IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, March 2024

Design and Analysis of Clinical Trials Concept and Methodology

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Abstract: *Clinical research is an alternative terminology used to describe medical research. Clinical research involves people, and it is generally carried out to evaluate the efficacy of a therapeutic drug, a medical/surgical procedure, or a device as a part of treatment and patient management. However, clinical trials are those studies that assess the potential of a therapeutic drug/device in the management, control, and prevention of disease. The recent focus of federal funding on comparative effectiveness research underscores the importance of clinical trials in the practice of evidence-based medicine and health care reform. The impact of clinical trials not only extends to the individual patient by establishing a broader selection of effective therapies, but also to society as a whole by enhancing the value of health care. According to WHO, the clinical trial is any research study that prospectively assigns human to one or more health-related interventions to evaluate the efR. H. American Recovery and Reinvestment Act of 2009. 1st Ed 2009.fects on health outcomes. The clinical trials can be divided in various phase which five phases 0,I,I,III and IV trials.*

Keywords: Clinical trials, phase I trial, phase II trial, phase III trial, phase IV trial,, clinical research.

I. INTRODUCTION

By participating in clinical research, you can help scientists develop new medications and other strategies to treat and prevent disease. Many effective treatments that are used today, such as chemotherapy, cholesterol-lowering drugs, vaccines, and cognitive-behavioral therapy, would not exist without research participants. Whether you're healthy or have a medical condition, people of all ages and backgrounds can participate in clinical trials. Clinical research is the study of health and illness in people. There are two main types of clinical research: observational studies and clinical trials.

1: Observational studies
2: Clinical trials

Observational studies:
monitor people in normal settings. Researchers gather information from people and compare changes over time. For example, researchers may ask a group of older adults about their exercise habits and provide monthly memory tests for a year to learn how physical activity is associated with cognitive health. Observational studies do not test a medical intervention, such as a drug or device, but may help identify new treatments or prevention strategies to test in clinical trials.

Clinical trials:
Clinical trials are research studies that test a medical, surgical, or behavioral intervention in people. These trials are the primary way that researchers determine if a new form of treatment or prevention, such as a new drug, diet, or medical device (for example, a pacemaker), is safe and effective in people. Often, a clinical trial is designed to learn if a new treatment is more effective or has less harmful side effects than existing treatments.

Include Other Aims of Clinical Research:
1 Improving quality of life Testing ways to diagnose a disease early, sometimes before there are symptoms

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2 Finding approaches to prevent a health problem, including in people who are healthy but at increased risk of developing for people living with a life-threatening disease or chronic health problem
3 Studying the role of caregivers or support groups
A clinical trial is a systematic process that is intended to find out the safety and efficacy of a drug/device in treating/preventing/diagnosing a disease or a medical condition Clinical trial includes various phases that include phase 0 (micro-dosing studies), phase 1, phase 2, phase 3, and phase 4 [1,2] Phase 0 and phase 2 are called exploratory trial phases, phase 1 is termed the non-therapeutic phase, phase 3 is known as the therapeutic confirmatory phase, and phase 4 is called the post-approval or the post-marketing surveillance phase. Phase 0, also called the micro-dosing phase, was previously done in animals but now it is carried out in human volunteers to understand the dose tolerability (pharmacokinetics) before being administered as a part of the phase 1 trial among healthy individuals.
Pre-clinical studies :
Pre-clinical studies involve in vitro (i.e., test tube or laboratory] studies and trials on animal populations.
Wideranging dosage of the study drug given to the animal subject or to an in vitro substrate in order to obtain preleiminaryefficancy , toxicity and pharmacokinetic information and to toxicity and pharmacokinetic information and to assist pharmacetucal companies in deciding whether it is worthwhile to go ahead with further testing .

II. VARIOUS PHASES OF CLINICAL TRIALS

Usually, clinical trials can be divided into five phases, I e 0, I, II,III,IV, and v trials based upon specific conditions and requirements

Phase 0:

Phase 0 is a recent designation for exploratory, first-inhuman trials conducted in accordance with the U.S. Food and drug administrations FDA 2006 guidance on exploratory investigational new drug IND studies phase 0 trials are designed to speed up the development of promising drug or imaging by establishing very early early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies.

