INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Effectiveness Of Clinical Method Evaluation

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ARTICLE INFO

Received: 23 Dec 2023
Accepted: 27 Dec 2023
Published: 16 Jan 2024

Keywords:
Types of clinical trial, Phases of clinical trial ,Clinical trail in India, Efficacy and effectiveness, Randomization, Blinding.

DOI:
10.5281/zenodo.10517844

ABSTRACT

Clinical trials test potential treatments in human volunteers (subjects) to see whether they should be approved for wider use in the general population. India stood as a global hub for clinical trials in past years due to various factors. In this paper we discuss about clinical trials and clinical trials in India. Clinical trials are classified into different types based on their objectives, such as treatment trials, prevention trials, diagnostic trials, and others. Each type aims to address specific research questions related to the intervention's effectiveness. Clinical trials typically progress through several phases (Phase I to Phase IV) to evaluate different aspects like safety, dosage, efficacy, and potential side effects of the intervention. Each phase serves a specific purpose in the research process. Efficiency in clinical trials refers to conducting trials in a cost-effective and timely manner. Effectiveness assesses how well an intervention works in real-world conditions compared to its efficacy in controlled settings. Blinding involves concealing certain information from participants, researchers, or both, to minimize bias. Randomization ensures that participants are allocated randomly to different treatment groups, enhancing the validity and reliability of trial results.

INTRODUCTION

The essential elements of a clinical review are assessments of the necessity and result of care; if the clinician determines that treatment is no longer necessary, additional evaluation is unnecessary; if treatment is required, effectiveness and unintended consequences must be taken into account; due to the significance of the patient-family relationship, emphasis may also be placed on satisfaction with care; other questions are typically ancillary; for instance, if the outcome has not been satisfactory, an explanation for the low compliance may be sought. Clinical reviews are very individualised. The clinician typically performs it, and they might find it challenging to be impartial. Incomplete data is frequently the basis for it, if only due to the urgency of making decisions. Complete and honest It is rare to have access to treatment effect

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

measurements. Additionally, until these effects are very specific or there is strong evidence of a dose-effect or time-effect relationship, it is difficult to determine if they are the result of the treatment. The standards by which efficacy is evaluated are rarely well-defined and may vary amongst physicians. When different physicians evaluate the same patients' care, disagreement is common[1].or when patient evaluations are compared with those made by doctors[2].Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies[3]. Clinical trials are experiments and observations conducted on human subjects to develop new treatments, interventions, or tests for various diseases or medical conditions. They help determine the effectiveness, safety, efficacy, and superiority of new interventions over existing treatments, preventing, detecting, treating, or managing various diseases. Drug discovery research focuses on developing new, safer, and more effective drugs. It involves rigorous trials in animals and humans before being introduced to the market. Clinical trials are crucial for determining the effectiveness and safety of new medicines developed in the lab or using animal models, as well as the effectiveness of diagnostic tests in clinical settings[4-6].

History:

The term "clinical trial simulation" may have been initially used to describe the game "Instant Experience."[7] A teaching course for doctors and scientists focused on practical difficulties and error sources in trial design and performance. Participants were divided into groups to design a clinical trial to detect therapeutic differences between two drugs, with gender as the sole prognostic factor. The organizers created a computer program to generate simulated patients for future games.[8-10], Simulation programs are increasingly focusing on complex statistical aspects of clinical trial design, such as prognostic factors influencing patient response to treatment. Traditional methods are inadequate for analysing these situations, leading to the development of a new sequential treatment assignment method tested using simulation[11]. The study utilized clinical trial simulation to investigate various aspects of trials, such as sample size and the impact of dropouts.[12], The text discusses the issues associated with the premature termination of a clinical trial[13]. Traditional statistical theory was deemed invalid due to complex designs, and simulation provided a means to generate complex data sets and test new analysis methods[14].

