Clinical Trials

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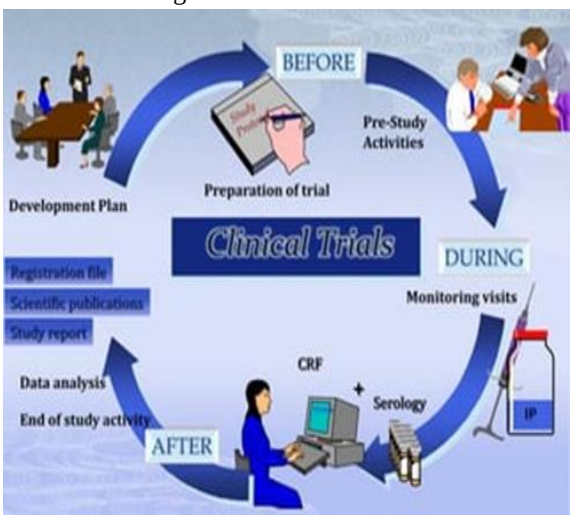
***Abstract*— This review article provides an introduction to clinical trials in India, focusing on their phases and current scenario. It provides a step-by-step guide on the process, including the role of the ethics committee, investigator, and sponsors, as well as DCGI workflow and study regulations. The article also discusses the involvement of the CDSCO, ICH-GCP government body in clinical trials. Clinical trials play a crucial role in providing good health to the public and developing new drug candidates for disease treatment. The development of Clinical Trial Regulation (CTRI) has been implemented to ensure proper follow-up of guidelines and to update serious injury during trial and informed consent forms. This review article provides essential information for readers to understand clinical trials in India, their conduct, and the regulatory bodies involved. Clinical trials minimizes bias and maximizes treatment effect estimates within budget. Over-collecting data may reduce recruitment and lead to bias. Administration mode affects data quality, cost, and completeness. Design features improve data completeness, but further research is needed to evaluate strategies. Theory-based guidelines for self-administered questionnaires are proposed but require evaluation.**

***Keywords*— Types of clinical trials, phases, guidelines, Protocol, Importance, Ethics Committee and Regulations**

I. INTRODUCTION

Clinical trials are human studies that test new treatment methods, drugs, and methods for measuring effectiveness on diseases or medical conditions. The purpose of these trials is to ensure the safety and effectiveness of these new treatments. This article provides information on different clinical trial phases, including participant characteristics, study length, and researcher goals. It aims to help participants, their loved ones, and caregivers feel confident in selecting a clinical trial to join, regardless of the treatment or medical condition being studied.[1] Clinical trials are studies that test new drugs, devices, or treatments, focusing on detecting, diagnosing, or measuring disease extent. Cancer trials can take years to complete, making them essential for understanding the effectiveness and safety of new treatments. [2] Clinical trials are a series of experiments and observations conducted in human subjects to develop new treatments, interventions, or tests for various diseases or medical conditions. They help determine the effectiveness, safety, and efficacy of a new intervention and whether it is better than existing treatments. The World Health Organization defines clinical trials as research studies that prospectively assign human participants to health-related interventions to evaluate their effects on health outcomes. The main aspect of drug discovery leads to newer, safer, and more efficacious drugs being made available for mankind. Clinical trials are crucial for determining the effectiveness and safety of new medicines developed in the laboratory or using animal models, as well as the effectiveness of diagnostic tests in clinical settings.



Types of clinical trials:
Clinical trials can be categorized based on the mode of study.

Interventional study:
Involves researchers measuring health changes in subjects by administering a specific medicine and comparing the treated subjects with those receiving no treatment or standard treatment.

Clinical observational study:
This clinical observational study involves researchers observing subjects who are given new medicine and measuring their outcomes. Another way is to classify trials is by their purpose.

Prevention trials:
Aim to prevent diseases in previously unaffected individuals or prevent their recurrence through various methods such as medicines, vitamins, vaccines, minerals, or lifestyle changes.

Screening tria
It is used to detect diseases or health conditions, while diagnostic trials focus on finding better tests or procedures for diagnosing a specific condition.

