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CLINICAL AND PRECLINICAL TRAILS: A REVIEW ARTICLE

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ABSTRACT

A clinical trials is a research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are fastest and safest way to find treatment that work in people and way to improve health. Investigational trials determine whether treatment or new way of using known therapies is safe and effective under controlled environment. Observational trials address health issue in large group of people or population in natural setting. Clinical trials aim to measure therapeutic effectiveness an important highly specialized form of biological assay. In Phase I pharmacokinetics, safety, gross effect are studied on human volunteers, by clinical pharmacologist. If the drug passes test, it enters Phase II testing, where pharmacokinetics, safety, therapeutic efficiency are studied on selected patients by clinical pharmacologist, if passes hundreds of selected patients are now studied, primarily safety and therapeutic effectiveness by clinical investigators in Phase III. If this is passed the drugs is now approved and marketed. Even after marketing, physicians from various hospitals and clinics send their opinions about the drug, regarding ADR, efficacy in Phase IV.

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 disease¹. For any new drug to enter in clinical trial, it must pass pre clinical studies. Pre clinical 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.

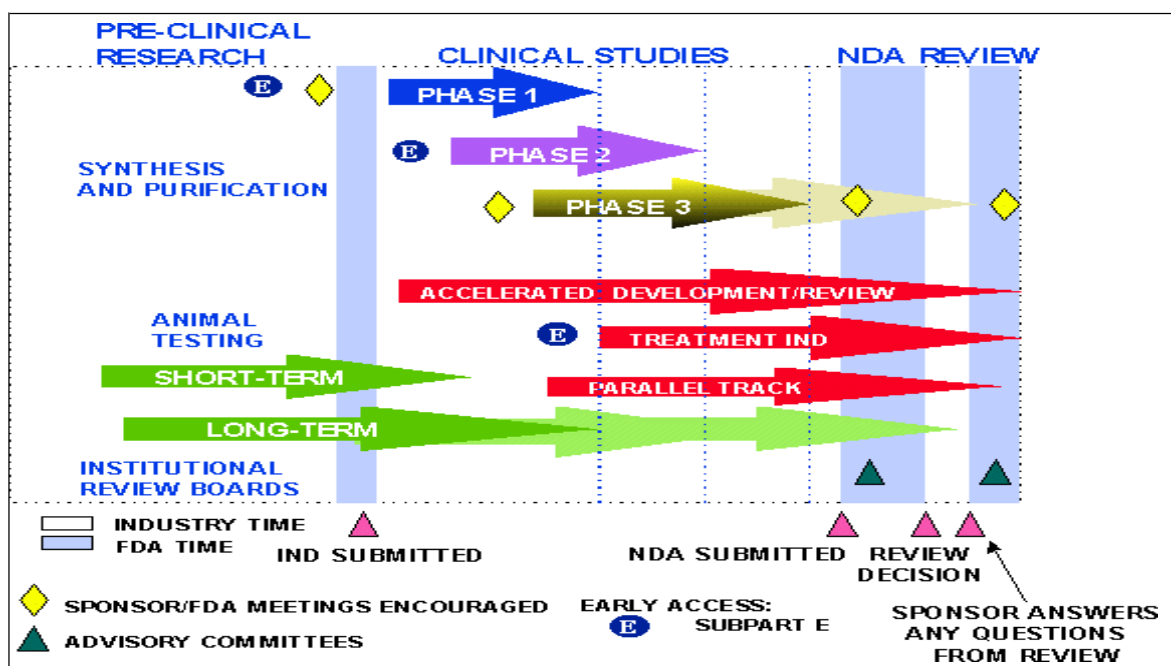


Fig.1.1: Clinical and Preclinical Studies.

PHASES OF CLINICAL TRIAL

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

Pre-clinical studies

Pre-clinical studies involve in vitro (test tube or laboratory) studies and trials on animal populations. Wide-ranging 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 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.

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 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), etc.).

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 authorize in 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).

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 participating 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)

NDAAs (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 in 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 six months and two years.

TYPES OF CINICAL TRIAL

- 1. Treatment trials:** Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
- 2. 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.
- 3. Diagnostic trials:** Conducted to find better tests or procedures for diagnosing a particular disease or condition
- 4. Screening trials:** Test the best way to detect certain diseases or health conditions.
- 5. Quality of Life:** Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

MONITORING CLINICAL TRIAL'S

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 and which were given approval/ favorable 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 to trial subject, or when the change involves only logistical or administrative aspect of the trial (e.g. change in monitor, change of telephone no

The 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 trial: 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:

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 most 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.

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 IRBs 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 informed consent of participating human subjects. (One of the IRB'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 California, the state has prioritized the individuals who can serve as the 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.

ICH GCP GUIDELINES

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.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks.

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

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.

12. Investigational products should be manufactured, handled, and stored in accordance with applicable

13. Good manufacturing practice (GMP). They should be used in accordance with the approval protocol.

14. Systems with procedures that assure the quality of every aspect of the trial should be implanted

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 trial.

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 pharmacodynamics 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. This is because of their faith in the doctor that things will go well in his hands. Placebos can often produce relief of subjective symptoms associated with psychological disturbances. This includes relief from anxiety, headache, pain, insomnia and

breathlessness. Hence placebos are often employed in the treatment of certain diseases where the psychic element is suspected to be responsible for subjective symptoms. Objective responses such as increase or decrease in Erythrocytes 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 properties 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.

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 at controlled 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 counseled 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 injectable 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.

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 pre clinical development, investigational new drug passes through clinical phases I, II, III and IV. These phases provide in detail explanation of pharmacokinetic, pharmacodynamics profile and side effect which may be harmful or beneficial, adverse effect and post marketing surveillance.,

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