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A CRITICAL REVIEW ON THE PHASES OF CLINICAL TRIALS

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ABSTRACT

Clinical trial as defined by the World Health Organization, is any research studies that allocate people prospectively to one or more interventions related to health in order to assess the impact on health outcomes. Global adoption has occurred of the use of clinical trial technique. During the drug discovery process, clinical research plays a crucial role in ensuring the safety and effectiveness of novel medications. Clinical trials are now required in the global scientific era to introduce improved and novel medications to the market. Clinical trials evaluate possible treatments on human participants, or subjects, in order to determine whether or not they should be licensed for broader usage in the general public. The study addresses clinical trials, namely those conducted in India. Phase 0 to phase IV are the five stages into which clinical studies can be separated. With reference to drug trials, the current review is to explore the different stages of clinical trials and their characterization.

KEYWORDS: Clinical trials, Phases, discovery, efficacy.

INTRODUCTION

Clinical trials is defined as the procedure used to assess a medicine or device's safety and effectiveness in human subjects.[1-2] According to the World Health Organization, clinical trial is characterized by any research study that aims to assign humans to one or more health-related interventions and assess the impact on health outcomes.[3] Clinical trials is typically been carried out when sufficient data about the quality of nonclinical safety are available and have been authorized by the governing body of the medicine or device.[4] Trials have historically been known to be dependent on the quality of the product as well as the different phases of the product's development. First, the clinical trials are carried out by the investigators using a small number of volunteers or patients.[4-6] The number of patients is expanded as soon as encouraging results on safety and efficacy are gathered. In addition, the clinical trials were conducted across multiple nations. Moreover, novel medications that fall into four phases are tested in clinical trials. For the purpose of approving medications, each stage is handled as a distinct clinical trial. Clinical trials can often be categorized into five stages: 0, I, II, III, and IV.[7-8] Phase 0 trials are for pharmacodynamic and pharmacokinetic investigations; Phase I is for screening and safety; Phase II is for testing protocol establishment; Phase III is for final testing; and Phase IV is for post-approval research.[4-6] Furthermore, clinical trial stages are the procedures where researchers do experiments under healthy supervision to obtain adequate evidence for methods that proved beneficial as medical treatments.[9-10]

Pharmaceutical research goes through several stages starting with drug design and discovery.

TYPES OF CLINICAL RESEARCH DESIGN

Clinical Studies are categorized as follows-

Observational study: - In this study, participants are given new medication and researchers watch the people and track their results.[17-19] Based on the time, observational study designs are further categorized into analytical study and descriptive study. And main goal of the various study designs include Descriptive study is to generate hypothesis, Analytical study is to test hypothesis and Experimental study is to prove hypothesis. Example-Epidemiological studies like cohort

studies, case control studies, case series and case studies.[29, 30, 34]

A. Analytical Study

1. Cohort Study

The latin word "cohor" and roman literature refer to a cohort as a group of warriors or troops marching together. A cohort study is also known as a longitudinal study, an incidence study, a follow-up study (prospective research), or a forward-looking study.[29-30] A cohort study is a type of research where the outcome (illness) is studied after the exposure (risk factor) is determined. This indicates that there are two groups in the study: the first group is exposed to a risk factor, and the second group is not exposed. Then, to ascertain the disease condition, proceed with each group. Compare the risk of disease in the exposed and unexposed groups.[34-36]

2. Case-control study

Case-control studies are retrospective studies in which, in contrast to cohort studies or mirror images of cohort studies, the study begins with the outcome and uses case records to identify the risk factor. For comparison, this study comprises a case group of individuals with diseases and a control group of individuals without disorders.[27-29] The research starts with the end result and works backward to determine the exposure (risk factor) using case histories extracted from medical records. Interviews are also conducted as part of this process. The terms "historical study," "backward looking," "retrospective/retrolective study," "longitudinal study," and "case-reference study" are other names for case-control studies.[31-33]

3. Cross-sectional study

Studies that assess an association between an exposure and an outcome simultaneously are called cross-sectional studies. It can be categorized as analytical or descriptive, depending on the investigator's goal in answering the question.[29-30] Cross-sectional studies offer a chance to quantify the prevalence of the exposure or the result because they are designed to collect data at the same moment in time. To estimate the worldwide need for pediatric palliative care, for instance, a cross-sectional study design was used, utilizing a representative sample of nations from every continent and income category as defined by the World Bank. Because data is gathered at the same time for each cross-sectional study, temporal connection cannot be demonstrated.[21-23]

B. Descriptive study

1. Case Report

A case report is typically a summary of events and specific patient experiences about drug exposure and outcome in a single patient. Case studies are helpful in establishing theories regarding the cause of an occurrence. Therefore, it sends a concerning message to other medical professionals about the situation. However, a case report needs to include information about an uncommon illness, an aberrant medication reaction, and adverse drug reactions. The WHO's Uppsala Monitoring Center has gathered data on these uncommon occurrences.[24]

2. Case Series

A case series is an assortment of case reports, or several patients with identical results, who had comparable single exposures or comparable treatment outcomes; the series may be based on exposure or outcome. The greater the number of case reports that are available, indicating that the event occurred in the patient, the more robust the confirmation will be. The primary application of case series is to determine the ADRS. Another name for it is "open trail.[25]

3. Survey

Information gathered from a group is referred to as a survey. Information types include knowledge, behaviors, attitudes, opinions, and demographics. Patients, students, researchers, and colleagues may make up the population. This survey is conducted in person between the surveyor and the responder; it can also be completed over the phone, via mail, fax, or the internet without requiring any physical contact. Questionnaires need to be carefully developed since they are the primary mean of gathering information.[26]

Experimental Study (Interventional Study)

In this study, the researchers track changes in the participant's health. The study participants are administered a certain medication and the outcomes are compared between the treated group and the control group. This kind of study is a comparative study. Based on the randomization, experimental study designs are further categorized as follows. Example-All experimental studies and clinical trials are interventional studies. Interventional trial determines whether experimental treatment or new ways of using know therapies are safe and effective under controlled environment.[22]

A. Randomized Study

1. Randomized Controlled Study

The highly dependable design of a randomized control study provides high-level data for the practice of medicine. The control group serves as a comparison group for the interventional group, as implied by its name. A placebo or the old medication is given to the control group in this study, whereas the interventional group receives the interventional drug. Trials may be open, blind or double-blind.

Open trial -An open RCT is a randomized trial in which everybody involved in the trial knows which intervention is given to each participant. Most trials comparing different surgical interventions or comparing surgery and medication are open RCTs. This is also called Zero blind trial.

Blind RCT/Blinding/Masking- An RCT may be blinded (Masked) by procedures that prevent study participants, care givers or outcome assessors from knowing which intervention was received. Unlike allocation concealment, blinding is sometimes inappropriate or impossible to perform in an RCT, for example if an RCT involves a treatment in which active participation of the patient is necessary (e.g. physical therapy), participants can't be blinded to the interventions.
Blinding is classified as-
(i) Single-blind
(ii) Double-blind
(iii) Triple-blind

(i) Single-blind- It is a randomized trial in which one group of individuals involved in the trial does not know the identity of the intervention that is given to each participant. Usually it is the participant or the investigator assessing the outcomes who do not know the identity of the intervention. In this trial only investigator knows about subjects receiving trial and control but subject himself doesn't know to which group he belongs. Single blind designs are used frequently to evaluate educational or surgical interventions.

(ii) Double-blind-A double-blind RCT is a randomized trial in which two groups of individuals involved in the trial do not know the identity of the intervention that is given to each participant. Usually these two groups include the participants and the investigators in charge of assessing the outcomes of the intervention. In this trial investigator and subject (patient) both of them are unaware of subject's distribution to trial group and control group. Guide or monitoring committee knows about distribution. The double-blind RCTs, in which the control group receives a placebo are also called double blind, randomized, placebo control trials. When the RCT is designed to compare a new intervention with a standard treatment the RCTs are called active controlled. Achieving double blinding in active controlled trials is often difficult and frequently requires the use of what is called as double dummy. In a double-blind, double-dummy RCT, each group of participants receive one of active interventions and a placebo (in this case called a dummy) that looks and tastes the same as the other intervention. The double-dummy technique is particularly useful when the investigators want to compare interventions that are administered by different routes or that require different techniques of administration.

