WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A REVIEW ON CLINICAL TRIAL

Nilesh Ramesh More[1], Nayana Machindra Shinde[2], Vrushali Balasaheb Bhosale[3]

ADITYA INSTITUTE OF PHARMACY, DERABARDI, CHALISGAON.

ABSTRACT :

A clinical trial is a research investigation involving human participants designed to address specific health-related inquiries. Thoroughly executed clinical trials represent the most efficient and secure method for identifying effective treatments and enhancing health outcomes. These trials are categorized into several phases, specifically phases 0, I, II, III, and IV. The primary objective of clinical trials is to evaluate therapeutic efficacy, and they serve as a crucial and highly specialized type of biological assessment. In phase I, the focus is on pharmacokinetics, safety, and the overall effects of the treatment on human volunteers, conducted by clinical pharmacologists. If the drug successfully meets the criteria, it progresses to phase II, where pharmacokinetics, safety, and therapeutic efficacy are assessed in a selected group of patients by clinical pharmacologists. Upon successful completion of this phase, hundreds of selected patients are involved in phase III, where clinical investigators primarily evaluate safety and therapeutic effectiveness. Once a drug passes this phase, it receives approval for marketing. Even post-approval, healthcare professionals from various hospitals and clinics continue to provide feedback regarding adverse drug reactions (ADRs) and efficacy during phase IV.

Keywords: Clinical Trials, Preclinical Studies, Clinical studies, Phases.

INTRODUCTION :

A clinical trial is a research investigation designed to evaluate a novel medical intervention or an innovative application of an existing treatment. The objective is to determine whether this approach offers improved methods for the prevention, screening, diagnosis, or treatment of a disease. [1] The World Health Organization defines a clinical trial as a research study that prospectively allocates human participants to one or more health-related interventions in order to assess their impact on health outcomes. [2The World Health Organization defines a clinical trial as a research study that prospectively allocates human participants to one or more health-related interventions in order to assess their impact on health outcomes. [3] Clinical trials represent the most secure and efficient method for identifying effective treatments for individuals, as well as discovering innovative approaches to enhance health.

There are different kinds of clinical trials, including those to study:

- Prevention options
- New treatments or new ways to use existing treatments
- New screening and diagnostic techniques
- Options for improving the quality of life for people who have serious medical conditions

Clinical trials recruit healthy volunteers and/or patients based on the product type and its developmental phase. Initially, these trials involve small studies, which are subsequently followed by larger-scale studies that often compare the new product with existing prescribed treatments. As favorable safety data is collected, the patient population is generally expanded.. [4]

Preclinical Studies – Following the synthesis or identification of a potential compound or series of compounds, testing is conducted on animals to reveal the complete pharmacological profile. Initial experiments are typically carried out on smaller rodents, such as mice, rats, guinea pigs, hamsters, or rabbits, before progressing to larger animals like cats, dogs, or monkeys. Throughout the evaluation process, compounds that demonstrate unfavorable characteristics are eliminated at each stage, resulting in only a select few from thousands advancing to the point where human administration is contemplated.

The following types of tests are performed:

1. **Screening Tests:** These tests are straightforward and can be conducted quickly to determine whether a specific pharmacodynamic activity, such as analgesic or hypoglycemic effects, is present or absent.
2. **Tests on Isolated Organs, Bacterial Cultures, etc.:** These are also initial assessments aimed at identifying particular activities, including antihistamines, anti-secretory agents, vasodilators, and antibacterial substances, among others.
3. **Test on animal models of human disease:** Various conditions have been studied, including spontaneous seizures in genetically hypertensive rats, experimental tuberculosis in mice, and alloxan-induced diabetes in rats or dogs, among others.
4. **General Observational Test:** The initial phase involves administering the compound, particularly when dealing with novel substances or upon identifying promising activity during screening tests. The compound is injected in incremental doses into small groups of mice, which are then monitored for any resultant effects. Preliminary insights are derived from the observed effect profiles.

