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A REVIEW ON: CLINICAL TRIALS: PHASES, ETHICS, AND CHALLENGES

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ABSTRACT

Evidence-based medicine relies on clinical trials to gather the necessary information about new medications, biologics, devices and treatments regarding their safety, and efficacy. This article describes the various phases of clinical trial development along with the ethical principles that guide the structure of these trials and key factors considered during the conduct of these trials. Clinical trials begin with preclinical testing and continue through Phase 0 through Phase IV of clinical development with each phase having specific objectives, including safety, efficacy, verification and long-term follow-up monitoring. While scientific based, clinical research has been developed using ethical principles derived from previous mistakes and from the application of the principles of justice, informed consent and the use of Independent Ethical Committee (IEC) reviews to protect the welfare of the participant. Unfortunately, clinical trials experience many problems, including extended time frames, expensive costs, complicated regulations, and substantial issues related to patient recruitment and retention. However, new methods of conducting clinical trials (such as decentralized trials, utilizing Artificial Intelligence, or adaptive designs) are being introduced to enhance the efficiency and inclusivity of clinical trials. Ultimately, clinical trials carried out under ethical standards have an impact on the ability to guarantee that new treatments will be both effective and safe, as well as be available to the populations that benefit from them.

KEYWORDS: Clinical Trials, Phases of Clinical Trials, Research Ethics, Informed Consent.

INTRODUCTION

Developing a novel medication is among the most important and ambitious enterprise humans engage in. It is a process involving the transformation of a scientific idea, developed in the laboratory, into a clinical solution that can relieve pain, cure illness, and save lives. At the centerpiece of this process, is the clinical trial. A carefully designed and controlled research project in human subjects designed to provide a scientific answer to the two most important questions that everyone desires to know: "Is it safe?" and, "Does it work?". Clinical trials are the crucial bridge between scientific theory and medical practice and offer the definitive evidence to translate between useful treatments and useless or harmful treatments.

Clinical trials are the foundation of evidence-based medicine. Before any new drug, vaccine, or medical device can be used in the general public, it must undergo this process of scientific testing. Usually, the questions of safety and effectiveness cannot be assumed from laboratory testing or animal studies as the human body is a much more complex biological system. Clinical trials are more than a formality. They are an essential step and cannot be avoided in the progress of modern medicine. Clinical trials provide assurance that medicines used in practice are not only innovative but safe.[1]

The journey from discovering a molecule to having it available at your local pharmacy is a long, complex, and expensive process, sometimes taking over a decade and costing billions of dollars.[18] This trajectory is carefully mapped out in a series of defined steps known as the

phases of clinical development. The phased approach is meant to minimize risk and maximize learning, starting with small studies that focus mainly on safety (Phase I), followed by larger studies that focus on safety and efficacy (Phases II and III) This thoughtful, stepwise approach ensures that a potential treatment is thoroughly evaluated and vetted before it is allowed into widespread use.[2]

Additionally, the International Council for Harmonisation developed Good Clinical Practice (ICH-GCP) guidelines which have established an international standard of quality expectation for the design, conduct, monitoring, and reporting of clinical trials These guidelines help facilitate the establishment of data integrity, while maintaining consistency for participant protections globally, including the United States and Europe to India.[3]

Although clinical trials are essential to drug development, executing the studies is often problematic. Patient recruitment and retention are common bottlenecks that can delay the trial, lengthen timelines, and subsequently increase costs overall. The large financial implications, as well as lengthy and arduous timelines during the drug development process, are always a significant concern. Additively, operational challenges concerning logistics, data management, and the compliance with the multiple rules of various countries all complicate the overall process These issues can delay the drive for new innovation and also delay the delivery of life-saving treatments to patients.[4]