(iii) Triple-blind-In a triple blind RCT, three groups of individuals involved in the trial do not know the identity of the intervention that is given to each participant. These groups could include the participants the investigators giving the intervention and those evaluating the outcomes or the participant the investigator evaluating the outcomes and the data analyst. All the three i.e. subject, investigator and monitoring committee do not know about subject distribution to both groups. This work is handled at the national level and details of each subjects assigned are kept confidential. This is made open at the time of results, analysis and drawing conclusions.[4]

2. Randomized Uncontrolled Study
There is only one randomization group present in this study; there is no control group. When this study is contrasted with the randomized control study, it is much weaker.

B. Non - randomized Study
1. Non - randomized Controlled Study
The research is identical to the randomized control study; however, randomization is absent. The experimental group receives the interventional drug, which is ultimately measured, whereas the control group receives a placebo or an older medication. Data from hospital records that have been published in the literature may occasionally be utilized as a control group in non-randomized, out-of-date research known as historical control studies.

2. Non - randomized Uncontrolled Study
This study is identical to a randomized uncontrolled study; however it lacks a control group and randomization.

TYPES OF CLINICAL TRIAL[5]
Treatment trials - Test novel drug combinations, innovative surgical or radiation therapy techniques and experimental treatments.

Prevention trials - Look out more effective strategies to stop diseases from spreading to persons who have never had them or to stop diseases from coming back. Medications, vitamins, immunizations, minerals and lifestyle modifications are a few examples of these methods.

Diagnostic trials - Conducted with the goal of developing more accurate diagnostic tools or techniques for a certain illness.

Screening trials - Experiment with the best ways to diagnose particular diseases or health conditions.

Quality of Life - Supportive care trials often known as trials look into ways to make people with chronic illness more comfortable and enhance their quality of life.

PHASE OF CLINICAL TRIAL
Clinical trials are conducted in a series of steps called phases and each phase is designed to answer a separate research question. All clinical trials of new drug or treatment go through a series of phases to test whether the drug or treatment is safe and whether they work. In case of pharmaceutical study the phases starts with drug

design and drug discovery go on to animal testing then testing it in only few human subjects and expand to test in many study participants if the trial seems safe and useful. Duration & Cost-The entire process of a drug from pre-clinical phase to phase IV may take approximately 12-18 years often costing over 1 billion dollar.[4]

Phases

1. Pre-clinical
2. Phase-0
3. Phase-I
4. Phase-II
5. Phase-III
6. Phase-IV

Preclinical- Pharmaceutical companies conduct preclinical investigations which include in-vitro (animal) and in-vivo (cell culture) experiments utilizing a wide variety of doses to acquire primary efficacy, toxicity and pharmacokinetic information prior to initiating clinical trials of a medicine. Pharmaceutical firms use these tests to determine whether or not a medicine has scientific worth. Furthermore, the choice of whether it needs to be developed further as an experimental new medicine.[11-12]

Phase 0 (Human-micro-dosing study)- Phase 0 is thought of as the trials fresh debut for investigation. The US Food and Drug Administration's (FDA) 2006 guidelines on exploratory investigational new drug (IND) research were followed initially when conducting the human trials. Micro dose studies also known as phase 0 trials are created with the goal of developing a prospective medication with the precise qualities that were anticipated from preclinical research.[11-13]

In addition, Phase 0 differs from other phases in that it gathers preliminary data on the drug's pharmacokinetic and pharmacodynamic properties by giving a single sub therapeutic dose of the study medicine to a limited group of volunteers or patients (10–15). Surprisingly, Phase 0 trials don't offer any precise information regarding the test drug's safety or effectiveness.

Moreover, Phase 0 investigations are carried out by pharmaceutical development corporations to select drug candidates and determine the pharmacokinetic parameters on humans for future development.[12]

Phase I studies: (Human pharmacology) - This stage determines if a medication or device is safe. Testing may take several months to complete and this is the first phase. About 20 to 100 healthy individuals often participate in this phase. The goal of the phase I trial is to ascertain the drug's or device's effects on humans, including their absorption, metabolism and excretion (ADME). The dose-related adverse effects are also being looked into in this phase. Seventy percent of experimental medications survive this stage of testing. These studies are usually conducted in tightly controlled clinics called central pharmacological units (CPUs) where participants receive 24-hour medical attention and over sight.

