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Original Article

A Comprehensive Review on - Clinical Trails

Sandesh Dhadambe*, Anish Mane, Suraj Chavan, Snehal Pise

Mandesh Institute of Pharmaceutical Science and Research Center, Mhaswad, Dr. Babasaheb Ambedkar Technological University, Lonere, Raigad MS India - 415509

ABSTRACT

Clinical trials are carefully conducted research studies involving human volunteers. They are done to answer specific health-related questions. Clinical trials help determine if a treatment or therapy is safe and effective. These studies are carried out in a suitable and controlled environment. Clinical trials are also used to test the effectiveness of a drug or substance through biological testing. There are five main phases in clinical trials: Phase 0, Phase I, Phase II, Phase III, and Phase IV.Clinical trials play an important role in drug discovery. They help find out how well a drug works. Today, clinical trials are necessary before a new drug can be released to the market. In clinical trials, data is collected by testing on humans or animals through biological studies. This review aims to discuss the different phases of clinical trials. Clinical trials are essential for evaluating the safety, efficacy, and overall impact of new drugs, medical devices, and therapeutic approaches before they are made available to the public. These studies are conducted in a phased manner, beginning with preclinical testing in laboratory and animal models, followed by human trials across four distinct phases. Each phase serves a specific purpose—from understanding basic pharmacological properties in Phase 0 and assessing safety in Phase I to evaluating effectiveness in Phase II, confirming benefits and monitoring risks in Phase III, and observing long-term effects post-approval in Phase IV. Clinical trials follow strict international guidelines, such as the ICH-GCP (International Conference on Harmonisation – Good Clinical Practice), to ensure ethical standards, scientific rigor, and participant safety. Various trial types and designs, including treatment, diagnostic, and screening trials, as well as open-label and blinded studies, are used based on research goals. Together, these trials contribute significantly to medical innovation, improved healthcare outcomes, and the development of evidence-based treatments.

Keywords: Clinical trials Introduction, Phases of clinical trials, Types of Clinical Trials, Types of Trial Designs, ICH-GCP (International Conference on Harmonisation – Good Clinical Practice), Conclusion

INTRODUCTION

Clinical trials are studies done to check how safe and effective a new drug or medical device is when used on people. These trials are usually done only after enough basic information about the drug has been collected. [3] Before testing a drug in people, it must go through pre-clinical studies**.** These include in vitro (lab tests using cells or tissues) and in vivo (tests on animals). These early studies help researchers understand how well the drug works and how it behaves in the body (its pharmacokinetics). Currently, there are two main international guidelines that researchers follow to ensure clinical trials are done properly and ethically. [1][5] The main goal of clinical research is to bring new, effective, and safe medicines to the market to improve human health. In this process, drugs are first tested on animals and then, if they are found to be safe, tested on people. Clinical trials play a vital role in the advancement of medical science and the development of new treatments. These carefully designed research studies are conducted to evaluate the safety, efficacy, and potential side effects of medical interventions, including drugs, medical devices, and therapeutic procedures. Before any new treatment becomes widely available, it must undergo rigorous testing through clinical trials to ensure that it meets the necessary standards for patient care. [2] The significance of clinical trials extends beyond individual therapies; they contribute to the broader understanding of diseases and help improve healthcare outcomes on a global scale. With the increasing complexity of modern medicine, clinical trials have evolved to incorporate innovative methodologies, ethical considerations, and regulatory guidelines. This review aims to provide a comprehensive overview of clinical trials, focusing on

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their design, phases, ethical frameworks, challenges, and their critical role in evidence-based medicine.

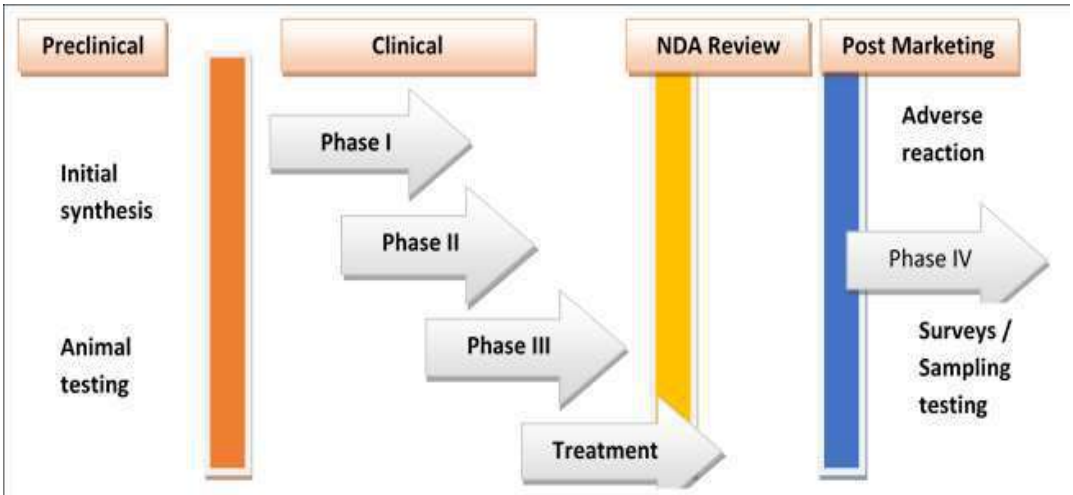

Fig. Drug development process

Preclinical studies -

Pre-clinical studies**,** also called in vitro studies, are tests done in labs, usually on animals. [1] These studies help check the purity**,** production process**,** and how the drug works in the body **(**pharmacokinetics and pharmacodynamics). Pre-clinical trials are done before testing the drug on humans in clinical trials. They help pharmaceutical companies find out if the drug has any medical benefits. These studies also show if any changes need to be made to the drug before moving forward with development. [3]