LITERATURE REVIEW

1. Wang et al. presented a the structured transition of a drug from laboratory research to human testing. The paper highlights clinical trial phases, adaptive trial designs, and modern tools such as AI and biomarkers that improve efficiency and safety. The authors emphasized the importance of ethical oversight and regulatory compliance in ensuring reliable and patient-centered outcomes.[1]
2. Dhadambe et al. presented study design, ethical considerations, as well as post marketing surveillance. The authors discussed guiding principles of ICH-GCP and WHO guidelines that will assure global trial harmonization. The paper also covered current innovation such as an AI-based monitoring system, remote data collections, and decentralized trial options. All of which have contributed towards making trials more efficient, than ever while maintaining participant safety.[2]
3. Rohilla et al. provided a comprehensive review on the Phases of Clinical Trial, discussing each phase (I-IV) in terms of objectives, subject size, study duration, and study design. Their work traces the steps from a traditional single center study through multicenter study to an adaptive trial. The authors emphasized that each phase contributes to the goals of assuring safety, efficacy, and therapeutic benefit before market authorization.[3]
4. Iftikhar et al. wrote an assessment on Clinical Trials for Medical Materials, which focused on study of biomaterials and medical devices within different phases of a trial. The paper provided details of how trials evaluate toxicity and compatibility and functional efficiency of materials used in an implant or device population. The authors highlighted how regulated studies differ between drug trials and device/material trials and the significance of specialized safety testing and long-term evaluation of performance.[4]
5. Lind documented citrus fruit supplementation was proven effective in treating scurvy among sailors. His study introduced organized comparison groups and outcome-based evaluation, becoming the foundation for modern clinical trial methodology and evidence-based practice.[5]
6. Barkan I.D. presented an influential historical analysis widespread public health scandals and unsafe drug practices led to major legislative reform in the United States, resulting in the first national law enforcing drug purity and safety. This landmark event marked the beginning of structured regulatory oversight and laid the foundation for modern clinical trial regulation and pharmaceutical accountability.[6]
7. Weindling P. provided atrocities of non-consensual human experimentation during World War II and how the Nuremberg Trials established voluntary participation as an ethical and legal obligation. The study highlights how the Nuremberg Code became the first formal international ethical guideline protecting participants, reinforcing that scientific progress cannot occur at the expense of human welfare.[7]
8. The World Medical Association developed the Declaration of Helsinki, a cornerstone ethical document that guided responsible human research and introduced crucial concepts such as independent ethical review, risk-benefit analysis, and participant welfare above scientific priority. This document continues to serve as the universal standard for ethical research worldwide and influences national laws, regulatory committees, and modern clinical trial frameworks.[8]
9. Salhia and Olaiya addressing how ethical guidelines evolved in low-resource countries and the importance of equitable participation in global clinical research. Their study emphasized disparities in research environments, exploitation risks, and the need for culturally sensitive ethical review systems in multinational trials, especially within vulnerable populations.[9]
10. Ravinetto R.A. critically evaluated the revision of ICH-GCP guidelines, pointing out limitations in adapting the framework to modern challenges such as decentralized trials, digital technologies, transparency requirements, and global regulatory inequality. The paper argues that revisions missed an opportunity to strengthen protections for participants

in developing countries and highlights the need for actionable reform in global harmonization.[10]

11. Evangeline et al. investigate the Regulatory Process and Ethics for Clinical Trials in India. Their study describes the steps involved in obtaining trial approval, obtaining ethical review through an Institutional Ethics Committee (IEC), and the requirement to register in the Clinical Trial Registry of India (CTRI). The paper reveals the development of regulatory issues that arose in India after 2013 and involved the introduction of compensation and transparency norms to ensure participant safety and data integrity.[11]
12. Fayad et al.'s article about Phases of Clinical Trials directly addresses translational pulmonology. It highlights how the trial model applies to respiratory disease studies and what endpoints such as lung function tests, imaging biomarkers, and patient-reported outcomes are applicable. This article illustrates how real-world applicability of phase-based clinical research (and more) makes it possible to translate laboratory discoveries into therapeutic practice in pulmonary medicine.[12]
13. Institute of Medicine addressing structural barriers in clinical research including rising costs, slow recruitment, and growing complexity of trial execution. The report emphasized the urgent need for modernization of trial processes and improved collaboration frameworks to support faster delivery of innovative therapies.[13]
14. Moreno, Schmidt & Joffe reviewed the lasting legacy of the Nuremberg Code in "The Nuremberg Code, 70 Years Later", demonstrating how ethical reflection continues to shape research norms in the modern scientific era. The authors reinforced the continued relevance of voluntariness, informed consent, and respect for persons in contemporary biomedical innovation.[14]
15. White explained the importance of human subject protection in medical research, addressing vulnerabilities in participant understanding, especially in low-literacy groups and under-resourced healthcare settings. The paper emphasizes education, transparency, and fairness as critical elements needed to safeguard public trust and ethical study conduct.[15]
16. The Belmont Report provided the foundational ethical principles—Respect for Persons, Beneficence, and Justice—forming the philosophical framework for safeguarding research participants in clinical trials and governing informed consent, fair participant selection, and risk-benefit transparency. These principles remain the backbone of ethical clinical science.[16]

