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Review Article

Clinical Trials: Essential Stage in Development of Drug

Tamboli S.S., Surwade A.B., Mahale K.J., Khairnar K.B., Avhad K.B., Avhad A.V., Chavan A.G., Kaluse P.S., Darekar A.B.* , Ugale P.G*, Jadhav S.S.*

Krantiveer Vasantrao Narayanrao Naik Shikshan Prasarak Sanstha, Institute of Pharmaceutical Education and Research-422002

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Abstract

This article gives an idea about the clinical trials and way its importance in the development of the vaccine. The different phases which are involved in clinical trials like phase I, phase II, phase III, and phase IV. Each phase role in the development of vaccines and how clinical trials play an important role in the treatment of various diseases. The role of a clinical trial is to help society and the entire medical community by contributing to the research and development of new drugs concerning their safety and efficacy.

Keywords: Preclinical trials, phase I trial, phase II trial, phase III trial, phase IV trial

*Address for Correspondence:

Darekar A.B., Ugale P.G., Jadhav S.S., Krantiveer Vasantrao Narayanrao Naik Shikshan Prasarak Sanstha, Institute of Pharmaceutical Education and Research-422002

INTRODUCTION:

The clinical trial is an inseparable subject between the pharmaceutical industries and human health. It is the type of clinical study or research study that tests the effectiveness, and toxicity of the new drug. For any new drug to enter a clinical trial it must pass preclinical studies. In studies all about that chemical entity on human being like toxicity, effectiveness, pharmacokinetics, and pharmacodynamics information. Clinical research is a branch of health care science that determines the safety and effectiveness (efficiency) of medication, diagnostic products, and treatment intended for human use.¹

There are two main types of clinical studies:

- 1) Clinical trial (interventional studies).
- 2) Observational studies.

The first recorded clinical trial in the year 1747 by Scottish James Lind on scurvy disease now known as vitamin C deficiency. James Lind is known as the father of clinical trials. Then later first published a randomized control trial in 1948 on streptomycin treatment of pulmonary tuberculosis in MRS (medical Research council investigation).^{2,3}

Advantages of clinical trials:

- 1) Help to identify new vaccines in the treatment of various diseases
- 2) Help to study and learn more about the disease

- 3) Help to understand body action in response to the drug.
- 4) Help to improve pharmacological knowledge and help in the effective treatment of disease
- 5) Helps society and the entire medical community by contributing to research.

Disadvantages of clinical trials:

- 1) It is possible that the new treatment may not be better than the current treatment of the disease and may cause several side effects.
- 2) Some patients may give a placebo effect instead of the active new drug.
- 3) Patients have to frequently visit the hospital for treatment, regular dose, stay, etc.
- 4) Chances to cause several adverse effects.^{4,5}

Phases of a clinical trial:

1) **Preclinical studies**-Preclinical studies are performed in vitro (test tube or cell culture) & In vivo (Animal) experiments. It is also possible to execute in silico profiling using computer models of the drug-target interaction. There are several types to perform clinical trials. Those are the following;

1) Screening test- It is an easy and fast-performing test. That will be shown the presence or absence of pharmacodynamic activity. example-hypoglycemic activity.

2) Test on isolated organs, and bacterial cultures -This test can detect specific activity such as antihistaminic, antibacterial, etc.

3) Toxicity Tests- This test has the main aim to determine the safety of the compound in the minimum of two species.

4) Tests Animal models of human diseases- such as hyper-sensitive rats and experimental tuberculosis in mouse kindled seizures in rats.

5) Pharmacokinetics- The absorption, distribution, metabolism, excretion, the volume of distribution, plasma half-life of the drug, and pattern of tissue distribution of the drug can be identified.

6) Confirmatory tests & analogue activities- In this test confirms & characterizes the activity, other related activities.

Example- Antipyretic & Anti-inflammatory activities in analgesics are tested.

7) Quantitative Test- In that study about dose-response relationship, maximal effect & comparative potency/efficacy with existing drugs.