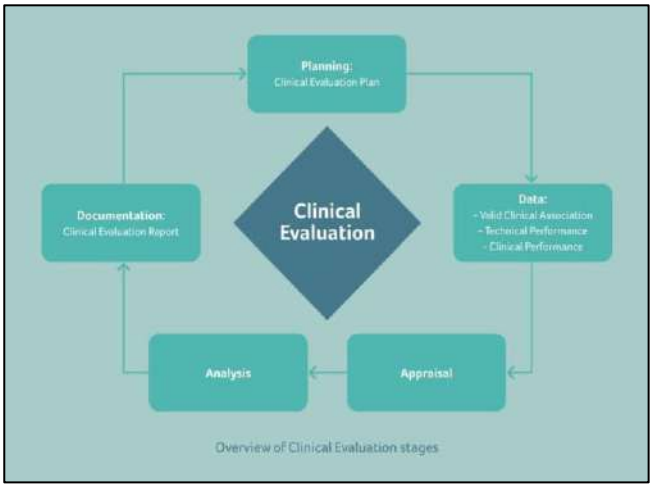

Fig 1: Clinical Evaluation

Hippocrates (460–370 BC):

Hippocrates, considered the father of modern medicine, emphasized systematic observation, clinical examination, and documentation of symptoms in his works, laying the foundation for clinical evaluation methods and detailed observations of diseases.

René Laennec (1781–1826):

Laennec's 1816 invention of the stethoscope, particularly his publication "De l'Auscultation Médiate," revolutionized clinical evaluation by providing a more precise method for diagnosing heart and lung diseases, significantly enhancing diagnosis.

William Osler (1849–1919): Osler, a prominent modern medicine figure, emphasized the importance of detailed patient history, clinical

examination, careful observation, and clinical reasoning in diagnosis, as emphasized in his teachings and writings.

Evidence-Based Medicine (EBM) Movement:

The late 20th century saw a paradigm shift in clinical practice with the publication of "Evidence-Based Medicine: How to Practice and Teach EBM," which highlighted the significance of integrating research evidence into clinical decision-making.

Advancements in Diagnostic Imaging:

Wilhelm Roentgen's 1895 discovery of X-rays and radiology advancements have significantly influenced clinical evaluation methods, with technologies like CT scans, MRI, and ultrasound revolutionizing diagnostic capabilities.

Clinical Trials and Validation Studies:

The development of rigorous methodologies for clinical trials and validation studies has significantly improved the effectiveness and accuracy of diagnostic methods, with landmark studies contributing to evidence-based clinical evaluation[15-19].

Types of clinical trial:

Clinical trials can be categorized based on the mode of study.

1. An Interventional Study involves researchers measuring health changes in subjects by administering a specific medicine and comparing the treated subjects with those receiving no treatment or standard treatment.
2. This study uses clinical observation to measure outcomes of subjects given new medicine, classifying trials by purpose.
3. Preventive trials aim to prevent or prevent disease in previously unaffected individuals or its recurrence through various methods such as medicines, vitamins, vaccines, minerals, or lifestyle changes.
4. Screening trials are conducted to determine the most effective method for detecting specific diseases or health conditions.
5. Diagnostic trials aim to identify more effective tests or procedures for diagnosing a specific disease or condition.
6. Treatment trials are conducted to test new treatments, drug combinations, or surgical or radiation therapy approaches.
7. Quality of life trials (supportive care trials) aim to enhance comfort and quality of life for individuals with chronic illnesses.
8. Compassionate use trials or expanded access trials offer partially tested, unapproved therapeutics to a select few patients who have no other viable options, such as those with no approved treatments or those who have already failed all standard treatments and are too compromised to participate in randomized clinical trials.

Clinical evaluation methods encompass various approaches used to assess patients' health conditions :

1. Patient history, including medical history, symptoms, and personal information, is crucial for clinical evaluation, aiding in diagnosis and treatment planning by clinicians by understanding the patient's condition.
2. Clinical evaluation involves a comprehensive physical examination, including inspection, palpation, percussion, and auscultation, to evaluate a patient's health, detect abnormalities, and identify signs of medical conditions.
3. Diagnostic imaging, including X-rays, CT, MRI, ultrasound, and nuclear medicine scans, provides detailed images of internal structures for disease diagnosis and injury monitoring.
4. Laboratory tests, such as blood, urine, and genetic tests, aid in diagnosing illnesses, monitoring disease progression, and evaluating treatment effectiveness by analysing patient samples.
5. Tissue biopsies and pathological examinations under a microscope aid in

6. diagnosing various diseases, particularly cancers and conditions affecting organs or tissues.
7. Functional tests evaluate the health and performance of specific systems or organs, including pulmonary function tests, cardiac stress tests, and neurological assessments.
8. Mental health assessments involve interviews, questionnaires, and standardized assessments to diagnose and monitor mental health conditions like depression, anxiety disorders, and schizophrenia.
9. Outcome measures evaluate the impact of interventions on patients' quality of life, functional abilities, and overall well-being, in addition to diagnosing conditions and evaluating treatment effectiveness.