HISTORY AND DEVELOPMENT OF CLINICAL TRIALS

Table no. 1: Event and Their Impact.[11]

Period	Milestone Event	Impact
1747	First controlled clinical trial	Foundation of experimental medicine
1906	U.S. Pure Food and Drug Act	Drug quality and purity control
1947	Nuremberg Code formulated	Voluntary consent becomes mandatory
1964	Declaration of Helsinki	Ethical conduct in human research was established
1979	Belmont Report	Introduced core principles
1996	ICH-GCP Guidelines	Standardized ethical & scientific practices
2019	Clinical Trial Rules, India	Introduced compensation & transparency mandates

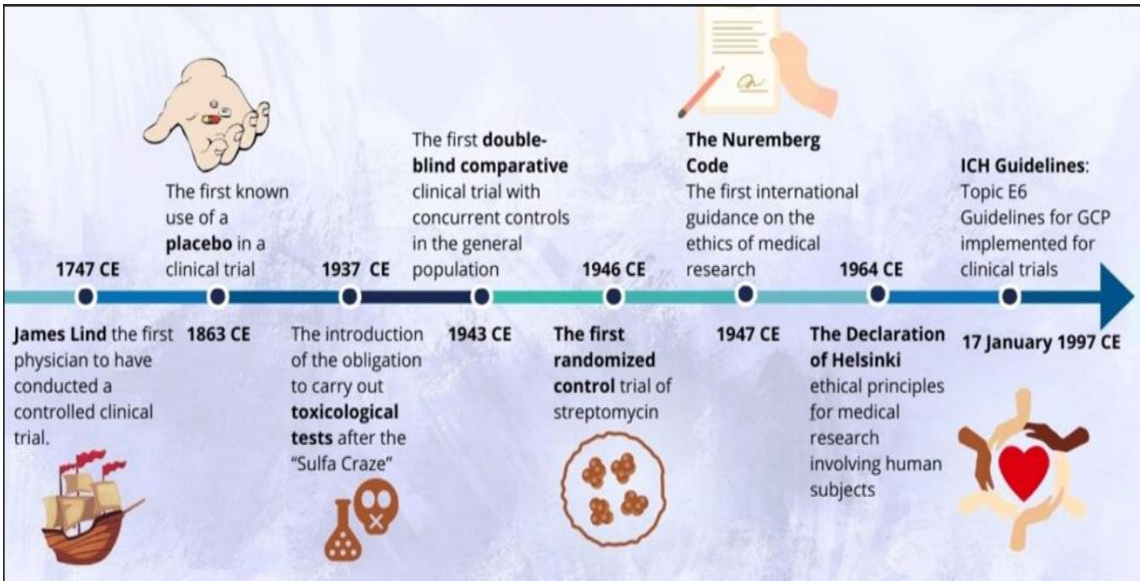

Fig. no. 1. History in clinical Trials.

PHASES IN CLINICAL TRIALS

Clinical trial processes are sequenced in phases, which have been designed both scientifically and ethically. Each phase has a special role in evaluating the safety, effectiveness, dosage, pharmacokinetics, and long-term human effects of a drug. This careful approach establishes a systematic progression of events whereby only medicines with an exceptional standard will be made available to the public.

Before entering human trials, a drug candidate will undergo preclinical studies in a laboratory or animal model to evaluate possible biological activity, toxicity, or pharmacological profile. The sponsor, once they possess sufficient evidence of safety, will then submit their application for the investigational new drug (IND) to the relevant governing body (e.g. CDSCO in India or FDA in the USA) to be granted permission to initiate clinical trials on human subjects.

1. Preclinical Studies (Before Human Testing)

Prior to initiation of human studies, a drug must first undergo preclinical research, involving testing in laboratory and animal models, to assess its pharmacological and toxicological profile. These tests evaluate how the drug behaves in the body (ADME—absorption, distribution, metabolism, and excretion) and potential toxic effects on major organs, such as liver, kidneys, and heart.

All preclinical studies must follow Good Laboratory Practice (GLP), and once enough safety data is gathered, the sponsor submits an Investigational New Drug (IND) application with the regulatory authority (e.g., CDSCO in India, or FDA in the U.S.) to obtain approval.[12]

2. Phase 0 – Exploratory or Microdosing Studies

Phase 0 is an exploratory first-in-human study that collects early data on the behavior of an investigational drug in humans. Generally, less than 20 healthy volunteers receive very small, sub-therapeutic doses of drug (less than 1% of the pharmacologically effective dose) in Phase 0 studies. The primary goal is not to test efficacy, but rather to examine pharmacokinetics, which is how a drug is absorbed, metabolized, and eliminated.[13]

3. Phase I – Safety and Dosage Determination

Phase I is the first formal testing stage among humans, with the aim of assessing the investigational drug for safety, tolerability, and dosage range.[2–4,8] This approximately involves 20–100 healthy volunteers, unless the drug is highly toxic (e.g., an anti-cancer drug), in which case the investigator may instead include patients from the target indication rather than healthy volunteers.

Phase I studies generally last between 6 months to 1 year. The Phase I study will be used to determine that the drug is safe for the next phase of development by identifying the safe dosage and dosing schedule. If severe or unpredictable events are experienced in Phase I, that will effectively stop the development of the drug.[14]

4. Phase II – Therapeutic Exploration

Upon successfully exhibiting safety during Phase I, the drug is then advanced to Phase II, which examines therapeutic efficacy, and dose optimization.[1,2,4] In this phase, a larger sample of 100-300 patients who actually have the disease or condition of interest is included. The main goals are to assess the drug's efficacy and to continue to assess safety.

Typically Phase II lasts 1 to 2 years. If the investigational drug demonstrates a large enough therapeutic benefit with acceptable safety the trial will then be advanced to Phase III. Otherwise, the development of the investigational drug may or may not be continued.[15]

5. Phase III – Confirmatory Clinical Trials

The most important and resource intensive of clinical product development is Phase III clinical trials. The goal of this phase is to validate the drug's effectiveness, conduct an investigation of adverse effects, and compare results with either standard therapy or placebo within an extensive patient population that includes different demographics. Phase III trials usually include 1,000–3,000 patients treated across numerous hospitals, oftentimes in various different countries, so they are multicentric and internationally coordinated.

Data generated during Phase III trials is utilized to form a New Drug Application (NDA) or Marketing Authorization Application (MAA) to submit to regulatory and/or governing agencies (FDA, EMA, CDSCO) for regulatory review. If Phase III trials validate significant clinical benefit (positive benefit-risk ratio) with an acceptable safety profile, then the drug is approved for marketing. If severe adverse effects emerge during Phase III trials, then the process will stop, or funding agencies may require further studies.[16]

6. Phase IV – Post-Marketing Surveillance

After a drug has been received approval and is available on the market it enters Phase IV or post-marketing surveillance stage. This phase of drug development is meant to help continue the assessment of the drugs long-term safety, efficacy, and rare side effects in the general population.

Phase IV studies might cause changes to product labelling, increase or decrease dosage, have a warning placed on the drug or remove it from the market entirely. One example of this is that the pain killer Rofecoxib (Vioxx) was removed from the market following post-marketing studies indicated increased risk of cardiovascular complications.[17]

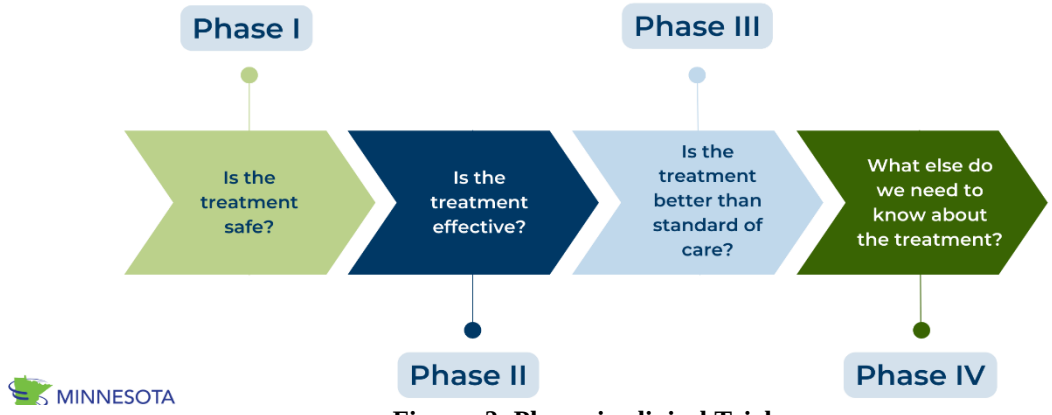

Fig. no. 2: Phases in clinical Trials.

ETHICS IN CLINICAL TRIALS

Ethics are central to the process of conducting clinical trials. When human subjects are part of scientific research studies, it is the highest obligation of researchers to respect and protect human dignity, safety, and rights. Clinical trials may be intended to provide medical innovations, but no hypothesis justifies human suffering or exploitation for the sake of progress. Ethics make medical research humane — every trial, every experiment, and every datum is respectful of the life behind it.

The recognition of the necessity for ethics in clinical trials has been influenced by innovation and traumatizing lessons learned from research gone wrong throughout history. In the early days of the medical research field, few guidelines or oversight systems existed, and researchers partook in many unethical inquiries. One particularly heinous example is the Nazi medical experiments conducted during World War II, where prisoners were subjected to extremely harmful procedures without informed consent to determine how long it would take for their bodies to die. Following WWII, the Nuremberg Trials (1947) brought these horrors to light and led to the first formal ethical framework and review in research, the Nuremberg Code, which stipulated that voluntary consent is essential.

1. Core Principles of Research Ethics

Three principles of modern research ethics derived from the Belmont Report (1979) are Respect for Persons, Beneficence and Justice.

Justice refers to fairness - in the selection of participants and in who benefits from the results. No group of people should be unfairly burdened simply because they are economically disadvantaged, less educated, and/or a convenient group to study. Likewise, benefit of research findings should be shared by all groups participating in medical interventions and studies.[18]

Together, the three principles form a moral framework for clinical research.

2. Major International Ethical Guidelines

After the tragedies of the early 20th century, the world began developing strong international ethical norms in the conduct of research.

Then in 1996, the International Council for Harmonisation (ICH) formalized Good Clinical Practice (GCP) guidelines - a singular global standard that ensures the clinical trial is based on sound scientific and ethical standards. The ICH-GCP principles are now recognized worldwide, ensuring that participants' rights, integrity, and confidentiality are protected no matter where the study takes place.[19]

3. Informed Consent – The Heart of Ethical Research

The notion of informed consent sits at the heart of all ethical clinical trials. This principle supports a person's voluntary participation based on a full understanding of what they are agreeing to. Informed consent is more than just the act of signing a form; it is about understanding and communication.[20]

It is important to note that informed consent is an ongoing process, not an experience that happens just one time. If during a trial new information arises that may affect a participant's decision, the researcher must disclose this information and permit the participant to decide whether they wish to continue. This demonstrates respect for human autonomy and dignity.[20]

4. Ethics Committees and Institutional Review Boards

To ensure that research is conducted ethically, clinical trials must be approved by an independent committee (an Ethics Committee (EC) or Institutional Review Board (IRB)). They are the guardians of participant safety. An ethics committee is usually comprised of physicians, scientists, legal professionals, social workers, and even laypersons to provide a fair consideration of all perspectives of the study.