Treatment trials:
Test experimental treatments, drug combinations, or new surgical or radiation approaches.

Quality of life trials:
Explore ways to improve comfort and quality of life for chronic illness patients.

Compassionate use trials:
Expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options, such as those with no effective therapy or who have already failed all standard treatments.

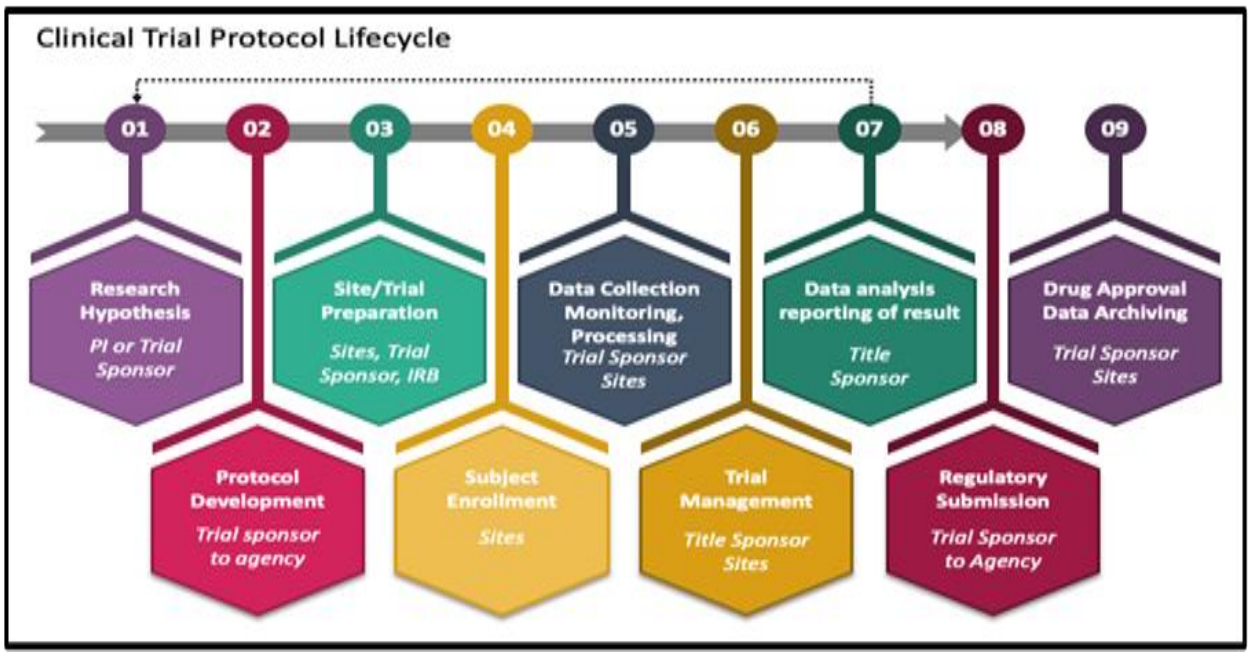
Design of clinical trials:
Adaptive clinical trials:
Aim to quickly identify drugs with therapeutic effects by adjusting dosing levels. They evaluate medical devices or treatments by observing participant outcomes and modifying trial protocol parameters.

Randomized trials:
Reduce bias by randomly assigning subjects to receive either the treatment or a placebo, with the placebo group serving as the control group. Both trials evaluate the effectiveness of medical devices or treatments.

Blind trials:
Involve subjects and investigators not knowing which treatment they receive or for what purpose, while double blind trials keep patients and researchers unaware until the study is over. Both methods effectively reduce bias by ensuring no one knows which patient is receiving which treatment.[2]

Importance of clinical trials : Clinical trials are crucial for enhancing medical knowledge and patient care, leading to the development of new treatments, diagnostic methods, and disease prevention strategies. These trials are conducted when doctors are uncertain about the safety and effectiveness of a new approach. Institutional review boards (IRBs) are committees formed by institutions sponsoring clinical trials, providing scientific oversight and ensuring the trials are morally sound and participants' rights are protected. IRBs include doctors, statisticians, and community member.