Phases of clinical trial:

Phase I studies:

Phase 1 of a drug or device testing process assesses its safety and effectiveness on humans. Phase 1 of a drug or device testing process assesses its safety and effectiveness on humans. This initial phase, which may take several months, involves a small number of healthy volunteers (20-100) and investigates the drug's absorption, metabolism, and excretion (ADME) effects. It also investigates dose-related side effects. Around 70% of experimental drugs pass this phase.

Phase II studies:

Phase II of testing is the second phase of a drug or device, involving up to hundreds of patients. It takes several months to two years and is typically randomized, with one group receiving the experimental drug and a control group receiving a standard treatment or placebo. These studies are often "blinded," allowing researchers to provide comparative information about the safety and effectiveness of the new drug. About one-third of experimental drugs successfully complete both phases.

Phase III studies:

Phase III is a large-scale testing phase that assesses randomized and blind trials in hundreds to thousands of patients. It lasts up to several years and provides researchers and regulatory authorities with a comprehensive understanding of a drug's effectiveness, benefits, and potential adverse reactions. Around 70% to 90% of Phase III drugs successfully complete this phase.

Phase IV studies:

Post Marketing Surveillance Trials, also known as Phase IV, are conducted after a drug or device has been approved for consumer sale by regulatory authorities. The objectives of these trials include comparing a drug with existing ones, monitoring its long-term effectiveness, and determining its cost-effectiveness compared to other therapies. Phase IV studies can lead to a drug or device being removed from the market or imposed restrictions on use, depending on the findings[20-22].

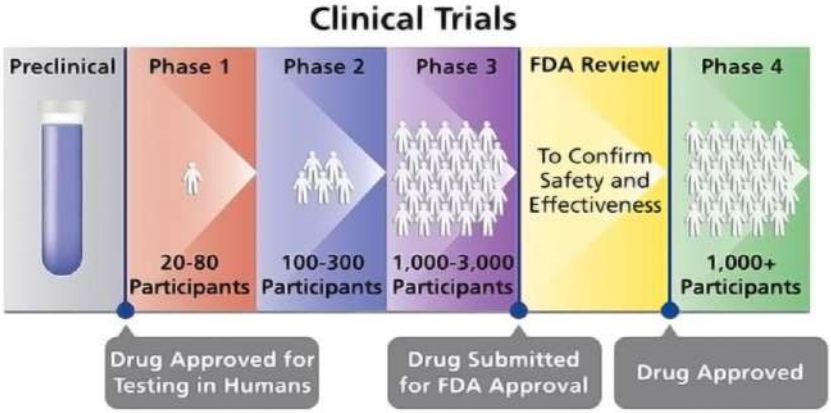

Fig 2: Phases of Clinical Trials

Clinical trials in India

India is a popular destination for global clinical trials, with nearly 20% of all trials taking place in the country. As the second-largest populated country, India can significantly contribute to global drug development programs due to its large patient populations, educated talent, wide disease spectrum, lower operational costs, and favourable economic and intellectual property environment. The Drugs Controller General (India) (DCGI) is responsible for all pharmaceutical-related issues in India, equivalent to the US FDA and European Medicines Agency (EMEA). India follows schedule Y for drug trials, which is equivalent to IND regulations 21CFR:312. The DCGI is not subdivided into multiple centres to regulate different products, but signs on all applications filed with his office, including clinical trial applications, marketing approval, import and export of regulated products, and manufacturing. India follows ICH E6 guidance for clinical trials.[23-25].