5. **Confirmatory Tests and Analogous Activities:** Active compounds are subjected to comprehensive examination through more sophisticated tests that validate and characterize their activity. Additional related activities, such as antipyretic, anti-inflammatory, and analgesic effects, are also evaluated.
6. **Mechanism of Action:** Efforts are being undertaken to elucidate the mechanism of action, such as determining whether an antihypertensive functions as a blocker, calcium channel blocker, ACE inhibitor, or a centrally acting agent, among others.
7. **Systemic Pharmacology:** The impact of the drug on major organ systems, including the nervous, cardiovascular, respiratory, and renal systems, remains significant regardless of its primary action.
8. **Quantitative Tests:** The relationship between dose and response, the maximum effect, and the comparative efficacy with current medications have been determined.
9. **Pharmacokinetics:** The drug's absorption, distribution within tissues, metabolism, excretion, volume of distribution, and half-life are all measured.
10. **The toxicity tests:** The goal is to investigate the safety of the compound in at least two types of animals, particularly mice or rats and dogs, by using both oral and injection methods. [5]

Clinical Trials: Clinical research may span a duration of 3 to 7 years. The Clinical Trials Rules establish fundamental principles and practices governing clinical trials, emphasizing the ongoing assessment of data to ensure the safety of trial participants. Each clinical trial must be structured based on robust scientific principles, and the outcomes should be evaluated in line with the established clinical trial protocol. [6,7]

Phase 0:

Phase 0 is a new concept that has been introduced for exploring trials. At first, human trials were conducted following the guidelines set by the US Food and Drug Administration (FDA) in 2006 for exploratory investigational new drug (IND) studies. [8,9] Phase 0 has some unique characteristics, including giving a small, sub-therapeutic dose of the study drug to a limited group of patients or volunteers, usually between 10 and 150 people. The main goal is to gather initial data on how the drug behaves in the body and its effects. Interestingly, these studies don't actually provide detailed information about the drug's safety or effectiveness. Additionally, companies involved in drug development often conduct Phase 0 studies to evaluate and rank drug candidates, helping them determine the pharmacokinetic properties in humans for future research. [10] The purpose of these studies is to help make decisions about a drug's future during the early stages of development by using human models instead of relying on animal data. Exploratory IND studies, also referred to as Phase 0 studies, are conducted early in clinical trials and in vitro research. Volve has limited human exposure and is not meant for therapeutic or diagnostic use. It is administered in sub-therapeutic and pediatric doses, and the clinical researcher monitors the patients closely. [11,12]

These studies were designed to speed up the drug development process, explore how INDs behave in the human body, help find new potential drugs, and reduce both the time and expenses involved in development. [13]

Phase I: Human Pharmacology and safety:

A Phase I clinical trial is all about figuring out the best way to give a new drug, including how often and how much to give. It looks at the highest dose that patients can handle without serious side effects, along with how the body processes the drug and its effects. The main focus of these trials is to ensure the treatment is safe. Typically, they involve 20 to 100 participants and are closely watched by researchers. If patients don't experience major side effects, the doses may be increased, and researchers check how well the patients are responding to the treatment. These studies help find the safest and most effective dose, which is usually much lower than what caused issues in animal tests. The key goal of Phase I trials is to avoid giving patients doses that are too low while still keeping safety in mind and allowing for quick enrollment.[14] Phase I trials involve testing a range of doses, which is why they are often referred to as dose-finding studies. The main goal is to figure out the safest and most effective dose for future treatments. Typically, these trials include healthy volunteers. They take place in controlled environments known as Central Pharmacological Units (CPUs), where volunteers get round-the-clock medical care and are closely monitored by a dedicated clinical team. [15]

There are different kinds of phase I trials:

- **SAD:** Single ascending dose studies involve giving small groups of people one dose of a medication and then monitoring them for a certain period. If the participants don't show any negative side effects and the pharmacokinetic data aligns closely with the expected safe levels, the dose is considered acceptable.
- 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:** Researchers conduct multiple ascending dose studies to gain insights into how the body processes different doses of a drug. In these studies, a group of patients is given several small doses of the drug, and samples of blood and other fluids are taken at different times. This helps scientists analyze how the drug behaves in the body. Afterward, the dose is increased for additional groups until a set limit is reached.