Phase I:

Phase I trials are the first stage of testing in human subjects. Will be selected this phase includes trials designed to assess the safety[Phamacovigilance], tolerability, pharmacokinetic, and pharmacodynamics of a drugthese are often conducted in an inpatient clinic where the subject can be observed by full-time staff.

There are different kinds of Phase I trials:

1. SAD

Single Ascending Dose studies are those in which small group of subject are a given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects , and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated
And a new group of subjects is then given a higher dose. This is continued until precalculated pharmacokinetics safety levels are reached or intolerable side effects start showing up at which point .

2. MAD

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple dose of the drug.

Phase II

Once the initial safety of the study drug has been confirmed in phase I trials are performed on larger groups [20-300] and are designed to assess how well the drug works ,as well as to continue phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fais .

Phase III

Phase III studies are randomized controlled multicenter tirals on large patient groups [300-3,000 or more depending upon the disease /medical condition studied] and are aimed at being the definitive, Assessment of how effective the drug is, in comparison with current gold stadndard treatment. Because of their size and comparatively long duration, phase III trials are the most expensive time –cousuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

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Phase IV

Phase IV trial is also known as Post Marketing surveillance trial. Phase IV trial involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it recives permission to be sold. Phase IV studies may be requied by egulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug)or other reasons example the drug may not have been tested for interactios with other drugs, oroncetain population groups such as pregnant women, who are unlikely to subject themselves to trials.

Phase V

Phase V, a new term used in the literature, is also termed as translational research to refer the effectiveness and community based research studies. It is used to find the interrogation of a new clinical treatment into a large number of public health practices.

III. FACTORS AFFECT WITH CLINICAL TRIALS

Background

Clinical trials for pharmaceuticals and medical devices offer many opportunities for failure. Failures can arise from a lack of efficacy, issues with safety, or a lack of funding to complete a trial, as well as other factors such as failing to maintain good manufacturing protocols, failing to follow FDA guidance, or problems with patient recruitment, enrollment, and retention. Generating accurate and sufficient results to determine whether or not there is merit in continuing is important at each stage in the clinical trial process.

Failing to demonstrate efficacy or safety

The primary source of trial failure has been and remains an inability to demonstrate efficacy. Hwang et al. [58] assessed 640 phase 3 trials with novel therapeutics and found that 54% failed in clinical development, with 57% of those failing due to inadequate efficacy. There are many reasons that potentially efficacious drugs can still fail to demonstrate efficacy, including a flawed study design, an inappropriate statistical endpoint, or simply having an underpowered clinical trial (i.e., sample size too small to reject the null hypothesis), which may result from patient dropouts and insufficient enrollment.

Financial impact

Hewing. noted that 22% of the failed phase 3 studies they examined failed due to lack of funding. The costs required to complete the entire development process from discovery to bringing a drug to market vary, and so do estimates of these costs; however, they have been reported in excess of $2.5 billion.

Eligibility criteria

Ideally, inclusion/exclusion criteria should result in a population that matches statistically the intended general patient population [48,124]; however, study designers must account for additional concerns, including whether or not particular segments of a target population may have too many comorbities, leading to additional higher risk of withdrawal and adverse events. For example, Hill et al.

Additional costs associated with recruitment

Beyond remuneration, the additional costs associated with patient recruitment can be difficult to estimate and highly variable, even within the same investigative area [21]. For example, Okuyemi

Respecting the patient's concerns

Patient recruitment and retention is affected negatively when patients are concerned about being assigned to a control group rather than receiving active study drug. Part of this effect may be due to patients having poor knowledge about placebos

Poor recruitment, dropouts, and underpowered trials

A repeated problematic pattern in the literature is that study centers report fewer eligible patients than anticipated Study centers with a track record of successful performance are historically more likely to meet enrollment targets

Employing quantitative measures

Formulating a list of factors to consider when designing and executing a clinical trial can provide a foundation for better outcomes. However, not all factors are equally important. A well-structured mathematical framework (e.g., a Valuated State Space

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Considering the patient's financial burden

Given the tremendous problem of clinical trials that fail to complete due to poor recruitment, enrollment, and retention, it's of primary importance in designing and executing clinical trials to consider the burden that each patient undergoes, with the belief that retention is correlated negatively with patient burden. All burdens to the patient should be given attention, but financial impacts deserve special consideration.

