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Review On Clinical Trial

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Abstract:

Clinical trials is a research study conducted in human volunteers to evaluate the safety and effectiveness of new drugs. Before performing clinical trials preclinical trials performed on animal. Clinical trials are the primary way to determine if new drug, treatment, or device is effective or safe for use in human. There are different types of clinical trials: Randomized controlled trials, Observational trials, Interventional trials. Clinical trials typically conducted in five phases: Phase 0, Phase 1, Phase 2, Phase 3, and Phase 4. Phase 0 is the micro dosing designed to accelerate the drug approval process. Phase 1 trials performed to determine the metabolic and pharmacodynamics effects in animal. Phase 2 for establishment of therapeutic efficacy and dose range. Phase 3 trials compare the new treatment to standard treatments, evaluating its overall safety and efficacy on a larger scale. Phase 4 trials, conducted to determine efficacy and safety within large population called as post marketed surveillance.

Keywords:

Clinical trials, NDA, Observational trials, Phases.

Introduction:

When creating a new medicine, it is crucial to assess its safety and effectiveness in human subjects. Clinical trials serve as scientific studies aimed at evaluating new medical treatments or novel applications of existing ones. Their primary goal is to determine whether a given therapy can enhance disease prevention, diagnosis, or treatment. For any new pharmaceutical, biological agent, or medical device to move forward in development, its safety must be validated, its effectiveness in humans proven, and its feasibility for large-scale manufacturing confirmed.

Before clinical testing in humans begins, drugs must first pass through preclinical evaluations. These include both laboratory (in vitro) assessments and tests on animals. Researchers expose these systems to different doses of the experimental drug to gain early insights into its potential benefits, toxicity levels, and how it behaves in the body (pharmacokinetics). A common issue in clinical trials is observer bias, where researchers' expectations or desires might unintentionally influence how results are interpreted, possibly leading to conclusions that are not entirely objective.

Currently, two globally accepted frameworks guide the ethical conduct of human involvement in clinical studies. These are known as ethical codes rather than mere guidelines, as codes establish professional standards for behaviour in a specific domain. Throughout the last hundred years, additional research ethics codes have been introduced—one notable example being the Nuremberg Code, which was developed in response to unethical human experimentation during World War II.

History of Clinical Trials

The history of clinical research spans a long and remarkable journey, with its origins traced back to ancient times. The earliest recorded account of a clinical trial dates to approximately 500 B.C., as described in the Bible's Book of Daniel. In this narrative, a controlled comparison was made between a diet of vegetables and a diet of royal food to assess their health effects.

Pre-James Lind Era (562 B.C.–1537)

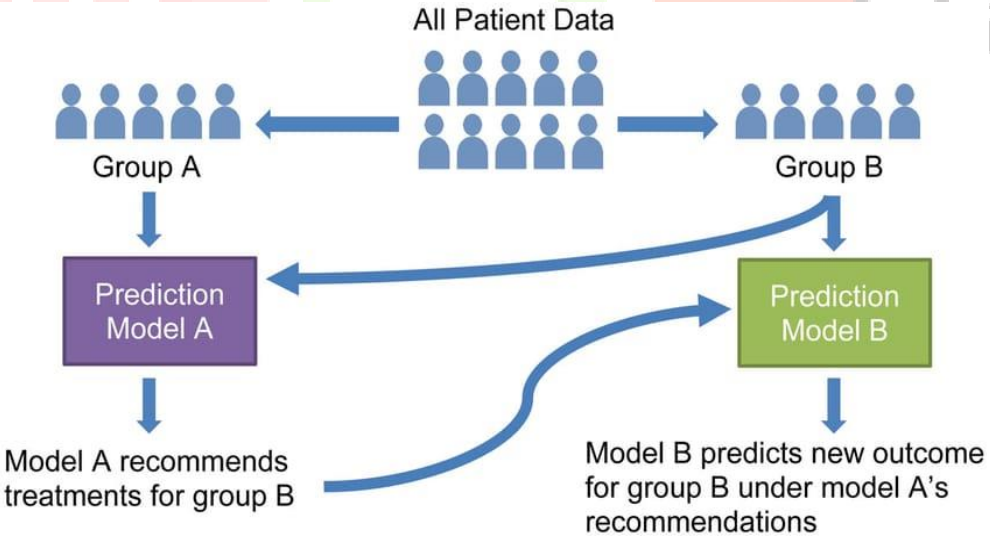
During this period, several key contributions laid the groundwork for clinical research. Avicenna, a renowned Persian physician, detailed principles for drug testing in his medical encyclopaedia, The Canon of Medicine (1025 AD). He emphasized that treatments should be tested in their natural state on uncomplicated diseases. The first accidental trial of a novel therapy occurred in 1537, when the surgeon Ambroise Paré tested a new wound treatment, marking a pivotal moment in the evolution of clinical trials.