Food's effect: A brief study aimed at exploring how eating before taking a drug affects how the body absorbs it. Typically, these studies are conducted as crossover trials, where participants receive two identical doses of the drug on separate days: one dose is taken on an empty stomach, and the other after eating. [16]

Phase II: Therapeutic exploration and Dose Ranging: In the Phase I trials, the dosage of the experimental drug has already been determined. The next step is to evaluate if the drug achieves the necessary biological and therapeutic levels. During Phase II trials, research is conducted on larger groups of participants, typically ranging from 100 to 300, to further assess the drug's effectiveness while also reviewing safety from the Phase I trials. Genetic testing is often performed if there is sufficient evidence of differences in how individuals metabolize the drug. Phase II trials are split into two categories: Phase IIa, which focuses on determining the appropriate dosage, and Phase IIb, which looks at how effective the drug is. Sometimes, these trials are referred to as Phase IIA and Phase IIB, with Phase IIA concentrating on dosage needs and Phase IIB on the drug's performance at those doses. Additionally, some studies may combine both Phase I and Phase II to evaluate both effectiveness and potential side effects. [17, 18]

Phase III: Therapeutic confirmation /Comparison:

Phase III clinical trials are proposed to be structured to evaluate the effectiveness of new medications and their therapeutic impact in clinical settings. These trials are typically conducted randomly with a substantial patient population, ranging from 300 to over 3,000 participants, aiming to provide a definitive assessment of the new drug in comparison to standard treatment options. Furthermore, due to their extended duration and larger scale, Phase III trials are regarded as the most costly, time-intensive, and complex to design and execute. In these trials, chronic diseases that require evaluation over the duration of the intervention can be effectively studied. [19, 20] 1. In typical situations, some Phase III trials keep going until the regulatory submission is waiting at the right agency. After the Phase III trials show that the drug meets the necessary standards, a report is created that includes a detailed description of the methods used, the results of the manufacturing process, the formulation details, and its half-life. This information is then sent in for regulatory submission, giving the sponsor hope for getting approval to market the drug. Additionally, if any side effects are reported, the drug is quickly pulled from the market.[21,22]

Phase IV: Post Marketing Surveillance/Studies:

Phase IV of clinical trials pertains to post-marketing surveillance studies that are required for every new drug that receives marketing approval. These studies are essential for monitoring any rare adverse events that may arise from the use of the drug in a broader population.[23] Once, the drug has been cleared by the regulator, it is made available to patients either with a prescription or over-the-counter. As the drug starts being used widely, data is gathered in order to enhance the understanding of its efficacy in different circumstances during the lifetime of the medicine. [24]This propels gradual developments. [25] Adverse reactions occurring in fewer than 1 in 3,000 to 5,000 patients are typically not identified during Phase I to III clinical trials and may remain unrecognized at the time of a drug's approval. Such rare adverse reactions are more likely to be discovered when a larger patient population is exposed to the drug post-approval and during its market availability. [26]

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: -** Research was carried out to identify improved tests or methods for diagnosing a specific disease or condition.
4. **Screening trials: -** Test the best way to detect certain diseases or health conditions.
5. **Quality of Life: -** Research studies, often referred to as Supportive Care trials, investigate methods to enhance comfort and overall quality of life for those living with chronic illnesses. [27]

Conclusion :

A clinical trial is crucial for testing a drug or device to ensure it is safe and effective for people before it can be used. After the initial development stage, a new experimental drug goes through several clinical phases: I, II, III, and IV. A detailed summary of what happens after these phases will be given. [28]

Drug development usually goes through several stages that can take many years to complete. Each stage gives a detailed look at how the drug works in the body, its effects, potential side effects that could be harmful or helpful, any adverse reactions, and monitoring after the drug is on the market.29]

REFERENCE:-

1. 1.Information about clinical trial. Available from: URL http://www.temple.edu/pascope/about_trials.html
2. 2.http://www.nhmrc.gov.au/healthethics/human-research-ethics/clinicaltrials. Assesed on April 15, 2013