Patient time investment

While some trial participants do need to relocate during a study, many are not willing to do so and most participate in local trials. Patient recruitment and retention depends in part on the willingness of the participant to travel to and from the local study center.

Discussion

Each of the facets of protocol design, execution, and successive trial planning offers opportunities for trading off different concerns, as well as simply making inappropriate judgments leading to poor outcomes.

IV. ETHICAL CONSIDERATION

An Independent body (a review board or a committee, institutional, regional, national or supranational, Constituted of medical professionals and non-medical members, whose responsibility it is to ensure the informed consent protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that by among other things, reviewing and approving /providing favorable opinion on, the trial protocol, the suitability of the investigators facilities, and the method and material to be used in obtaining and documenting of the trials subjects.

V. ETHICAL CONDUCT

Clinical trials are closely supervised by appropriate regulatory authorites. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial .the local ethics committee has discretion on how it will supervise nonintervention studies (observational studies or those using alredycollcetd data.) in the u.s this body is called the instituoinalreiew board irb . most ribs are located at the local investigators hospital or instituation but some sponsors aloow the use of a central (independent/for profit) IRB for investigators who work at smaller institutions.

VI. PLANS OF CLINICAL TRIALS

Trials may be open, blind or double-blind.

1. Open trial

In an open trial, the researcher knows the full details of the treatment and so does the patient. These trials are open to challenge for bias, and they do nothing to reduce the placebo effect. However sometimes they are unavoidable,as placebo treatment are not always possible see blinding. Usually this kind kind of study design is used in bioequivalence studies.

1. Blind trials

A. Single-blind trial

In a single-blind trial, the researcher knows the details of the treatment but the patient does not. Because the patien does not know which treatment is being administered (the new treatment or another treatment) there might be no placebo effect. In practice,since the researcher knows, it is possible for him to treat the patient differently or to subconsciously him to the patien important treatment related details thus influencing the outcome of the study.

B. Double-blind trial

In a double-blind trial, one researcher allocates a series of numbers to new treatment or old treatment. The second researcher is told the numbers, but not what they have been allocated to . since the second researcher does not know, he cannot possibly tell the patient, pressure to give him the new treatment . in this system ther is also often a more realistic disribuation of sexes and ages of patients. Therefore double –blind trials are preferred as they tend to give the most accurate results .

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C. Triple-blind trial

Some randomized controlled trials are considered tripleblinded, although the meaning of this may vary according to the exact study design. The most common meaning is that the subject, researcher and person administering the treatment (often a pharmacist) are bylined to what is being given.

VII. TYPES OF CINICAL TRIAL

1. Treatment trials

Test experimental treatments, new combinations of drugs,or new approaches to surgery or radiation therapy.

2. Prevention rials

Look for better ways to prevent disease in people who have never had the disease or to prevent a diseadr from returning. These approaches may include medicines vitamins ,vaccines , minerals, or lifestyle changes.

3. Diagnostic trials

Conducted to find better tests or procedures for diagnosing a particular disease or condition .

4. Screening trials

Test the best way to detect certain diseases or health conditions.

5. Quality of Life

Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness

VIII. COMPLIANCE WITH PROTOCOL

The investigator/institution should conduct the trial in compliance with the protocol freed to by the sponsor or and if required, by the regulatory authority ies and which were given approval /favourable opinion by the IRB/IEC.the investigator /instituation and the sponsor should sign the protocol ,or an alternative contract ,to confirm arreement.