8) Systemic Pharmacology-Irrespective primary action of the drug. Effects on the major organ system cardiovascular, respiratory, nervous, renal, and G.I. Track are worked out.^{6,7}

Phase-0 Micro-dosing Study:

Phase-0 is the latest designation for exploratory, the first in human trials conducted by U.S. Food & Drug Administration (FDA) 2006 Guidance on Exploratory. This is a recently developed strategy to reduce the money & Time of the drug development process. Pharmaceutical companies perform phase 0 to determine which of their drug candidates has the best pharmacokinetic parameter in humans. In that studied such a tool is the micro-dosing human study undertaken before the phase -1 trial and is also called phase '0' study. The numerous candidate drugs fail during clinical trials due to suboptimal human pharmacokinetics. Very low doses, generally about 1/100th of the estimated human dose, or a maximum of 100ug total dose of a candidate drug, maximum of 100ug total dose of the candidate drug are administered to healthy volunteers and pharmacokinetics is a workout using highly sophisticated instrumentation, such as accelerator mass Spectrometry (AMS) with Radio-labeled drug, or LC - Tandem mass Spectrometry (LC-MS-MS) to measure ultra-low drug levels. Moreover, the pharmacokinetics 0 phase data could be useful in a more precise selection of doses for the phase 1 study.^{6,8}

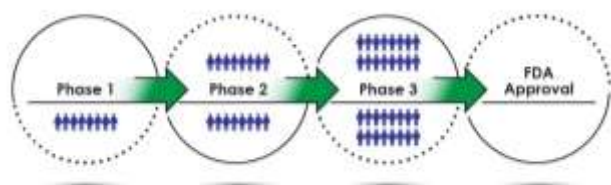


Figure 1: Steps in Clinical Trials⁹

Phase I Human pharmacology and safety: As consider the patient safety issue, the medicine should undergo clinical trials to ensure the safety, toxicity, efficacy, and tolerability of the new drug hence Phase I starting Process of a clinical trial. All clinical trials should be performed as per guidelines provided by WHO (World Health Organization). Phase I included the study of the effect of the drug on the body and how actually body responds to that effect of a drug that is ADME (absorption, distribution, metabolism, excretion) Also Food

and Drug or Drug and Drug interaction. Also included a study of the maximum tolerated dose (MTD) for the patient.¹⁰

Importance of Phase I clinical trials–It plays an important role in determining the safety of the new drug in pharma and medicinal companies –For combination therapy not only the discovered drug are used for clinical trials but also the drugs which are already present in the market. It is also performed on both healthy volunteers and illness patients both trials are conducted.

Patient study–It is small trails in healthy volunteers who have a normal immune response which is at low risk of medicinal infection Phase-I Trials are performed on different amount of dose in different age group –The route of administration, schedule of medicine others study related to their Physiology are studied in phase I. The phase I Trials required a low number of patients. The number of patients will vary on the dose level to be tested –In the case of cancer treatment, the duration of the phase I Trial is for approximately 6-10 months. There are 12-20 patients that are used for the clinical trials in phase I.

In phase I the clinical trials are dependent on three guidelines Safety, Ethical conduct, and Efficiency

2) During clinical trials vital signs, plasma & serum levels, and adverse effects are studied -The sample size should be administered is 20-80ml.

3) Therapeutic efficacy of phase I in clinical trials –Safety: death rate at lower toxicity (0.5~2.0%) -Dosing: don't include high doses of targeted and immunotherapeutic agent response rate. There are ~20% of patient-reported in phase I trials Example –study of a single dose of drug x in a normal subject.^{11,12}

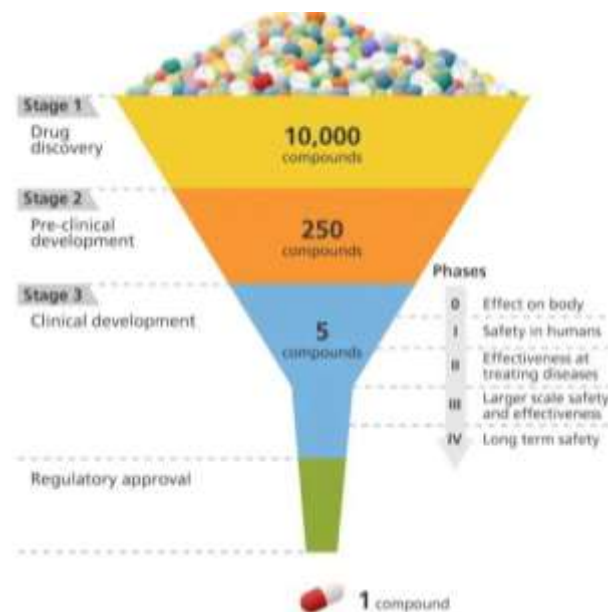


Figure 2: Stages in clinical trials with phases involved within it¹³

Phase-II Therapeutic exploration and dose ranging: As we get good results in phase I clinical trial. We proceed for phase II it mainly works on how safe is treatment and how well it works. Intermediate efficacy is properly established. During phase II, clinical trials information on further toxicity is gained. phase - II and phase - III -attrition once a drug has passed the phase - II efficiency trails less than one and half of them in sufficient efficiency in phase - III to produce it in the market place is a reason that might be; phase - II and phase-III studies many times to examine different endpoints phase - II studies can examine representative endpoint of disease, but in