Protocol of clinical trials : Encouraged to discuss the study's implications on clinical practice, focusing on the study's indication. These protocols are crucial for clinicians to stay updated on ongoing trials and provide a reference during the final publication of results.They should be limited to ongoing studies without available results.[4] The investigator is prohibited from implementing deviations or changes to the protocol without prior approval from the sponsor and the Institutional Review Board (IRB) or Integrated Clinical Trials Authority (IES). This exception is only when there is an immediate risk to the trial subject or if the change is only logistical or administrative. The investigator must document and explain any deviations from the approved protocol. If a deviation is implemented to eliminate an immediate hazard, the reasons for it and proposed protocol amendments should be submitted to the IRB/IEC, the sponsor, and the IES.[5]

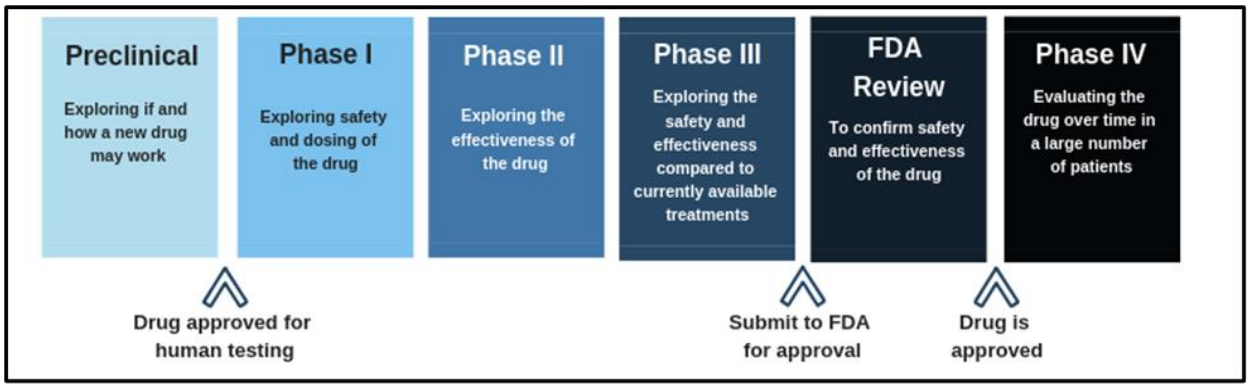


Ethics Committee: Ethics Committee (EC) in human research, requiring a research protocol to be reviewed and approved by a committee independent of the researcher, sponsor, and undue influence. The committee must consider the laws and regulations of the country and applicable international norms, but cannot reduce or eliminate any protections for research participants. This is not a legal enforcement, but a strong recommendation. The International Committee of the General Council on Ethics (ICH GCP) provides guidance on how an EC should operate, covering topics such as composition, function, operations, procedures, responsibilities, record-keeping, informed consent, and adverse event reporting. An EC must develop its own written standard operating procedure (SOP), often referencing the ICH GCP and local legal requirement[6]

ICH Guideline and Regulations: The International Conference on Harmonisation (ICH) emphasizes the importance of data collection and transfer in pharmaceuticals for human use. This can be done through various media, such as paper case record forms, remote site monitoring systems, medical computer systems, and electronic transfer. Variables must consider potential consequences, adverse effects, and trial duration. Coding should be performed by personnel blinded to treatment allocation. ICH and CIOMS warn against collecting too much data, which can waste time and resources. The trial protocol should be available in draft before questionnaire design, outlining outcomes and parameters of interest. A statistical analysis plan should be available to explain how each variable will be measured. [7]

Principals: Clinical trials should adhere to ethical principles originating from the Declaration of Helsinki and align with GCP and regulatory requirements. Risks and inconveniences should be weighed against anticipated benefits for the trial subject and society, with the rights, safety, and well-being of trial subjects being the top priority.The trial should be scientifically sound, detailed, and conducted in compliance with protocols approved by the Institutional Review Board (IRB) and Independent Ethics Committee (IEC).Confidentiality of records identifying subjects should be protected, and investigational products should be manufactured, handled, and stored in accordance with applicable regulations.[5]