The investigator should not implement in deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorableopinionfreom the IRB IES an anmendment except where necessary to elimainate an immediate hazards (s) involves only logistical or administrative aspect of the trial (e.g.change in monitor (S),change of telephone no. (s).

IX. ROLE OF PHARMACISTS IN CLINICAL TRIALS

Pharmacists have an active role to play in research and clinical trials first of all, we provide the necessary facilties required for proper storage of the investigational medicinal product (IMPS) either in the fridge or at controlled room temperature. Regular temperature monitoring is ensured and recorded.it is also the pharmacist dudty to ensure there is constant supply of IMPS at all times and that they are dispensed to patients accordingly. Patients are counselled on the correct use of the IMPS in addition to any written information consent form or the patient information leaflet. IMPS returns from patients are counted and documented to dertminecompliance to the treatment. For inject able IMPS, PHARMACISTS will also ensure that they are prepared in accordance to the specifications, stipulated in the trial, and that they are administered appropriately.

Overview of Drug Development

The general road to drug development and approval has been defined and regulated by the US Food and Drug Administration (FDA) for decades. Safety has historically been its primary focus, followed by efficacy. If a drug appears promising in pre-clinical studies, a drug sponsor or sponsor-investigator can submit an investigational new drug (IND) application. This detailed proposal contains investigator qualifications and all pre-clinical drug information and data, and a request for exemption from the federal statutes that prohibit interstate transport of unapproved drugs. After approval, the drug is studied (phase I–III trials, described below) and if demonstrated safe and efficacious in the intended population, the drug sponsor can then submit a New Drug Application (NDA) to the FDA. After an extensive review by the FDA that often involves a recommendation by an external committee, the FDA determines whether the therapeutic can be granted an indication and marketed.

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Clinical Trial Oversight

Historic abuses and modern day tragedies highlight the importance of Institutional Review Boards (IRBs) and Data and Safety Monitoring Boards (DSMBs) in ensuring that human research conforms to local and national standards of safety and ethics. In order to ensure compliance with the strict and detailed guidelines of the CFR, members of IRBs (one of whom must be a non-scientist, and one of whom must be independent of the board's home institution) are authorized under the "Common Rule" to approve, require modification to, or reject a research activity. Based on the perceived risk of the study, IRBs have a number of levels of review from exempt for "minimal risk" studies (defined by the "Common Rule" as risks that are no greater than those encountered in daily life or routine clinical examinations or tests) to the more lengthy and involved full board reviews for higher-risk studies. General criteria for IRB approval include: 1) risks to subjects are minimized, and are reasonable in relation to benefits; 2) selection of subjects is equitable; 3) informed consent is sought; 4) sufficient provisions for data monitoring exist to maintain subjects' safety; 5) adequate mechanisms are in place to ensure subject confidentiality; and 6) rights and welfare of vulnerable populations are protected. The complexity and expense of monitoring human research has prompted the establishment of Contract Research Organizations (CROs) to oversee clinical trials. They are commonly commercial or academic organizations hired by the study sponsor "to perform one or more of a sponsor's trial-related duties and functions," such as organizing and managing a DSMB, or managing and auditing trial data to maintain data quality.

XI. NEW DRUG APPLICATION (NDA)/MARKETING AUTHORIZATION APPLICATION (MAA)

NDAS (is the U.S.) and MAAS (in the U.K) are examples of applications to market a new drug. Such application document safety and efficacy of the investigational drug and contain all the information collected during the drug development process . at the conclusion of successful preclinical and clinical testing. This series of documents is submitted to the FDA in the U.S.

REVIEW

A clinical trial involves the study of the effect of an investigational drug/any other intervention in a defined population/participant. The clinical research includes a treatment group and a placebo wherein each group is evaluated for the efficacy of the intervention (improved/not improved). Clinical trials are broadly classified into controlled and uncontrolled trials. The uncontrolled trials are potentially biased, and the results of such research are not considered as equally as the controlled studies. Randomized controlled trials (RCTs) are considered the most effective clinical trials wherein the bias is minimized, and the results are considered reliable.