3. Clinical trial Wikipedia , the free encyclopedia. Jan 28 2008. Available from: URL http://en.wikipedia.org/ wiki/clinical _trial. 28 Jan 2008.
4. Indian Good Clinical Practice Guideline
5. 5.A textbook of Pharmacology I ,by Adhikrao Vyankatrao Yadav ,Dr. Atul Ramchandra Chopade By Nirali Prakashan, Second issue Feb ,2022 page no . 2.23 -2.24 .
6. 6.(v)Ethical Guidelines for Application of AI in Biomedical Research and Healthcare, accessible here:https://main.icmr.nic.in/sites/default/files/upload_documents/Ethical_Guidelines_AI_Healthcare_2023.pdf, last accessed on April 29, 2023.
7. 7.ICMR Guidelines for Good Clinical Laboratory Practices, 2021, accessible here: https://main.icmr.nic.in/sites/default/files/upload_documents/ GCLP_Guidelines_2020_Final.pdf, last accessed on January 26, 2023
8. 8.DeMets D, Friedman L, and Furberg C. Fundamentals of Clinical Trials. Springer 4th Edition, 2010; ISBN 978-1-4419- 1585-6.
9. CDER. "Exploratory IND Studies". Guidance for Industry, Investigators, and Reviewers. Food and Drug Administration, 2010.
10. The Lancet (2009). Phase 0 trials: a platform for drug development?. Lancet 2009; 374: 176
11. 11.Kumar, S., Kinders, R., Rubinstein, L., Parchment, R.E., Murgo, A.J., Collins, J., et al. (2007) Compressing Drug Development Timelines in Oncology Using Phase "0" Trials. Nature Reviews Cancer, 7, 131-139. http://dx.doi.org/10.1038/nrc2066
12. Schelers, J.H.M. (2009) Phase 0 (Zero) Clinical Trials: More than Zero Benefits? European Journal of Cancer, 45, 728-729. http://dx.doi.org/10.1016/j.ejca.2009.01.022Le Tourneau, C., Lee, J.J. and Siu, L.L. (2009) Dose Escalation Methods in Phase I Cancer Clinical Trials. Journal of the National Cancer Institute, 101, 708-720. http://dx.doi.org/10.1093/jnci/djp079
13. Le Tourneau, C., Lee, J.J. and Siu, L.L. (2009) Dose Escalation Methods in Phase I Cancer Clinical Trials. Journal of the National Cancer Institute, 101, 708-720. http://dx.doi.org/10.1093/jnci/djp079
14. Storer, B.E. (1989) Design and Analysis of Phase I Clinical Trials. Biometrics, 45, 795-798. http://dx.doi.org/10.2307/2531693
15. Guidance for Institutional Review Boards and Clinical Investigators. Food and Drug Administration, 2007.
16. 16.Ankur Rohilla*, Ravi Kumar Singh, Deepti Sharma, Rahul Keshari and Ashok Kushnoor, Phases of clinical trial: A review, Published in International Journal of pharmaceutical, chemical and biological sciences, Published in 2013.
17. http://www.pdtrials.org/en/about_PDtri als_what. Assesses on March 20, 2013.
18. http://www.mlanet.org/resources/hlth_t utorial/mod4c.html. Assessed on March 31, 2013
19. Paul J, Seib R, Prescott T. The Internet and Clinical Trials: Background, Online Resources, Examples and Issues. J Med Int Res 2005; 7: e5.
20. Melinda C. Experimental Labour – Offshoring Clinical Trials to China East Asian Science, Technology and Society. An Int J 2008; 2: 73-92.
21. Poole V, Peterson AM. Pharmacotherapeutics for Advanced Practice: A Practical Approach, 2005; Lippincott Williams & Wilkins. ISBN 0-7817-5784-3.
22. John H. Fixing a broken drug development process. J Comm Biotech 2013; 19,: 588.
23. Supra note 32.
24. Supra note 14.
25. Supra note 15.
26. Viraj Suvarna, Phase IV of Drug Development, available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3148611/, last accessed on January 26, 2023
27. 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.
28. Clinical Trials: A General Review Dr. Akhilesh Tiwari, Megha Joshi, Dr. Kamlesh Dashora by International Journal of Contemporary Research and Review, Vol. 7, Issue. 12, Page no: 22131-22135.
29. 29.S. B. Thorat*, S. K. Banarjee, D. D. Gaikwad, S. L. Jadhav, R. M. Thorat; Clinical trial: A review; Published in International Journal og Pharmaceutical Sciences Review and Research, Volume 1, Issue 2 March April 2010, Article 019
30. 30.John H. Fixing a broken drug development process. J Comm Biotech 2013; 19,: 588
31. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf