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REVIEWARTICLE: CLINICAL RESEARCH AND CLINICAL TRIALS

Aher Shailendra[*1] , Momin Mohammad Sajid[2] ,
Mahankale Pratik[3] , Momin Furkan[4]

Jagdamba Education Society's SND College of Pharmacy Babhulgaon-Yeola , Nashik-423401,India

Abstract

An alternate word for medical research is clinical research. Clinical research is done on human subjects and is typically done to assess a therapeutic drug's, a medical or surgical procedure's, or a device's effectiveness in treating or managing a patient. Additionally, clinical research can refer to any study that assesses the aetiology, symptoms, risk factors, and other aspects of a disease. Clinical trials, on the other hand, are research projects that evaluate a therapeutic medicine or device's potential for illness management, control, and prevention. The emphasis on clinical research becomes even more crucial in light of the rising rates of both communicable and non-communicable diseases, particularly in light of the impact that COVID-19 has had on public health globally. Understanding clinical research can help in the development of medications, equipment, and vaccines, which will enhance readiness for public health emergencies. Thus, we provide a thorough description of the essential components of clinical research in this study, which includes the phases, kinds, and designs of clinical trials as well as their operations, audit, and management, as well as ethical considerations.

Keywords: clinical trials, therapeutic drug, efficacy, ethical concerns, audit, medical research, clinical research

Introduction And Background

A clinical trial is an organised procedure designed to determine if a medication or medical technology is safe and effective in treating, preventing, or diagnosing a disease or other medical condition. Phase 0 (micro-dosing studies), Phase 1, Phase 2, Phase 3, and Phase 4 are among the phases of a clinical trial. Phases 0 and 2 of the study are referred to as exploratory, Phase 1 as the non-therapeutic phase, Phase 3 as the therapeutic confirmatory phase, and Phase 4 as the post-approval or post-marketing surveillance phase. Phase 0, also known as the micro-dosing phase, was originally conducted on animals but is currently done on human volunteers in order to determine the dose tolerability prior to administration as part of the phase 1 trial among healthy participants.

The phases, types, and nature of clinic'l trial studies :u
(Table 1)

MTD: maximum tolerated dose; SAD: single ascending dose; MAD: multiple ascending doses; NDA: new drug application; FDA: food and drug administration

Clinical trial phase	Type of the study	Nature of study.
Phase 0	Exploratory	Investigates medication microdosing, or excessively low (1/100th) quantities, over shorter periods of time. Determine the dose for phase I investigations by studying the pharmacokinetics. Previously conducted on animals, but currently done on people.
Phase I, Phase IA, Phase IB	Non-therapeutic trial	The recruitment of about fifty healthy subjects occurs. Defines both the MTD and a safe dosage range. Looks at both the pharmacodynamic and pharmacokinetic impacts. Single-center investigations are common. Phase Ia includes MTD and SAD. The trial's duration can range from one week to several months, and it involves six to eight groups of three to six people each. Phase Ib: MAD with a sequential reduction in dosage. Each group consists of eight people.
Phase ii, Phase IIa,	Exploratory trial	Bringing in between five and one hundred patients of any gender. Investigates the therapeutic effects on

Phase IIb		patients as well as the optimal dosage. It determines the course of treatment and interactions between medications. Multicenter studies are typical. Phase IIa: Determines the medication dosage, involves twenty to thirty individuals, and may take many weeks or months. Phase IIb: Investigates drug-drug interactions, dose-response relationships, and comparisons with placebo.
Phase III	Therapeutic confirmatory trial	In this investigation, which is a multicentric trial, over 300 patients (up to 3000) of either sex are recruited. Drug efficacy and safety are assessed during the pre-marketing phase. Contrast between the test medication and the reference/placebo medicine. Notice is taken of any negative medication responses or incidents. With the relevant regulatory bodies, such as the FDA, start the NDA procedure.
Phase IV	Post-approval study	Following approval, post-licensure, post-marketing research, and monitoring studies. Monitoring the patients for an unusually extended period of time in order to look for possible drug interactions and bad effects.

Clinical trial designs, their advantages, and disadvantages :
(Table 2)

Non-interventional/observational studies and interventional/experimental studies are the two main categories of clinical research design. Analytical studies such as case-control and cohort studies may contain a comparator group, or the studies may be descriptive in nature and lack one. There are two types of experimental studies: non-randomized and randomised. A variety of designs are used in clinical trials, including factorial, adaptive, superiority, non-inferiority, randomised withdrawal, parallel, crossover, and factorial designs.

Trial design type	Type of the study	Nature of study	Advantages/disadvantages
Parallel	Randomized	This is the most common strategy in which a specific treatment (therapeutic medicine or placebo, an inert substance) is assigned to each arm of the study group.	Without the study medicine, the placebo arm might not benefit from it.
Crossover	Randomized	Each medicine is given to the patient in this experiment, who also acts as a self-control.	Minimises the risk of treatment participant bias and calls for a modest sample size. Research on acute disorders is not a good fit for this design.
Factorial	Non-randomized	Information on the interactions between the medications can be obtained from the study by implementing two or more treatments on the participants.	The study design is complex
Randomized withdrawal approach	Randomized	This study evaluates the time/duration of the drug therapy	To determine a drug's effectiveness in treating an illness, a placebo is used in the trial.
Matched pairs	Post-approval study	Recruit patients with the same characteristics	Less variability

Figure 1 :

Clinical trials are carried out for a variety of purposes, such as diagnosis, early detection/screening, therapy, and prevention. These investigations focus on the effects of experimental drugs on diseases and their consequences. They evaluate the effectiveness of a medical test to diagnose the disease or condition, the ability of a gadget to detect or screen for the disease, and the drug's ability to prevent the disease or condition. Figure 1 shows a graphic illustration of a disease's diagnosis, course of therapy, and prevention.

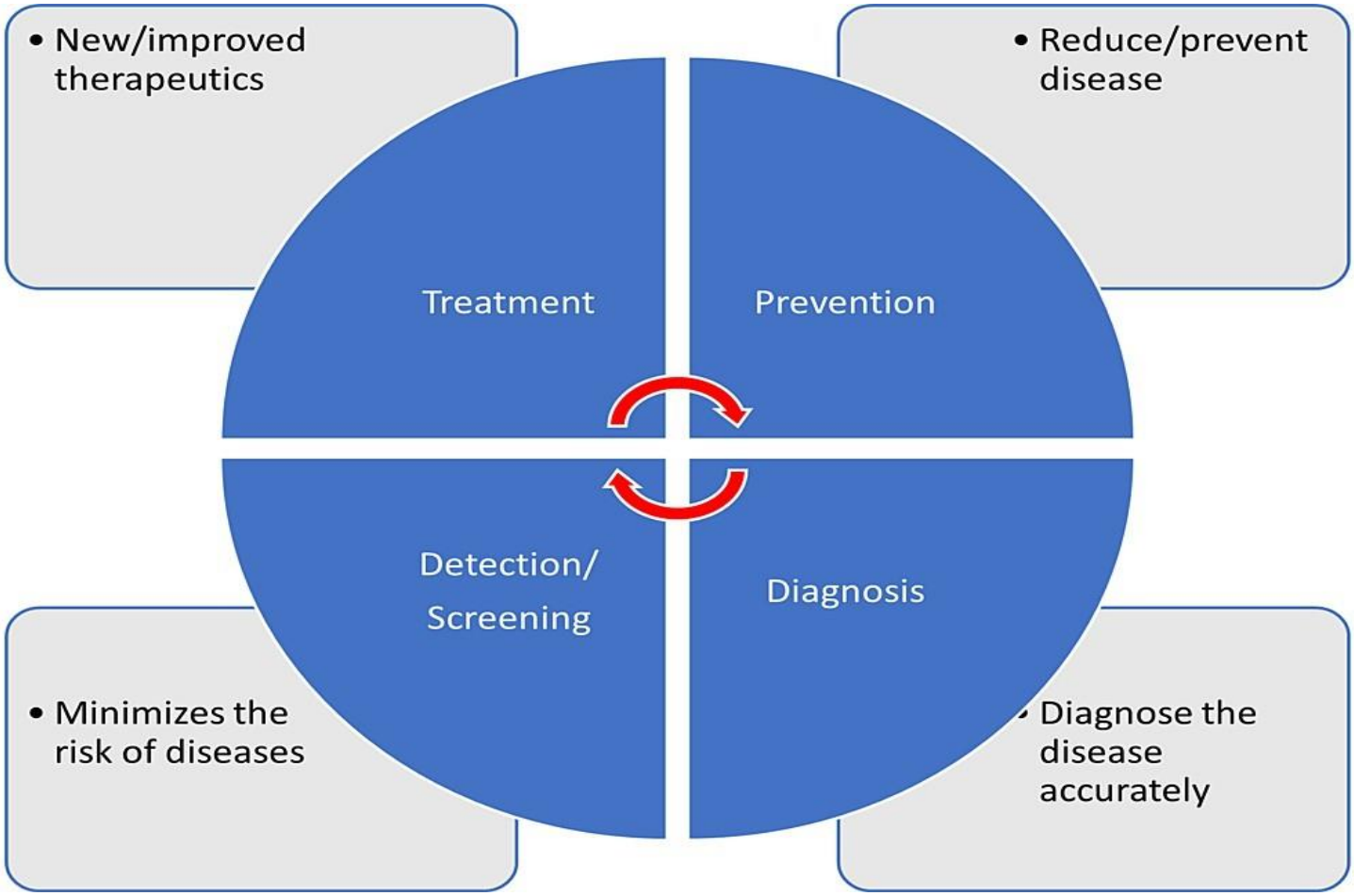
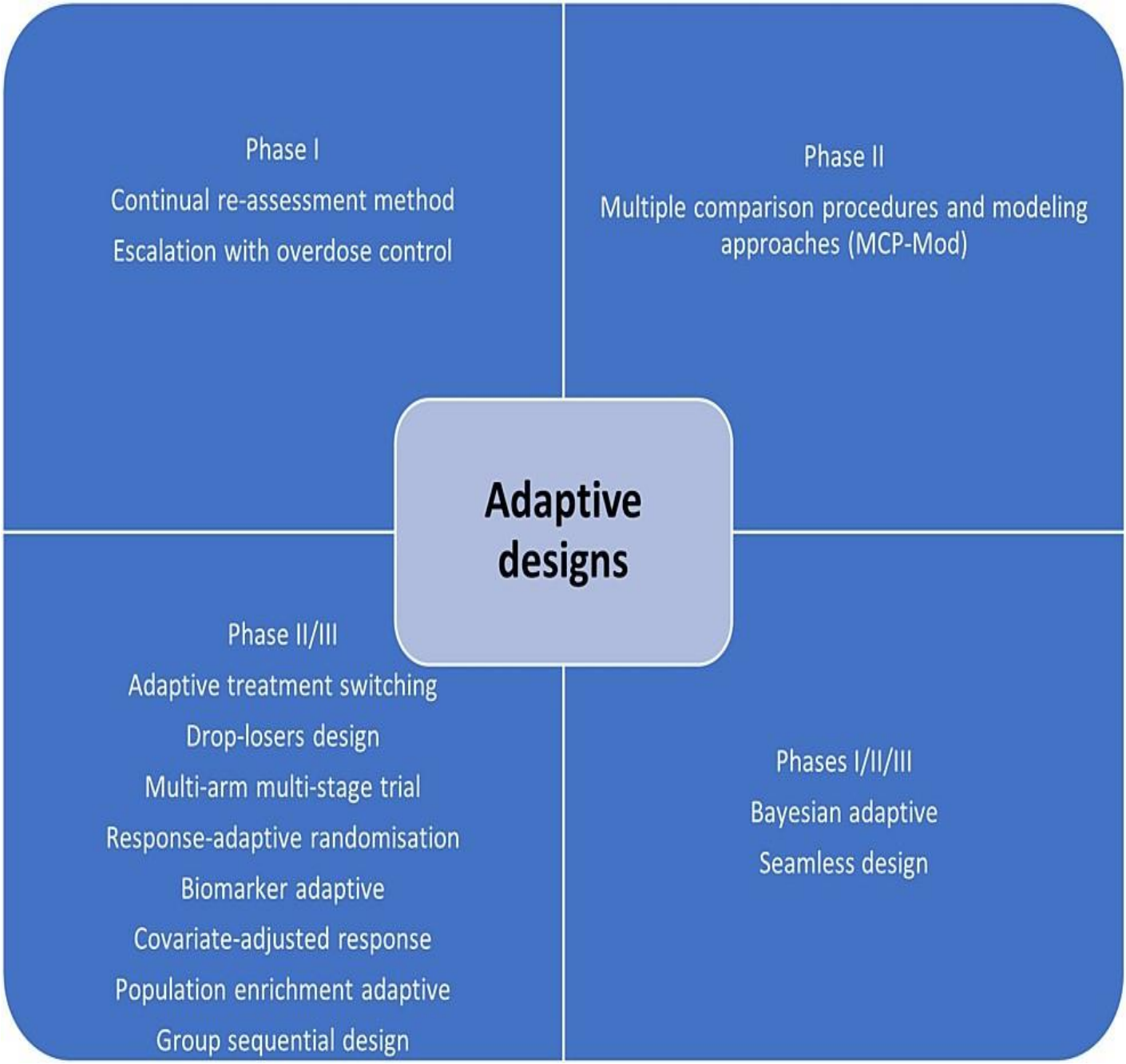


Figure 2 :

To ensure that the study's validity is kept, the clinical trial designs may need to be modified. Adaptive designs allow investigators to make adjustments as needed during a clinical study without compromising the accuracy and reliability of the findings. Additionally, it permits flexibility in the execution of trials and data collecting. Clinical researchers do not always agree with adaptive designs, despite these benefits. This may be explained by the research community's lack of experience with these kinds of designs. The adaptive designs have been used for a range of clinical diseases and at different stages of clinical trials. Figure 2 shows the adaptable designs used at various phases.



Particularly during the Coronavirus Disease-19 (COVID-19) pandemic, the Bayesian adaptive trial design has become increasingly prominent. A single master protocol might control these designs. It functions as a platform trial that allows for the testing of various medicines on various disease-affected patient populations.

The essential components of clinical research are covered in detail in this review, including project management, clinical trial operations at the investigation site, planning clinical trials, practical aspects of clinical trial operations, essentials of clinical trial applications, monitoring, and audit, clinical trial data analysis, regulatory audits, and ethical considerations in clinical research/trials.

Review :

An investigational medication or other intervention's impact on a specific participant or population is being studied in a clinical trial. The treatment group and the placebo group are included in the clinical study, and each group's effectiveness of the intervention—whether it is improved or not—is assessed. Clinical studies can be broadly divided into two categories: controlled and uncontrolled. The results of uncontrolled trials are not given the same weight as those from controlled studies since they may be biassed. Clinical trials with

minimal bias and dependable outcomes are seen to be most beneficial when they are designed as randomised controlled trials, or RCTs. Table 3 elaborates on the many forms of randomizations and their distinct roles.

Different types of randomizations in clinical trials :

(Table 3)

Randomization type	Functions
Simple randomization	By using a computer or flipping a coin, the participants are matched to either the case or the control group.
Block randomization	Equal and small groups of both cases and controls
Stratified randomization	Randomization based on the age of the participant and other covariates
Co-variate adaptive randomization/minimization	Adding a new member to a group in a sequential manner depending on factors
Randomization by body halves or paired organs (Split body trials)	A comparison intervention is applied to one half of the body, while an intervention is given to the other half.
Clustered randomization	To prevent contamination, interventions are given to clusters or groups randomly, with each group receiving either an active or comparator intervention.
Allocation by randomized consent (Zelen trials)	Patients are allocated to one of the two trial arms

Principles of clinical trial/research :

Clinical trials and research are undertaken to test hypotheses, advance knowledge of the unknown, and carry out investigations pertaining to public health. The main method for doing this is gathering the data and using analysis to draw conclusions. Clinical trials come in many forms, but they are primarily classified as analytical, observational, and experimental research. Drug trials, directed data collection, and non-directed data capture are more categories under which clinical research can be divided. Prospective or retrospective clinical studies are both possible. It could also be a cohort study or a case-control study. A disease or medical condition may be observed, treated, prevented, or diagnosed through the use of clinical trials.

In contrast, the medicine has no beneficial effect on the participant in a non-therapeutic clinical trial. The extra information on the medication from the non-therapeutic trials will help with future advancements. Table 4 lists many terms used in clinical studies.

Clinical trial methods and terminologies :
(Table 4)

Type of clinical trial	Definition
Randomized trial	Study participants are randomly assigned to a group
Open-label	The medication under test is known to the researchers and study participants.
Blinded (single-blind)	When conducting a study using single-blind methodology, the participant is blind to the test or control group they are assigned to.
Double-blind (double-blind)	In the double-blind study, the subjects as well as the investigator have no idea about the test/control group
Placebo	A substance that appears like a drug but has no active moiety
Add-on	A different drug given to a group of study subjects in addition to the one used in the clinical trial
Single center	A research project underway at a certain site, location, or centre
Multi-center	A study is being carried out at multiple places/locations/centers

Planning clinical trial/research :

The creation of protocols, the creation of case record/report forms (CRFs), and the operation of institutional review boards (IRBs) are all steps in the clinical trial process. It also covers data management and activity monitoring at clinical study sites. Within a clinical investigation, the CRF is the most important document. It includes the data that the researcher gathered about every participant in a clinical study or trial. The CRF, which documents the pharmaceutical drug's or product's safety and effectiveness in test subjects, can be an optical, printed, or electronic document, according to the International Council for Harmonisation (ICH). The sponsor who starts the clinical investigation is the intended recipient of this information.
Following the methodology, the CRF is created and then carefully examined to ensure that all the questions are relevant and structured before being finalised. setting up the trial by recruiting participants, organising, creating procedural manuals, ensuring quality, training investigators, and so forth.

Practical aspects of a clinical trial operations :

Clinical research comes in a variety of forms. Clinical research started by individuals or investigators, industry-sponsored research, and nationally financed research can all be used to start the development of a new medication. As per the 21 Code of Federal Regulations (CFR) 312.3 and ICH E-6 Good Clinical Practice (GCP) 1.54 documents, an investigator is a person who originates and carries out clinical research.The researcher plans, organises, executes, keeps an eye on, organises data, creates reports, and oversees ethical and regulatory matters pertaining to study. An investigator must provide a letter of intent, compose a proposal, establish a timeframe, create a protocol and any necessary supporting documentation, such as case record forms, specify the budget, and locate financing sources in order to successfully oversee a clinical trial project.

Obtaining IRB clearance, conducting and supervising the study, reviewing and analysing the results are additional crucial processes in the clinical research process. A letter of intent—which is the documentation that demonstrates the researcher's motivation to study drugs—as well as a timeframe, funding source, supplier, and participant profiles are all necessary components of a successful clinical study.

Clinical trial applications, monitoring, and audit :

In a clinical trial, the audit is one of the most important parts. Analysing clinical trial procedures at the location in a methodical manner is called an audit. The audit makes sure that the protocol, established quality system procedures, GCP principles, regulatory authority requirements, and clinical trial process are all followed. Without the assistance of the sponsors, CROs, or trial site staff, the auditors are expected to operate independently. The auditors guarantee that qualified professionals with sufficient training, assigned to the trial, and with clear responsibilities carry out the proceedings. Along with ensuring the integrity and efficacy of institutional review and ethics, the auditors also verify the legitimacy of investigational drugs.

The FDA regulatory forms for the submission of inspection results :

(Table 5)

Regulatory (FDA) form number	Components of the form
483	Compiled by the FDA investigator and provided to the auditee at the conclusion of the inspection is a list of unacceptable circumstances and procedures.
482	The auditors provide the clinical investigators with their identity documents and notice of inspections, and then they record their observations.
1571	This document states that the clinical study cannot begin earlier than 30 days after the IND has been submitted to the FDA for approval. The document attests to the IRB's compliance with 21 CFR Part 56. The form lists all the participants who oversee the conduct and advancement of the study and assess the clinical trial's safety, as well as the agreement to abide by regulatory standards.
1572	This form certifies that the study is conducted in accordance with protocol, informed consent, and IRB approval by outlining the fact that it was approved by ethics.

The rights, safety, and well-being of research participants are more important than data integrity while conducting clinical trials, hence regular process audits and monitoring seem essential. The manner in which the sponsors and investigators conduct the clinical study has a significant impact on its quality. Depending on the clinical trial site, multiple parties may be responsible for different aspects of the monitoring process. study monitoring is the responsibility of the corporation or sponsor in cases where the pharmaceutical industry

starts the study; in cases when an academic organisation conducts the trial, the primary investigator is in charge.

Clinical trial data analysis, regulatory audits, and project management :

The administration of the study, the site, personnel, subjects, contracts, data, and document management, integration of patient diaries, medical coding, monitoring, adverse event reporting, supplier management, lab data, external interfaces, and randomization are among the fundamental components of clinical trial management systems (CDMS). Establishing a start and end time, goals for the study, enrollment and termination requirements, comments, and design management are all part of the CDMS.

Medical coding, which employs terminology related to drugs and adverse events/serious adverse events that must be entered into the CDMS, is used in clinical trial data management. The clinical trial project needs to be planned out with timetables and objectives in advance. Typically, schedules are established for the creation of the protocol, the CRF, project planning, selecting the initial subject, and the patient data recording for the initial visit.

Types of clinical trial audits :

(Table 6)

Product-specific audits program	Pharmacovigilance audits program
Protocol, CRF, IC, CSR	
Supplier	
Clinical database	Safety data management
Investigator site	
Clinical site visit	
Study management	Communications and regulatory reporting
SAE reporting	
Supplier audits program	
Supplier qualification	Signal detection and evaluation
Sponsor data audit during the trial	
Preferred vendor list after the trials	
Process/System audits program	Risk management and PV planning
Clinical safety reporting	
Data management	
Clinical supply	Computerized system
Study monitoring	
	Suppliers
	Regulatory inspection management program
	Assist with the audit response
Computerized system	Pre-inspection audit

Clinical trial operations at the investigator's site :

Prior to initiating a clinical experiment, the investigation site must be chosen carefully. The participants in the research must fulfil the trial's inclusion requirements, and the protocol design and the deadlines established by the regulatory bodies, such as the IRBs, must be accepted by the patient and the investigator. An investigator must accept the terms and circumstances of the agreement and uphold the protocol's confidentiality before beginning clinical research. During the site selection visit, the sponsor evaluates the protocol for practicability in terms of infrastructure, resources, availability of study subjects, availability of competent and trained people, and benefits to the investigator and institution.

Clinical trials: true experiments :

Per the updated schedule "Y" of the Drugs and Cosmetics Act (DCA) (2005), a systematic investigation of a novel drug component is what constitutes a drug trial. The purpose of the clinical trials is to assess novel medications' pharmacodynamic and pharmacokinetic qualities, such as ADME, effectiveness, and safety. A new chemical entity (NCE) is any innovative drug that is approved for a specific ailment or condition, in a prescribed method, and at a specific dosage, as per the drug and cosmetic rules (DCR), 1945. It might also be a novel medication combination made out of already-approved medications.

Three different kinds of clinical trials can be conducted: one to determine the effectiveness of a new prescription entity (NCE); another to compare two medications against a medical condition; and a third to conduct clinical research on an approved medication versus a medical condition. Additionally, studies of the bioavailability and BE of generic medications and medications that have already received approval in other nations are conducted to determine the efficacy of new medications.

Ethics and concerns in clinical trial/research :

Respecting ethics and ethical procedures becomes even more important in clinical research because it involves both human and animal subjects. In 1947, the Nuremberg code was developed, which established guidelines for acceptable human subjects for medical research, in response to the unethical research done on military troops following World military II. told consent is recommended by the Nuremberg code to be required for all clinical trial participants. Research volunteers should also be told on the nature, duration, and goal of the study, as well as any potential health risks (both known and unknown). When a medical emergency arises, study participants should be free to select a doctor and to leave the trial at any moment.

Conclusions :

From the standpoint of public health, clinical research and clinical trials are crucial. Clinical research helps people, public health officials, and scientists better understand and prepare for the diseases that are common in many parts of the world. Additionally, as the current Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic and other newly and re-emerging microbial illnesses demonstrate, clinical research aids in minimising health-related issues. The development of medications, gadgets, and vaccinations depends heavily on clinical trials. Hence, as this paper thoroughly discusses, scientists must be current on the methods and processes of clinical research and trials.

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