Phase 0-

Phase 0 **i**s a new step added before the main clinical trials. It is designed as an early test, following guidelines from the U.S. Food and Drug Administration (FDA)**.** [1] In Phase 0**,** a very small dose of the drug is given to a small group of people (about 10 to 15) to collect preliminary information**.** This phase does not provide full details about the safety or effectiveness of the drug. [3]

- Phase 0 trials mainly focus on three things:

a) Understanding how the drug moves through the body (pharmacokinetics).
b) Learning how the drug works (mechanism of action**).**
c) Finding the right dose that shows some effect (significant dose determination**).** [2]

- Purpose of Phase 0 Trials:

The main goal of a Phase 0 trial is to understand how a drug is absorbed, distributed, metabolized, and excreted in humans—collectively known as pharmacokinetics. Additionally, researchers may study how the drug interacts with its target (pharmacodynamics). These trials help determine whether the drug performs as expected based on laboratory and animal studies.

- Key Features:
  - Small Sample Size: Typically involves fewer than 15 participants.
  - Microdoses: Participants receive very low, sub-therapeutic doses of the drug, ensuring minimal risk.
  - Short Duration: These trials are usually brief, often lasting only a few days or weeks.
  - No Therapeutic Intent: The doses used are too low to produce any therapeutic benefit; the focus is strictly on safety and behavior of the drug in the body.

Phase I -

Phase I studies are the first stage of testing a new drug in humans. In this phase, a small group of people (about 20 to 100) are selected, usually healthy volunteers. The main goal is to check how the drug works in the body — including how it moves through the body (pharmacokinetics), how it affects the body

(pharmacodynamics), and whether it is safe and well-tolerated. [1] This phase can take several months and helps identify any side effects and the right dose range. Around 70% of drugs make it through Phase I. There are two main types of studies in this phase:

- SAD (Single Ascending Dose) – where a single dose is given and gradually increased in different groups.
- MAD (Multiple Ascending Dose) – where multiple doses are given over time to study longer-term effects. [3][2]
- Key Objectives:
  - Safety Assessment: The main goal is to determine whether the drug is safe to administer to humans.
  - Dosage Evaluation: Researchers test different doses to find the best balance between effectiveness and tolerable side effects.

At the end of Phase 1, researchers decide whether the drug is safe enough to proceed to Phase 2, where it will be tested for effectiveness in a larger group of patients. [2]

Phase II –

Phase II studies are done on a larger group of people (about 100 to 300), usually patients who have the condition the drug is meant to treat. The main goal of this phase is to find out how well the drug works and to continue checking its safety. Researchers also try to find the best dose — one that works well with the least side effects.

- Phase II is divided into two parts:
- Phase II (a) – focuses on finding the right dose.
- Phase II (b) – focuses on checking how effective the drug is. [1]

This phase helps drug companies compare the new drug's safety and effectiveness. About one-third of drugs that enter clinical trials make it through both Phase I and Phase II. [4]

- Key Objectives:
  - Effectiveness Testing: This phase aims to find out if the drug actually has the intended therapeutic effect on the disease or condition it is meant to treat.
  - Further Safety Monitoring: Researchers continue to observe side effects and determine whether the benefits of the treatment outweigh any risks.
  - Dose Optimization: Several doses may be tested to identify the most effective dose with the fewest side effects.

The data collected in Phase 2 helps determine whether the drug should move on to Phase 3, where it will be tested on a much larger population to confirm its effectiveness and monitor side effects more comprehensively. [3]

Phase-III -

Phase III is a large-scale stage of drug testing that can last from several months to a few years. It usually involves 300 to 3,000 or more volunteers**,** depending on the disease being studied. This phase helps researchers understand how effective the drug or device is and what side effects it might cause. [1] About 70% to 90% of drugs that enter Phase III trials pass successfully. After a drug passes this phase, the drug company can apply to the FDA for permission to sell the drug. Because Phase III takes a long time and involves many people, it is very expensive and hard to manage. [4]

- Key Objectives:
  - Confirm Effectiveness: Researchers test the drug on a larger population to verify its benefits seen in earlier phases.
  - Monitor Side Effects: Any less common or longer-term side effects that may not have appeared in earlier phases can be identified here.
  - Compare to Existing Treatments: The new drug is often compared with standard therapies to evaluate whether it offers improvements in safety, effectiveness, or quality of life.
  - Collect Comprehensive Data: Information gathered helps in developing labeling, usage guidelines, and risk-benefit assessments.