The Arrival of Placebos (1800s)

It was not until the 19th century that the concept of a placebo—a substance with no therapeutic effect used as a control in clinical trials—emerged as a significant advancement in modern clinical research. The term "placebo" first appeared in medical literature during the early 1800s, signifying a major milestone in trial methodology.

Clinical Trial Simulation

Clinical trial simulation is the study of effect of drug in virtual patient populations using mathematical tool. Simulations are particularly useful in the areas where clinical testing arises special concerns, such as children and pregnant women. The main aim of clinical trial simulation to understand the impact of some unknown factors. It can be used to measures uncertainty about dose selection and other issues related drug safety and efficacy.



Evolution of clinical trials in India:

India has emerged as a prime destination for conducting international clinical trials, accounting for approximately 20% of all global studies. As the world's second most populous country, India offers a significant opportunity to support global drug development efforts.

Several factors make India an attractive hub for clinical research. These include access to a large and diverse patient pool, a broad spectrum of diseases, a highly skilled medical and scientific workforce, and relatively lower costs associated with operations and drug development compared to developed nations. Additionally, the widespread use of English facilitates communication and simplifies the establishment of clinical trial sites across the country. The supportive environment in terms of intellectual property rights and economic factors further enhances India's appeal.

Regulatory oversight in India is provided by the Drugs Controller General of India (DCGI), the equivalent of the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The DCGI is responsible for regulating pharmaceuticals, including clinical trial approvals, marketing authorizations, and applications related to the import, export, and manufacture of drugs and medical devices.

India follows Schedule Y, a regulatory framework for clinical studies, which aligns with international guidelines such as the U.S. FDA's 21 CFR Part 312 governing Investigational New Drug (IND) applications. However, unlike regulatory bodies in some other countries, the DCGI office is not divided into multiple specialized branches. Instead, the DCGI personally signs off on every application, ensuring direct oversight.

Clinical trials in India are conducted in accordance with ICH-GCP E6 guidelines, and the Indian Council of Medical Research (ICMR) has also developed a localized version of Good Clinical Practice (GCP) tailored to the specific needs of Indian clinical research. Institutional Ethics Committees (IECs) in India serve a similar role to Institutional Review Boards (IRBs) in the United States. Before a trial can begin, each study site must obtain approvals from both the IEC and the DCGI.

While the approval timeline for clinical trial applications in the U.S., Europe, and Australia is typically two to four weeks, it generally takes between four to eight weeks in India. Despite this, India remains a strategic player in the global clinical research landscape, offering unique advantages for pharmaceutical development.

Modern trials:

Austin Bradford Hill played a pivotal role in the advancement of modern clinical trial methodology. His contributions, along with the work of Sir Ronald A. Fisher, established the foundation for scientific rigor in experimental design.

Sir Ronald A. Fisher, while working at the Roth Amsted Experimental Station in the 1920s, developed key principles of experimental design to ensure accuracy and reliability in research. These principles include:

1. Randomization: Fisher emphasized the importance of randomly assigning individuals to experimental groups. This approach helps minimize bias and ensures that the groups are comparable at the start of the trial.

2. Replication: To reduce uncertainty, Fisher advocated for repeating measurements and replicating experiments. This practice helps identify sources of variation and strengthens the reliability of results.

3. Blocking: Fisher proposed organizing experimental units into groups that are similar to each other. This reduces variability and improves the efficiency of evaluating the effects and potential interactions of multiple independent variables.

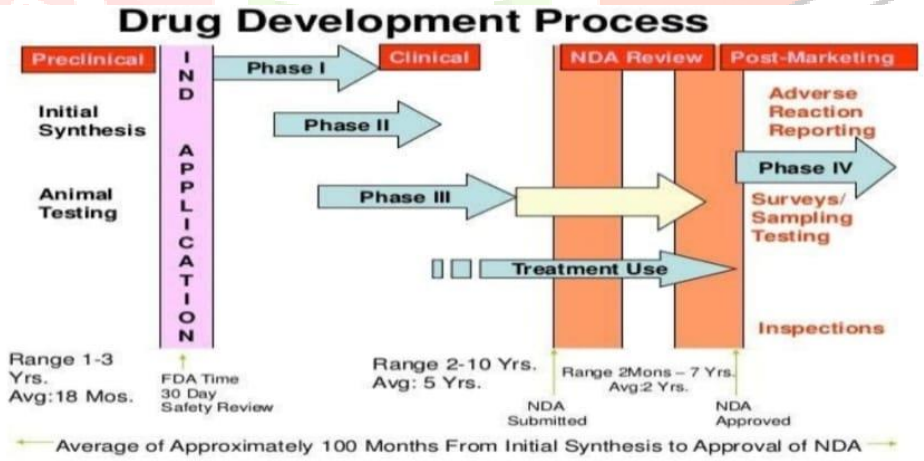
These principles laid the groundwork for the structured and scientifically valid clinical trials conducted today, ensuring that modern trials are robust, reproducible, and capable of providing reliable evidence for medical advancements.

Process of drug discovery and development:

Drug discovery is a complex process that entails identifying a chemically therapeutic medicine for treating and managing a disease. Researchers usually discover novel drugs by gaining fresh insights into the illness process, enabling them to develop a drug to prevent or counteract the consequences of the disease. Drug discovery involves identifying potential drugs, synthesizing them, characterizing them, screening them, and testing their therapeutic effectiveness. Once a chemical demonstrates satisfactory results in these investigations, it will proceed to drug development following clinical trials. Drug discovery and development is costly because of the substantial resources required for research and development as well as clinical trials. It typically takes approximately 13-15 years to produce a new drug molecule from its discovery to its availability on the market for patient treatment. The typical expenditure for research and development of each effective drug is estimated to range from $800 million to $1.5 billion. This statistic encompasses the expenses incurred due to several failures. Out of 4,000-10,500 chemicals that go through inquiry and development, just one receives approval. The complexity of the research and development process explains why many compounds fail and why it is a time-consuming endeavour to bring a single drug to patients. Success necessitates abundant resources, top scientific and logical brains, advanced laboratory technologies, and comprehensive project management. Persistence and good fortune are also required. Ultimately, the drug discovery process instils hope, faith, and relief in billions of patients.

Steps of drug discovery and development:-

- Objective Identification
- Objective Validation
- Direct Identification
- Direct Optimization
- Product Characterization
- Formulation Development



Challenges in Drug Development:-

The development of a new drug is a highly intricate and resource-intensive process, both in terms of time and financial investment. Before progressing to clinical trials, researchers must gather substantial evidence to demonstrate the drug's potential efficacy and safety. While animal testing remains a critical component of preclinical research, ethical obligations require scientists to reduce animal suffering and actively seek alternative testing methods whenever feasible.

Despite these conscientious efforts, the rate of success in drug development remains low. For instance, only about 5% of drugs aimed at treating conditions such as stroke or septic shock ultimately reach the market, despite considerable preclinical research and investment. Similarly, clinical trials for cancer treatments show a success rate of less than 5%, highlighting the significant challenges and uncertainties inherent in pharmaceutical development.

Pre-Clinical Study:-

Preclinical development refers to the stage of drug or therapy development that occurs before clinical trials in human. It is very important phase in research and development (R&D).