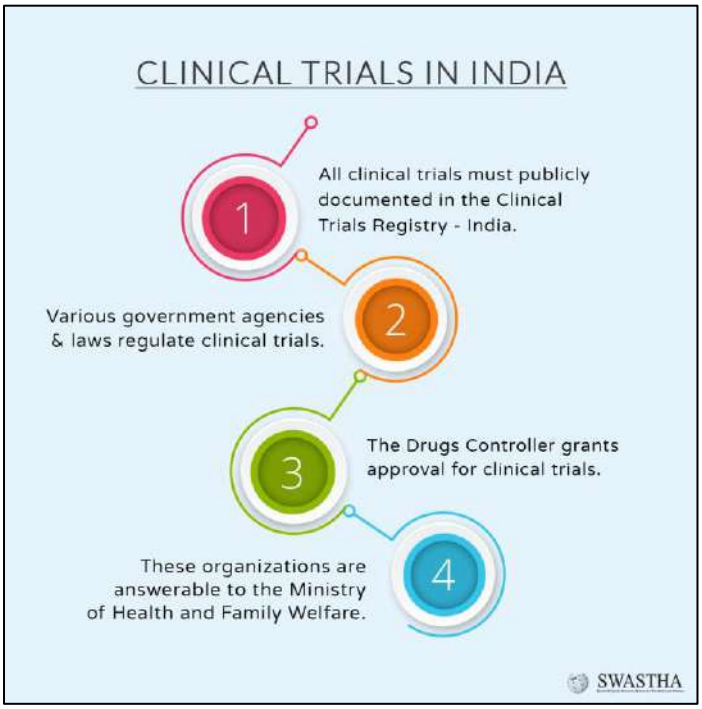

Fig 3: Clinical Trials in India

Efficacy and effectiveness

Human nutrition research trials (RCTs) differ significantly in efficacy versus effectiveness. Efficacy studies focus on the outcome of an intervention under ideal conditions, typically involving complete provision of foods, beverages, and nutrient formulations in either inpatient or free-living settings. Participants are closely monitored in inpatient settings or may eat ≥1 meal/d under supervision and balance on their own in free-living settings. The size and breadth of participant characteristics are typically limited by available resources, time, and logistics[26-27]. The trials include Dietary Approaches to Stop Hypertension (DASH and DASH-Sodium), Omni Heart and Omnicare[28-30]. An efficacy study yields clinically significant outcomes, which prompts an effectiveness trial. This pragmatic trial, or effectiveness trial, is designed to replicate a real-world situation with less-controlled conditions. It typically has a lower participant burden and involves a larger number of participants. Investigators instruct participants on how to modify their diet, either individually or through group settings. Examples of effectiveness

studies include the PREMIER study and Women's Health Initiative Intervention Study[31-32].

CLINICAL TRIAL DESIGN plays a crucible role in effectiveness of clinical method evaluation:

Randomization :

Randomization is a crucial methodology in research to prevent bias due to subject selection, which can affect the results of an experiment. It is a fundamental principle of experimental study designs and ensures scientific validity. Randomization prevents predicting which subjects are assigned to a group, preventing bias on final results. It also ensures comparability between groups, as most baseline characteristics are similar before randomization. There are three types of randomizations: simple randomization, block randomization, and stratified randomization. These methods can be as simple as flipping a coin using computer software and statistical methods.

Simple randomization:

Simple randomization involves assigning subjects to experiment/intervention groups based on a constant probability, such as a 0.5 probability of being allocated to either group A or B. This can be done through various methods, from flipping a coin to using random tables or numbers[33]. This methodology eliminates selection bias, but it also leads to imbalances in group allocation and prognostic factors, making it more challenging in studies with small sample sizes due to the potential for imbalances[34].

Block randomization:

Block randomization is a method where subjects with similar characteristics are divided into blocks to balance the number of subjects allocated to each experiment/intervention group. For instance, if there are four subjects in each block, two of them will be randomly assigned to each group, resulting in two subjects in one group and two in the other[35].

This methodology has a disadvantage as it doesn't randomize prognostic factors and still has predictability in subject selection, but it helps maintain balance between experiment and intervention groups.

Stratified randomization:

stratified randomization is a method where subjects are randomly assigned to specific strata, which are covariates[36]. The methodology of using prognostic factors like age as covariates allows for population randomization within age groups related to an experiment/intervention group, enhancing comparability and efficiency in result analysis. However, covariates must be measured and determined before randomization, and sample size is crucial in determining the number of strata needed for a study[37].