If the drug proves to be effective and safe, the data from Phase 3 is submitted to regulatory authorities (like the FDA or EMA) as part of the application for drug approval. A successful Phase 3 trial is usually the

final step before a drug becomes available to the general public. [4]

Phase-IV -

Phase IV trials, also known as post-marketing studies**,** are done after a drug has been approved by regulatory authorities and is available in the market. These studies mainly focus on pharmacovigilance**,** which means monitoring the drug's safety in the general population over the long term. [2]

- Phase IV aims to:
  - Compare the new drug with other drugs already available.
  - Check if the treatment is cost-effective**.**
  - Monitor how well the drug works over time and how it affects the quality of life of patients. [3]

This entire process—from early research in the lab to this post-marketing phase—can take around 12 to 18 years**.**

- Purpose of Phase 4:
  - While earlier phases of clinical trials (Phases 1–3) focus on testing the safety, appropriate dosage, and initial effectiveness of a treatment, Phase 4 provides additional insights that may not have been observed during those earlier stages. Key purposes include:
  - Detecting rare or long-term side effects that may only appear when a drug is used by thousands or millions of people.
  - Assessing the drug's performance in real-world conditions, beyond the controlled setting of a clinical trial.
  - Evaluating the drug's effectiveness in different patient populations, such as those with other medical conditions or who are taking other medications.
  - Monitoring for potential drug interactions and patterns of use or misuse.

Phase 4 is essential for ensuring long-term public health and safety. It allows for ongoing risk assessment and helps healthcare providers make better-informed decisions. Additionally, the results can influence clinical guidelines, labeling changes, or new recommendations for drug use. [1]

Types of Clinical Trials:

1) Treatment Trials – These trials test new medicines, treatments, or approaches like radiation to see how well they work.
2) Diagnostic Trials – These are done to find better ways to diagnose or detect a specific disease or health condition.
3) Screening Trials – These trials check how effective a test or procedure is at finding a disease early, even before symptoms appear.
4) Quality of Life Trials – These look at how a disease or its treatment affects a person's overall well-being, including their physical, mental, and social health. [1,2,4]

Types of Trial Designs:

1) Open Trials – In these trials, both the patient and the researcher know which treatment is being given. These are often used in studies like bioequivalence trials (to compare two similar drugs).
2) Blind Trials – In these trials, the person receiving the treatment doesn't know what treatment they are getting. There are three main types:

   a) Single-Blind Trials – The researcher knows the treatment details, but the patient does not.
   b) Double-Blind Trials – Neither the patient nor the researcher knows who is getting the real treatment and who is getting a placebo (a fake treatment).
   c) Triple-Blind Trials – The patient, the researcher, and the person analyzing the data all do not know who is receiving the actual treatment. This helps to reduce bias and make the results more accurate. [1,2,]

ICH-GCP (International Conference on Harmonisation – Good Clinical Practice):

Clinical trials must follow Good Clinical Practice (GCP) guidelines. These are international standards used to make sure that clinical trials are planned, carried out, monitored, recorded, and reported properly. GCP helps ensure that the data collected is

correct and that the people taking part in the trial are safe and treated ethically. [1,4]

Key Principles of ICH-GCP Guidelines:

- Ethical Conduct – Clinical trials must follow ethical rules based on the Declaration of Helsinki, as well as local laws and GCP standards.
- Risk vs. Benefit – Before starting a trial, the possible risks and discomforts must be compared to the expected benefits. A trial should only happen if the benefits are greater than the risks.
- Participant Protection – The rights, safety, and well-being of people in the trial are the most important and should come before science or society's interests.
- Scientific Support – Enough information from earlier studies (both lab and clinical) should be available to support starting a new trial.
- Scientific Quality – The trial should be based on good science and must be clearly described in a detailed plan called a protocol
- Ethics Approval – The trial must follow the approved protocol and get permission from an ethics committee (IRB or IEC) before it begins.
- Qualified Medical Supervision – A qualified doctor (or dentist, if appropriate) must be responsible for the medical care and decisions made for trial participants.
- Trained Staff – Everyone working on the trial must have the right education, training, and experience to do their specific job properly.
- Informed Consent – Every participant must give their clear and voluntary consent before joining the trial, after being fully informed about it.
- Proper Record Keeping – All trial data must be recorded, handled, and stored in a way that ensures it is accurate, easy to understand, and can be checked if needed.
- Participant Privacy – Personal information of participants must be kept private and protected according to laws and guidelines.
- Safe Handling of Trial Drugs – The trial drug must be made, stored, and handled following Good Manufacturing Practices (GMP) and according to the approved trial plan.
- Quality Assurance – There should be systems in place to ensure that every part of the trial is done with high quality. [1,4]

CONCLUSION:

Clinical trials for new drugs are usually divided into four phases. Each phase is treated as a separate step in the drug approval process. These phases help to clearly understand the drug's safety, how well it works (efficacy), how it acts in the body (pharmacodynamics and pharmacokinetics), possible side effects, and how the drug performs after it is approved and sold (post-marketing surveillance).

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