Preclinical development involves following:

In Vitro Studies: - Purpose of in vitro study is assess the mechanism of action, cytotoxicity and target engagement.

In Vivo Studies – To evaluate safety, efficacy, pharmacokinetics and pharmacodynamics.

Investigational new drug application (IND) – Results from preclinical studies are compiled into an IND which is submitted to regulatory agencies to request permission to start human trials.

Goals of Pre-Clinical Development

Pre-clinical development determines the safety and effectiveness of a drug before it enters clinical trials. During this stage, both in vitro (lab-based) and in vivo (animal-based) tests are conducted. If pre-clinical studies confirms that the drug is safe and effective, clinical trials start. Clinical trials are defined as "scientifically controlled studies that evaluate the safety and effectiveness of therapeutic agents using willing human subjects. “Possible outcomes of pre-clinical studies include:

a) Assessment of safety

b) Efficacy

c) Potential side effects

Clinical Study

Types of Clinical Trials:

Clinical trials can be categorized in several ways, one of which is based on the mode of study design. Under this classification, clinical trials are broadly divided into Interventional Studies and Observational Studies.

1. Interventional Study

In an interventional study, researchers actively administer a specific treatment, such as a drug or therapy, to a group of participants. The outcomes of these participants are then compared with those of a control group, which may receive a placebo, standard treatment, or no intervention at all. This approach helps evaluate the efficacy and safety of the proposed intervention.

2. Observational Study

In observational studies, researchers do not influence the course of treatment. Instead, they observe and analyse outcomes in participants who are either undergoing a specific treatment or are exposed to a certain condition naturally. This type of study helps in understanding associations and outcomes without introducing external interventions.

Another method of classification is based on the purpose of the clinical trial, which includes the following categories:

Classification by Purpose

1. Prevention Trials

These trials are designed to investigate ways to prevent the onset of diseases in healthy individuals or to prevent recurrence in those who have previously been affected. Interventions may include vaccines, medications, lifestyle modifications, vitamins, or minerals.

2. Screening Trials

Screening trials aim to identify the most effective techniques for early detection of specific diseases or health conditions, often before symptoms appear.

3. Diagnostic Trials

The goal of diagnostic trials is to develop or refine tests and procedures that can more accurately detect particular diseases or medical conditions.

4. Treatment Trials

These trials assess new treatments, such as investigational drugs, innovative combinations of existing therapies, or novel surgical and radio therapeutic techniques. They are conducted to determine the safety and efficacy of these interventions.

5. Quality of Life (Supportive Care) Trials

Supportive care or quality of life trials focus on improving the comfort, well-being, and overall quality of life of patients, particularly those living with chronic or terminal illnesses.

6. Compassionate Use (Expanded Access) Trials

These trials provide access to investigational drugs or therapies that are not yet approved, for patients with serious or life-threatening conditions who have exhausted all other treatment options. Such trials are typically conducted under regulatory guidelines to ensure patient safety while exploring the potential benefits of experimental therapies.

Phases of Clinical Trial:-

Phase 0 Clinical Trials: A Strategic Step in Modern Drug Development

Phase 0 trials are a relatively recent addition to the clinical trial landscape, introduced by the U.S. Food and Drug Administration (FDA) in 2006 through its guidance on Exploratory Investigational New Drug (IND) studies. These trials are considered preliminary, first-in-human studies, conducted before the traditional Phase I trials. Their primary goal is to streamline and accelerate the drug development process by allowing early evaluation of a drug's behaviour in the human body.

Unlike traditional clinical phases, Phase 0 trials do not aim to assess safety or efficacy. Instead, they focus on understanding two critical aspects:

Pharmacokinetics (PK): How the drug is absorbed, distributed, metabolized, and excreted in the body. Pharmacodynamics (PD): The biological effects of the drug on the body, even at low doses.

These trials usually involve a very small number of participants (typically 10–15) who receive sub-therapeutic doses of the investigational drug. Since the doses are too low to cause clinical effects, the risk to participants is minimized, and the data generated provides early insight into whether a drug behaves as predicted from animal and laboratory studies.