Blinding:

Blinding is a study design technique wherein information about group allocation is intentionally withheld from subject participants, investigators, and data analysts[38]. Blinding is a technique used to reduce the influence of group knowledge on study results, and can be divided into three forms: single-blinded, double-blinded, and triple-blinded[39]. Single-blind experiments involve participants not knowing whether they receive a test intervention or placebo. Double-blind trials do not reveal who belongs to the control and test groups, but the observer knows. Triple-blind RCTs are completely free from biases and influence, as none of the study components know the name or nature of the treatment. Keys identifying patients and groups are preserved by another party and given to the researcher at the end of the study[40].

Limitation of blinding:

Blinding is a widely accepted method for eliminating bias, but it has inherent limitations and requires significant effort and expense, making it crucial for clinicians and researchers to be aware of these[41].

Blinding has been suggested to potentially negatively affect subsequent care post-clinical trial conclusion[42].

Basic Statistical Concepts in Sample Size Estimation

The appropriate sample size depends on the study's design parameters, including the minimal meaningful detectable difference, estimated measurement variability, desired statistical power, and significance level, and basic statistical concepts are provided for this purpose.

Null and Alternative Hypotheses

The null and alternative hypotheses are two statements about a population, with the null hypothesis being rejected and the alternative hypothesis suggesting a potential result. The null hypothesis, denoted as H0, contradicts the investigator's expectations, while the alternative hypothesis, H1 or Ha, suggests a potential result. A hypothesis test uses sample data to determine whether to reject the null hypothesis, but not rejecting it does not necessarily mean it is true, but rather, there is insufficient evidence to reject it.

One-Sided and Two-Sided Tests

A one-sided test uses directional alternative hypothesis to determine if the population parameter is greater than or less than the hypothesized value, or if the parameter of group one is greater than or less than the parameter of group two. In contrast, a two-sided test uses nondirectional alternative hypothesis to determine if the population parameter differs from the hypothesized value or if the parameter of group one differs from group two regardless of which is larger.

Type I Error and Significance Level

A type I error is a false positive, with the significance level (a) representing the probability of rejecting the null hypothesis, typically set at 0.05 (5%), indicating acceptable 5% probability of incorrectly rejecting the null hypothesis.

Type II Error and Power

A type II error is a false negative, where the probability of rejecting the null hypothesis is not met, denoted by b. The power of a test is 1 b, typically set to 80% or 90% when calculating the sample size.

Minimal Detectable Difference

The minimal detectable difference in a clinical trial refers to the minimal difference between treatments that is considered clinically significant.

Variance or SD

Variance or SD is the average squared deviation from the mean, used to measure the spread of data points in a population. It can be obtained from previous or pilot studies, and is not necessary for sample size calculation when outcomes are binary.[43-44]

Applications

1. Treatment Efficacy and Safety Assessment.
2. Clinical Guidelines and Best Practices.
3. Healthcare Policy and Decision Making.
4. Quality Improvement and Patient Outcomes
5. Comparative Effectiveness Research
6. Medical Education and Training
7. Health Technology Assessment
8. Public Health Interventions

CONCLUSION:-

Clinical evaluation methods are crucial for assessing the safety and efficacy of medical interventions. Rigorous trials, ranging from Phase I to Phase III, provide a systematic framework for drug performance assessment. Well-designed studies, including endpoints, blinding, and randomization, ensure reliability and validity of results. These evaluations guide regulatory decisions, shape clinical practice, and enhance patient care. A commitment to robust evaluation methods is essential for ensuring healthcare and pharmaceutical advancements' integrity. Clinical evaluation methods are crucial for assessing the safety and efficacy of medical interventions. They involve a stepwise progression through Phase I, II, and III studies, ensuring comprehensive scrutiny

of drug performance. Rigorous trial designs, participant selection, and blinding contribute to reliability and validity. This systematic approach ensures regulatory standards are met, promoting evidence-based healthcare decision-making. Continuous improvement and innovation are vital for advancing medical knowledge and delivering safe treatments.

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HOW TO CITE: Shreyash Koli, Sourabh Patil, Sarthak Kothali, Suvarna Deshmukh, Sachin Navale, Nilesh chougule, Effectiveness of clinical method evaluation, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 1, 264-273. https://doi.org/10.5281/zenodo.10517844