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CLINICAL TRIALS- A REVIEW

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- **Abstract**

These are biological product which act by reinforcing the immunological defence of the Body against foreign agencies. The agents or product through which immunization is achieved Are called immunizing agents. Antisera and immune globulins impart passive immunity Readymade antibodies [produce by another person or animal who has been actively immunized] Are transferred. Antisera is purified and concentrated preparation of serum of horses/rabbits Actively immunized against a specific antigen. Sometimes it shows immediate type of allergic Reaction.

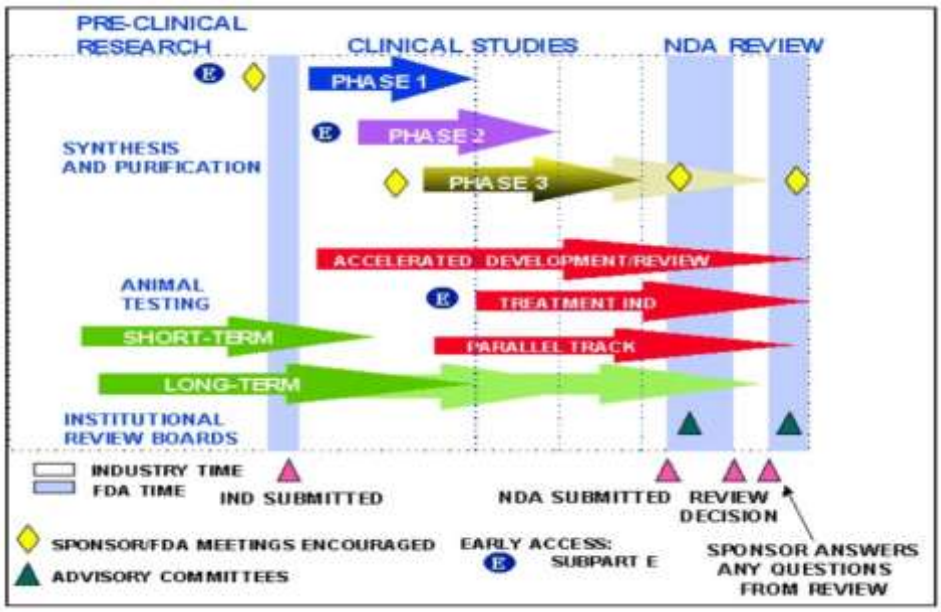
- **Keywords:** Preclinical trials, Clinical phases, Clinical phase trial, NDA.

- **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 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

- **Phases of clinical trials**



Before pharmaceutical company start clinical trials on a drug they conduct extensive preclinical Studies.

- **Pre-clinical studies**

Pre-clinical studies involve in vitro (i.e., 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 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 Investigational 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).

Table 1. Clinical phase trials.

Phases	Dosing	Number of subjects	Main goal of clinical phase
Preclinical	Unrestricted	Not applicable	Testing in non-humans (efficacy, toxicities, pharmacokinetics)
0	Subtherapeutic	About 10	Pharmacokinetics and pharmacodynamics
IA/IB	Ascending doses	20 - 100	Dose-ranging
IIA/IIB	Therapeutic dose	100 - 300	Drug efficacy
IIIA/IIIB	Therapeutic dose	1000 - 2000	Therapeutic effect
IV	Therapeutic dose	Anyone seeking treatment	Long-term effects
V	No dosing	All reported use	Research on data collected

- **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:

1. 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).

2. 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.The Phase II design depends on the quality and adequacy of Phase I studies. A vulnerable aspect of both Phases is the type of patient enrolled. Patients in Phase II trials generally have more exclusion criteria than those In Phase III trials. Case series and randomized clinical trial designs have been used. Single stage and multi-stage Phase II clinical trial designs are often developed on the basis that one endpoint is of interest. A commonly used Phase II design is based on the work of Gehan, a version of a two-stage design [46]. Other designs have more Stages or a sequential aspect. Hybrid designs have been used to improve efficiency. In an update, Gehan reviewed statistical aspects of plans for Phase II cancer clinical trials including a minimum number of patients Plan, a two-stage decision theory approach, a limited patient accrual plan, a predictive probability plan, and a One-sample multiple testing procedure plan. The author makes recommendations regarding the plan that best fits The needs of the study

- **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 authoritiesin 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).Initially, these trials were run much like Phase III studies and were conducted for marketing purposes. Studies Were done at institutions with investigators familiar with clinical trials and had inclusion and exclusion criteria Similar to those of Phase III studies. Results did not reflect what would happen under normal conditions. As a Result, innovative studies were designed to involve ordinary physicians in naïve research communities. Goals Have been broadened and include evaluation of specific pharmacological effects, establishing the incidence of Adverse reactions,determining effects of long-term administration of a therapy, establishing a new clinical indi-Cation for the therapy, evaluation of the therapy in higher risk populations, etc. A main issue of concern is the Mix of medical research and clinical practice.

- **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)**

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 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 TRIALS:**

The purposes of trial monitoring are to verify that:

- The rights and well being of human subjects are Protected
- The reported trial data are protected.
- The conduct of the trial is in compliance with the Currently approved protocol/amendment(s), with GCP, and with the applicable regulatory Requirement(s).

- **PLANS OF CLINICAL TRIALS**

Trials may be open, blind or double-blind.

1. 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.

2.Blind trials

A.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.

B. 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.

C. **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

- **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 applicablegood manufacturing practice (GMP). They should be used in accordance with the approval protocol.

13. Systems with procedures that assure the quality of Every aspect of the trial should be implanted.

- **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 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 Boften 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 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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