Phase-I clinical trials:

Phase I trial conducted on a small (20-80) population. Normally, a healthy volunteers selected. This phase designed to assess safety, tolerability, pharmacokinetics, pharmacodynamics of drug. Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have end-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIVdrug trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. Pay ranges from a small amount of money for a short period of residence, to a larger amount of up to approx. £4000 depending on length of participation.

Different kinds of phase 1 studies:

1. SAD:

(Single Ascending Dose Studies)

Subjects in a SAD study receive only one dose of the study drug.

A SAD study is a type of phase 1 trial which is almost always performed first in order to obtain a rough understanding of a drug's single dose pharmacokinetics and the safe dose range. It is recommended to dose subjects sequentially with an appropriate period of observation between dosing of individual subjects.

For SAD studies, the starting dose is based on the pre-clinical and animal studies. For MAD studies, the starting dose is usually based on results from the SAD study.

2 .MAD:

(Multiple Ascending dose studies)

Subjects in a MAD study receive the same drug multiple times over a certain period, increasing the dose of the study drug at each administration.

A MAD study is a type of phase 1 trial typically performed following a single ascending dose (SAD) study. SAD and MAD studies are done to understand how the body tolerates and processes a drug.

It is recommended to dose subjects sequentially with an appropriate period of observation between dosing of individual subjects (sentinel dosing). This is carried out for each dose level for an adequate period of time. The recent EMA guidance emphasised routine use of sentinel dosing within each dosing cohort, for both single and multiple dosing.

Phase 2 clinical trials

- Phase 2 clinical trials represent a critical stage in drug development, following successful completion of Phase 1 safety studies. The primary goal is to evaluate the efficacy of the investigational product in a target patient population while continuing to assess its safety profile Optimize dosing regimens (dose-ranging studies).
- Further characterize short-term side effects and risks.
- Provide data for designing Phase 3 trials.

Design Features:

Typically involve 100 to 300 patients.

Often randomized and controlled, with placebo or standard-of-care comparators.

Can be double-blind to reduce bias.

Frequently use biomarkers or surrogate endpoints to assess activity.

Divided into:

Phase 2a (exploratory efficacy and dosing)

Phase 2b (confirmatory efficacy with more statistical power)

Challenges:

High attrition rates—approximately 30–40% of drugs fail in Phase 2 due to lack of efficacy.

Need for robust endpoint selection and trial design to avoid misleading results.

Patient recruitment and adherence can impact results.

Innovations:

Use of adaptive trial designs to allow modifications based on interim results.

Integration of real-world data and patient-reported outcomes.

Increasing emphasis on precision medicine and biomarker-driven subpopulations.

Phase 3 clinical trial:

Phase III clinical trials represent a pivotal stage in the drug development process. These are large-scale, multicentre, randomized controlled trials typically involving between 300 to over 3,000 participants, depending on the specific disease or medical condition being studied. The primary objective of Phase III trials is to deliver a definitive evaluation of a drug's efficacy compared to existing standard treatments, often referred to as the "gold standard."

Due to their extensive scope and longer duration, Phase III studies are among the most complex, costly, and time-intensive components of clinical research—especially when targeting chronic health conditions. It is not uncommon for these trials to continue even as the regulatory review process is underway at agencies such as the FDA (United States), TGA (Australia), or EMA (European Union).

Although not always mandatory, regulatory authorities generally expect results from at least two successful Phase III trials that confirm both the safety and efficacy of the drug before granting approval. Once these trials yield satisfactory outcomes, their findings are compiled into a comprehensive dossier. This document includes detailed accounts of preclinical and clinical studies, manufacturing processes, formulation characteristics, and product shelf life, and it serves as the basis for the regulatory submission.

Under FDA guidelines, drugs in Phase III trials may sometimes be made available on the market with specific recommendations and monitoring requirements. However, if any adverse effects are reported post-launch, immediate recall of the product is mandated. While many pharmaceutical companies are cautious about marketing drugs during this phase, it is not unusual to see drugs from ongoing Phase III studies made available under certain regulatory provisions.