Phases of clinical trials:



Preclinical study :

Preclinical studies, also known as laboratory studies, are crucial for understanding the effectiveness of new treatments. These studies involve cell studies, which examine the effects of the treatment on cancer cells grown in a lab dish or test tube, either human or animal. Animal studies follow, testing promising treatments on live animals to assess their safety. However, these studies provide valuable information, but they are not sufficient as humans and mice differ in their drug absorption, processing, and elimination processes. Additionally, side effects and other problems may not be present in mice but could affect humans. [2] Pharmaceutical companies conduct preclinical studies before clinical trials, including in vitro and in vivo experiments, to determine the drug's scientific merit and whether it requires further development as an investigational new drug. These studies provide primary efficacy, toxicity, and pharmacokinetic information. [8] Pre-clinical studies involve in vitro trials on animal populations, administering varying dosages of the study drug to obtain preliminary efficacy, toxicity, and pharmacokinetic information. These studies help pharmaceutical companies decide if further research is worthwhile. [5]

Phase 0:

Phase 0 is a type of exploratory, first-in-human trial conducted by the U.S. Food and Drug Administration to speed up the development of promising drugs or imaging agents. These trials aim to establish early behaviour in human subjects, based on preclinical studies. They involve administering single sub-therapeutic doses to a small number of subjects to gather preliminary data on the drug's pharmacokinetics and pharmacodynamics.[5] Phase 0 trials are a recent introduction to drug trials, conducted in accordance with FDA guidelines. These trials, also known as micro dose studies, aim to develop promising drugs with specific characteristics. They involve administering a single sub therapeutic dose to a small number of patients or volunteers to collect preliminary data on the drug's pharmacokinetic and pharmacodynamics properties. However, Phase 0 studies do not provide specific data on the test drug's safety and efficacy. Drug development companies s often use Phase 0 studies to rank candidates for further development.[8] Phase 0 studies are a crucial phase in clinical trials, designed to expedite drug approval by testing the drug's effectiveness in a small group of people. These studies use a small dose of a new drug, examining its effects on tumour's, the human body, and cancer cell responses. The participants may require additional tests like biopsies, scans, and blood samples. Unlike other phases, phase 0 trials have minimal benefit for the participants, as the benefit will be for future patients. However, these studies are not widely used and may not be beneficial for some drugs. [2]

Phase I:

Phase I trials are the initial stage of drug testing in humans, typically involving 20-80 healthy volunteers. These trials assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of a drug, often in an inpatient clinic. The subjects are observed until several half-lives of the drug have passed. Dose-ranging studies are also conducted to determine the appropriate therapeutic dose. Most trials involve healthy volunteers, but some cases involve real patients with end-stage diseases. Volunteers are paid an inconvenience fee for their time in the centre, ranging from small amounts for short stays to up to

£4000 depending on the duration of the trial.[5] Phase I trials are the third phase of successful clinical trials, involving a small number of volunteers (20-100) to analyse the safety, tolerance, pharmacodynamics, and pharmacokinetic properties of a drug. These trials are often conducted in clinical centres or private contract research organizations (CROs) on behalf of researchers or pharmaceutical companies. Phase I trials consist of normal ranging doses and are also known as dose magnifying studies. Healthy volunteers are selected and treated under controlled conditions or CPUS (central pharmacological units) with 24-hour medical attention. Phase 1 trials can be categorized into single ascending dose (SAD) trials and multiple ascending dose (MAD) trials. In SAD trials, a small number of volunteers are administered a single dose of the drug, followed by an increase in the dose if no adverse effects are noted. In MAD trials, a group of patients is administered multiple low doses of the drug, and samples are collected at various time intervals to analyse drug processing inside the body. [8]

Key points of phase I clinical trial:

Phase I trials involve a small group of people receiving a low dose of a treatment, closely monitored for side effects.

Phase I trials typically include people with different types of cancer and are conducted in major cancer centers.