large effect and toxicities are usually the focus of phase-III studies. In addition lack of success in phase-II studies to predict phase-III success may be in parts due to statistical phenomenon

Therapeutic exploration and dose-ranging-It is held by physicians, who are trained as a clinical inspector, and includes 100-150 patients and they are selected according to particular exclusion and inclusion basis. The principal target is the formation of therapeutic effectiveness, dose scale and Ceiling result in a controlled position. Tolerability and pharmacokinetics are studied as additions to phase -I. These study is mainly controlled and arbitrary and may be blinded or open labeled. It is normally carried at 2-4 centers. The application drug may also get drop at these stages if the necessary level of clinical efficacy is not obtained.^{8,12}

Phase-III Therapeutic confirmation/ comparison: It is studied at are conducted at multiple centers with some hundred to some thousand patients for the drug intended. Phase III trials provide more information needed for packaging and labeling and insertion of medicine. It is also FDA-approved. A drug in this phase can be studied for several years and may be almost 25-30 % to be a passing phase I, II, and III. When phase III is completed then a pharmaceutical can be requested FDA approval for the market it is also known as a New Drug Application (NDA)^{15,16}. NDA contains all of the scientific data that the company gathered this data will be phases in all trials. It is an essential approval and registered to market of a vaccine, excess the effects of the final formulation. These trials are also mainly designed for safety and efficacy. Vaccine Efficacy is also defined as a percent reduction in the incidence of disease or infections during the vaccination process. Vaccine Efficacy is also denoted by VE. If the Incidence of disease in the unvaccinated subject is to I_u . If the incidence of disease in vaccinated subject to I_v then VE is calculated as

$$(I_u - I_v / I_u) \times 100\% = (1 - I_v / I_u) \times 100\% = (1 - RR) \times 100\%$$

Where,

I_u is the incidence of in unvaccinated population

I_v is the incidence in a vaccinated population

RR is a relative risk. Occurancy in disease is the most common endpoint however the trial may be based on another clinical endpoint. It is such as incidence of infections and immunological.^{17,18}

Phase-IV Post-marketing surveillance/data gathering studies: A phase-IV clinical trial begins after a drug has been approved for use in the general population following phase I, II, and III trials to rigorously test its efficacy and safety. According to the World Health Organization (WHO) phase-IV studies are conducted after a drug has been already marketed their purpose is to know the feedback of general populations about the safety and adverse effect of drugs. Involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. This trials look for side effects that were not seen in earlier trials and may also study how well a new treatment works over a long period of time.

Methods of clinical trials Statistical analysis

The trials were classified into two characteristics as only safety and safety or efficacy and mental health cardiovascular disorder and oncology; these are the three mandatory facilities. The registration time is determined by examining the date which is received by the clinical trials.gov website with the start date of trials. The factors associated with the use of the blinding and randomization with the regression analysis were used for evaluation.²⁰

Data collection

Dispenser or investigators were reported to data as per the requirement of the clinical trials.gov registry. The record included all information relating to the study's condition, environment, eligibility criteria comma studied design location, and other information protocol. Study selection the eligible data is selected by the two authors (AB and CD) according to their results. The analysis was restricted to phase 4 clinical trials registered between 1 January 2004 to 13 December 2014 ($n = 18642$). According to the first date submitted to clinical trials.gov. A data set of 19359 of phase 4 clinical studies registered with clinical trials.²⁰



Figure 3: Phases of clinical trials with objective and timeline²¹

Conclusion:

To give patients the most effective and safest medicine possible, it is important to understand the concept of the clinical trial. However well designated and executed clinical trials can contribute significantly to society and communities

to improve the effectiveness and efficiency of health care in the whole world. This review gives an idea about clinical trials with different phases involved in clinical trials and their role in the development of vaccines and medicines.

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