In conclusion, Phase III trials represent the culmination of years of preclinical and early-phase clinical research, serving as the final and most crucial checkpoint before a new therapeutic agent can transition from experimental status to standard medical practice. The successful execution and interpretation of these trials not only validate the clinical utility of new interventions but also set the foundation for regulatory decision-making, public health policy, and

Phase 4:

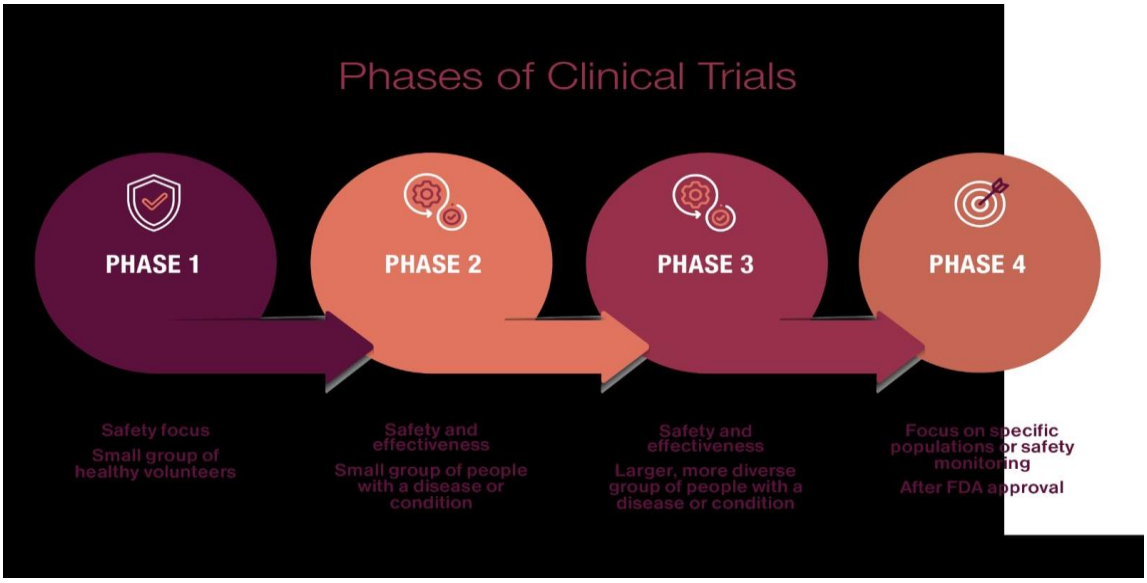
Phase IV clinical trials, commonly referred to as post-marketing surveillance studies, represent the final and ongoing phase in the lifecycle of a pharmaceutical product. These trials commence only after a drug has received regulatory approval for commercial distribution and focus primarily on the long-term monitoring of its safety, efficacy, and real-world impact across a broader patient population.

The central objective of Phase IV studies is to conduct comprehensive pharmacovigilance, which entails the systematic detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) that may not have been apparent during earlier phases of clinical development. These post-marketing investigations are particularly crucial for identifying rare, delayed, or population-specific adverse effects that may emerge only after prolonged and widespread use in routine clinical settings. Such effects often go undetected in Phase I–III trials due to the limited sample sizes, relatively short durations, and controlled environments inherent in those earlier phases.

Phase IV trials may be initiated as a regulatory requirement, particularly when conditional or accelerated approvals have been granted, or they may be voluntarily undertaken by pharmaceutical companies. Voluntary studies are often driven by strategic objectives, such as exploring additional therapeutic indications, evaluating the drug's performance in special populations (e.g., elderly individuals, pregnant women, or those with co-morbidities), or assessing potential drug–drug interactions. These studies also serve as a platform for collecting real-world evidence (RWE), which can support future labelling changes, guide clinical practice, and inform healthcare policy decisions.