Placebos are not used in these trials, and the study carries the most potential risk. While phase I trials may help some patients with life-threatening illnesses, careful weighing of risks and benefits is crucial.[2]

Phase II:

Phase II trials are conducted after Phase I trials confirm the initial safety of a study drug. These trials are conducted on larger groups (20-300) to assess the drug's effectiveness and continue Phase I safety assessments. Phase II trials can fail if the drug fails as planned or has toxic effects. Phase II studies can be divided into Phase IIA and Phase IIB, with some trials combining Phase I and Phase II to test both efficacy and toxicity.[5] Phase I trials involve calculating the dose of a test drug and assessing its biological and therapeutic levels. Phase II trials, conducted in large groups (100-300), analyse the drug's workings and safety assessment in larger participants. Genetic testing is common if there is evidence of metabolic rate variation. Phase II trials are divided into two groups: Phase II a clinical trials, which analyse dosing requirements, and Phase II b trials, which analyse drug efficacy. Some trials combine efficacy and toxicity, and are conducted at special clinical centres like universities and hospitals. Phase II trials detect a wide range of toxicity, with the highest failure rate. Only 25% of inventive drugs move to phase II trials. [8]

Phase III:

Phase III studies are randomized controlled multicentre trials on large patient groups to assess the effectiveness of a drug compared to current 'gold standard' treatments. These trials are expensive, time-consuming, and difficult to design and run, especially in chronic medical conditions. It is common for some Phase III trials to continue while regulatory submissions are pending. At least two successful Phase III trials are expected to demonstrate a drug's safety and efficacy for approval from regulatory agencies like FDA, TGA, and EMEA. Once a drug proves satisfactory, the results are combined into a regulatory submission, which is reviewed by regulatory authorities in different countries. Most drugs undergoing Phase III trials can be marketed under FDA norms, but adverse effects may require immediate recall.[5] Phase III clinical trials are designed to analyze the efficacy of new drugs in clinical practices. These trials are conducted on a large number of patients, aiming to assess the new drug's therapeutic effect compared to standard treatments. Due to their longer duration and size, Phase III trials are considered expensive, time-consuming, and difficult to design and run. Some Phase III trials continue until regulatory submission is submitted. After drug satisfaction, the report includes a comprehensive description of manufacturing techniques, formulation details, and half-life. The collected information is submitted to the regulatory submission for approval to market the drug.[8]

Phase IV :

Phase IV trials, also known as Post Marketing Surveillance Trials, are crucial for ensuring the safety and technical support of a drug after it is approved for sale. These trials may be required by regulatory authorities or sponsored by companies for competitive reasons or to detect rare or long-term adverse effects

over a larger patient population and longer period. Harmful effects discovered during Phase IV trials may lead to a drug being no longer sold or restricted to specific uses. The safety surveillance is designed to detect potential adverse effects over a longer period.[5] Phase IV, also known as post-marketing surveillance, involves the technical support of a drug after selling permission is obtained. These studies can be conducted with regulatory authority or sponsoring companies to identify new markets for the drug. They aim to detect long-term adverse effects on a large patient population that were not possible during Phase II and III trials. The entire drug development process takes 12-18 years. [8]

Key points of phase IV clinical trial:
Phase IV studies examine FDA-approved drugs, involving thousands of people and potentially involving many people.
These studies are often the safest type of clinical trial as the treatment has already been extensively studied and given to many people.[2]

CONCLUSION

Clinical trials are mandatory for drugs and devices to ensure safety and efficacy in humans before use. In India, the application process is lengthy and involves multiple committees. However, changes since 2008 have made India a global hub for clinical trials. As the second-most populated country, India can significantly contribute to global drug development. Clinical trials provide answers about the use of therapeutic agents, benefiting millions of patients worldwide. [3] Clinical trials for new drugs follow ICH and GCP guidelines, conducted in human volunteers. Phases I, II, III, and IV provide detailed explanations of pharmacokinetic, pharmacodynamics profile, side effects, adverse effects, and post-marketing surveillance.[5] While extensive research has been conducted on the requirements and agreements of these phases, further studies are needed to fully understand the basic conditions and parameters for successful clinical trials.[8]

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