Phase II studies: (Therapeutic Exploratory Trial) - Phase II trials are conducted on bigger groups (20–300) once phase I trials have verified the research drug's initial safety. In this stage a medication or device's effectiveness is evaluated. The testing is now in its second phase. Completing the process can take many months to two years and it involves hundreds of patients. The majority of phase II trials are randomized clinical trials in which an experimental medicine is administered to one group of patients while a second "control" group is given a placebo or standard treatment. The experimental medicine is often administered in a "blinded" manner, meaning that neither the patients nor the researchers are aware of who has got it. This makes it possible for researchers to give comparative data regarding the relative safety and efficacy of the novel medication to the FDA and the pharmaceutical business. Phase II trials are conducted on bigger groups (20–300) once phase I trials have verified the research drug's initial safety. Phase I and Phase II trials are successfully completed by about one-third of investigational medications. Phase-II studies are sometimes divided into phase-II A and phase-II B. Phase-II A is specifically designed to assess dosing requirements and Phase-II B is specifically designed to study efficacy.

Phase III studies:(Therapeutic conformity trial /Pre-Marketing Surveillance)- Phase 3 studies are tested over a longer period than phase 1 or phase 2 studies and include many more participants with the targeted disease often between 300 to 3000. This stage evaluates trials that are blind and randomized among hundreds to thousands of patients. Large-scale testing like this can go on for several years. It gives the researchers and regulatory bodies a more comprehensive grasp of the advantages, potential side effects and efficacy of the medication or technology. Of all medications enrolled in Phase III trials between 70% and 90% successfully finish this stage of testing. Most drugs undergoing phase III clinical trials can be marketed under FDA through a New Drug Application (NDA) containing all manufacturing, pre-clinical and clinical data. If any adverse effect reported anywhere, the drug needs to be recalled immediately from the market.

Phase IV studies: (Post-Marketing Surveillance)- Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug is safety, efficacy and dose definition. Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Commonly conducted studies include additional drug-drug

interaction, dose-response or safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies.

Table No 1: Depicting the Phases of a Clinical Trial.

Phase 0	Phase 1	Phase 2	Phase 3	Phase 4
• Primary goal • Pharmacokinetic and Pharmacodynamic • Dose Very small sub therapeutic • Clinical researcher • Number of participant's 10-15 people.	• Safety • Evaluation of safety on inter action of drug with human body • Duration: Several Months • 20-100 healthy patients.	• Safety and Dosing • To further evaluate safety • Monitor the side effects • Check best Dose for effectiveness in smaller population • Duration: Several Months to 2 years. • 100-300 patients.	• Safety and Efficacy • Phase to confirm effectiveness • Monitoring Safety in larger population • Duration: 1 to 4 years. • 300-3000 patients	• Post Marketing • Safety and Efficacy • Gathering information on drug's effect in larger • Population outside controlled environments To detect further adverse reactions of drugs

DISCUSSION

Clinical trials evaluate the effectiveness and safety of medications or medical devices by monitoring their effect on large group of people. A Clinical trial is a research study in human volunteers to answer specific health questions. Clinical trials are experiments done in clinical research. Clinical trials are also interventional type of research which is designed to answer specific questions about biomedical or behavioral interventions, including new treatments and known interventions which warrant further study and comparison. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people and ways to improve health. Clinical trials aim to ensure scientific validity and reproducibility of the results. Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed a suitable dosage range and administration schedule for initial exploratory therapeutic trials. Later confirmatory studies are generally larger and include a more diverse patient population. Dose response information should be obtained at all stages of development form early tolerance studies to studies of short-term pharmacodynamic effect to large efficacy studies. Throughout development, new data may suggest the need for additional studies that are typically part of an earlier phase. Clinical trial is conducted in a series of steps, called phases. All new drugs must undergo clinical trials which are carried out in human volunteers to verify the drug's beneficial qualities in accordance with ICH and GCP principles. The investigational novel medicine goes through phases I, II, III, and IV of clinical development after preclinical development. The pharmacokinetic, pharmacodynamic, adverse and post-marketing surveillance as well as potential positive and dangerous side effects are all thoroughly explained in these phases.

CONCLUSION

New drug clinical trials are typically divided into four stages with a distinct clinical trial for each stage of the medication approval process. Drug development often moves through several stages over a number of years. While a lot of research has been done on the specifications and agreements of the various clinical trial phases more work is needed to fully study the fundamental requirements and guidelines that should be followed for the subsequent completion of clinical trials. Clinical studies can provide answers regarding the use or not of a therapeutic agent that can assist millions of patients globally. Clinical trials are required for drugs and devices to establish their safety and efficacy in humans prior to their usage.

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