In some instances, Phase IV trials have led to significant regulatory actions. When serious or previously unrecognized adverse events are detected, regulatory agencies may impose restrictions on the drug’s use, modify prescribing guidelines, or, in severe cases, mandate the withdrawal of the product from the market. Notable historical examples include cerivastatin (marketed as Baycol and Lipobay), troglitazone (Rezulin), and rofecoxib, all of which were withdrawn due to the emergence of life-threatening side effects during post-marketing surveillance.

Ultimately, Phase IV trials play a vital role in the continuous assessment of a drug’s benefit-risk profile. They help ensure that therapeutic interventions remain safe and effective in real-world conditions, beyond the controlled setting of clinical trials. This ongoing scrutiny is indispensable for maintaining public trust, refining clinical guidelines, and safeguarding patient health on a global scale.



Ethical Conduct in Clinical Trial

Clinical trials, especially those involving medical or therapeutic interventions, are stringently regulated and require approval from an ethics committee before commencing. These ethics committees oversee compliance and ensure participant safety throughout the study. While interventional studies require formal approval, observational or data-based studies may be supervised with greater flexibility at the discretion of the local ethics committee.

In the United States, Institutional Review Boards (IRBs) are typically based within the investigator's institution. However, smaller institutions may utilize central or independent IRBs approved by the sponsor. Ethical research mandates obtaining fully informed consent from all participants. One of the primary responsibilities of the IRB is to ensure that participants are properly informed about the study. In cases where individuals are unable to provide consent themselves, authorization must be obtained from a legally authorized representative, as prioritized by state regulations (e.g., in California).

Additionally, in some jurisdictions within the U.S., researchers and their staff are required to undergo certification by the local IRB before initiating any clinical studies. This includes understanding the federal regulations related to patient privacy under the Health Insurance Portability and Accountability Act (HIPAA), as well as adhering to Good Clinical Practice (GCP) guidelines.

Globally, clinical trials are expected to comply with the International Council for Harmonisation's Good Clinical Practice (ICH-GCP) standards. These guidelines are designed to protect the rights, safety, and wellbeing of all trial participants. Ethical principles outlined in the Declaration of Helsinki by the World Medical Association also serve as a foundational guide for conducting clinical research.

COMPLIANCE WITH PROTOCOL

The investigator/institution should conduct the trial in Compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority (ies) and which were given approval/ favourable opinion by the

IRB/IEC. The investigator/ institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The investigator should not implement in deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval / favourable opinion from the IRB / IES of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subject, or when the change(s) involves only logistical or administrative aspect of the trial (e.g. change in monitor (s), change of telephone no.(s).The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/ favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment(s) should be submitted.

1. To the IRB/IEC for review and approval/favourable

Opinion.

2. To the sponsor for agreement.

3. To the regulatory authority (IES).

ICH GCP GUIDELINES

The principals of ICH GCP --

1. Clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement.

2. 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.

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

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

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

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

7. The medical care given to and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician, or when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks.

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

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

11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement.

12. Investigational products should be manufactured,

Handled, and stored in accordance with applicable good manufacturing practice.

13. Systems with procedure that assures the quality of every aspect of the trial should be implant

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E1A: The Extent of Population Exposure to Assess Clinical Safety

E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

E2B: Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

E3: Structure and Content of Clinical Study Reports

E4: Dose-Response Information to Support Drug Registration

E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

E6: Good Clinical Practice: Consolidated Guideline

E7: Studies in Support of Special Populations: Geriatrics

E8: General Considerations for Clinical Trials

E10: Choice of Control Group in Clinical Trials

M1: Standardization of Medical Terminology for Regulatory Purposes

M3: Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for conduct of human Clinical trials for pharmaceutical.

Conclusion:

Clinical trials for a new drug are conducted in accordance with ICH-GCP (International Council for Harmonisation - Good Clinical Practice) guidelines and are carried out on human volunteers. Before entering clinical trials, the drug undergoes preclinical testing. Following this, it proceeds through Phases 1, 2, 3, and 4 of clinical trials. Each of these phases helps to systematically evaluate the drug's pharmacodynamics and pharmacokinetic characteristics, as well as its safety, efficacy, and potential side effects.

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