugs. Very often, pharmacy students who are adequately trained to conduct research are assigned to survey the patients. We would like to take this opportunity to thank all our patients who have consented to participate in the survey(10).

# CONCLUSION

A clinical trial for any new drug follows under the guidelines of ICH and GCP, clinical trial are conducted in human volunteers for confirmation of useful properties of new drug. After preclinical development, investigational new drug passes through clinical phases I, II, III and IV. These phases provide in detail explanation of pharmacokinetic, pharmacodynamic profile and side effect which may be harmful or beneficial, adverse effect and post marketing surveillance.,

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