ROLE OF PLACEBO

Placebo is a Latin term which means " I may please you ''. The placebo effect is an effect attributable to a medicament as a procedure, and is not due to any specific pharmacodynamics property of the substance for the condition being treated .placebo effect may be defined as 'how the patients perception of treatment influences his/ her response .'' placebos are used , during the clinical trial , to eliminate the possibility that the benefit of the drug is solely due to chance , and as therapeutic agents that work psychologically.

THE PRINCIPALS OF ICH GCP :

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.

Clinical trial should be conducted in accordance with the ethical principals that have their origin in the declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requriment.

The rights, safety, and well being of the trial subjects are the most important considerations and should prevail over intersts of science and society

The available nonclinical and clinical information on an investigational product an investigational product should be adequate to support the proposed clinical trial

Clinical trials should be scientifically sound, and described in clear, detailed in a clear ,detailed protocol.

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A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) independent ethics committee (IEC) approval/favorable opinion.

The confidentiality of records that could identify subjects should be protected, repecting the privacy and confidentiality rules in accordance with the applicable regulatory requriment

All clinical trial information should be recorded, handled and stored in a way that allow its accurate reporting , interpretation and verification .

CLINICAL TRIAL PHASE :

Clinical trial phase	Type of study	Nature of study
Phase 0	Exploratory	Examine to flow (1/100) concentration (micro-design) of the drug for less time. Study the pharmacokinetic and determine the dose of phase I studies previously done in animal but how is carried out in humans.
Phase I IA , IB PHASE	Notherapeutic trials	Around <50 healthy subjects are recruited la – SAD and MTD . duration one weak to several months depending on the trial and includes 6-8groups of 3-6participants. IB phase MAD and the dose in gradually narrowed down. Three groups of 8 individual each
Phase II	EXPLORATORY TRIAL	Recruiting around 5-100patients of either sex.phase IIA decides the drug dosage includes 20-30patients. And takew up to weeks /month. Phase IIB – studies dose response relationship drug-drug interaction and comprision with a placebo.
Phase III	15Therapeutic confirmatory trial	More than 3000 patient (up to 3000)of either sex are recruipated in this study are multicentric trials.
Phase IV	Post approval trial	After approval /post lincensure and post marketing studies. / survalliance studies. Following up on the patients for an exceptionally long time for potential adverse reaction and drug- drug interaction.

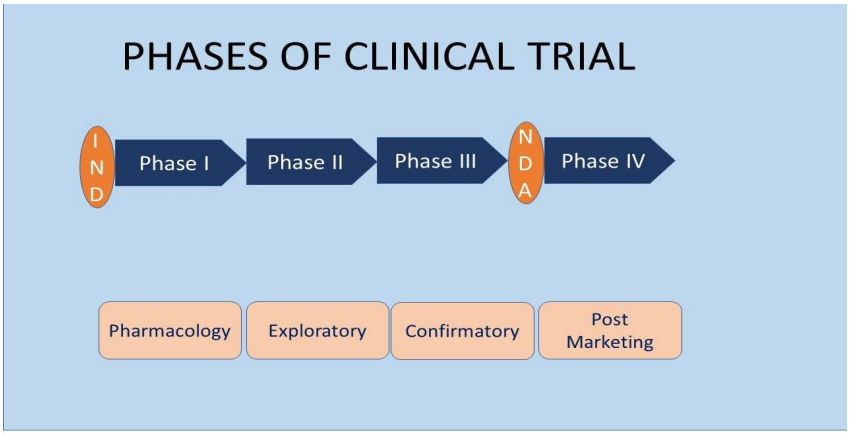

Fig: Phases of Clinical Trial

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XII. CONCLUSION

A clinical trial for any new drug follows under the guidelines of ICH and GCP, clinical trial are conducted in human volunteers for confirmation of useful properties of new drug. After preclinical development, investigational new drug passes through clinical phases I, II, III and IV.

These stages offer a thorough explanation of the pharmacokinetic, pharmacodynamic, and adverse effects, which can be either useful or harmful a marketing campaign.

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