All ethics committees in India must be registered with the Central Drugs Standard Control Organization

(CDSCO) as per the New Drugs and Clinical Trials Rules of 2019. The rules have improved transparency and accountability, ensuring that approved studies adhere to ethical standards that are acceptable in both national and international settings.[21,22]

5. Ethical Framework in India

India observes ethical practices that are recognized worldwide applied to their local context. The combination of these frameworks positions India as a world leader in ethical and high-quality global clinical research.[21]

6. Modern Ethical Challenges

With advances in technology and globalization, new ethical dilemmas continue to arise. Today, many clinical trials are multi-national in scope (e.g., aimed at a single outcome yet conducted in more than one country) and often involve populations with different cultural values and or economic contexts. The investigator should be sure that persons enrolled in clinical trials are protected, regardless of location, and contributions are not exploited simply for the sake of convenience or cost.[21]

An ongoing debate, often situational in practice, is an issue of post-trial access. Once the study is complete, should participants of an ethical study that produced positive outcomes have access to that intervention? Benefits, derived using elements of ethical research, should be distributed fairly to potential beneficiaries of that resource, particularly if the individuals aided in producing the discovery.[22]

REGULATORY GUIDELINES AND BODIES

Regulatory guidelines and oversight play a key role in the ethical, safe, and scientific conduct of clinical trials. The regulatory systems offer a structured legal framework to protect subjects, observance of evidence-based therapeutic standards, and with an expectation that data generated will be of sufficient quality to inform drug approval discussion.

In most jurisdictions, the oversight authority will review the scientific design and ethical protections verified to balance the risk and benefit ratio and feasibility of executing a clinical trial.[23]

1. International Guidelines

The International Council for Harmonisation (ICH) **introduced the globally accepted** Good Clinical Practice (GCP) guidelines, which outline the scientific and ethical requirements for designing and conducting human trials. ICH-GCP ensures that participant rights are protected and that data generated are credible and reproducible across countries.[23]

The Declaration of Helsinki**,** issued by the World Medical Association, remains the foundational ethical document for clinical research. It mandates voluntary informed consent, independent ethics review, and prioritizing participant well-being over scientific interests.[23]

These guidelines continue to influence national regulatory frameworks and reinforce ethical safeguards worldwide.

2. National Regulatory Authorities

Countries maintain dedicated agencies to oversee clinical trials:

- **India – Central Drugs Standard Control Organization (CDSCO):** Oversees trial approvals, ensures ethical compliance, and enforces the New Drugs and Clinical Trials Rules, 2019. These rules strengthen participant protection, streamline approvals, and increase transparency in trial conduct
- **United States – Food and Drug Administration (FDA):** Regulates clinical research through Investigational New Drug (IND) applications and ensures adherence to safety and reporting standards.
- **European Union – European Medicines Agency (EMA):** Coordinates centralized trial approvals and harmonizes clinical trial practices across member states.
- **Japan – Pharmaceuticals and Medical Devices Agency (PMDA):** Ensures scientific and regulatory harmonization under ICH principles.

These bodies ensure that trials meet legal, ethical, and scientific requirements before participants can be enrolled.[24]

3. Ethics Committees and Institutional Review Boards

Ethics Committees (ECs) or Institutional Review Boards (IRBs) provide independent ethical oversight. They review trial protocols, consent documents, investigator qualifications, and risk–benefit assessments before granting approval.

Ethics committees also monitor ongoing trials by reviewing adverse event reports and ensuring participant safety throughout the study. In India, ECs must be registered with CDSCO and follow ICMR's national ethical guidelines for biomedical research.[24]

4. Clinical Trial Registries

To promote transparency and prevent selective reporting, clinical trials must be registered in publicly accessible databases:

- India: The Clinical Trials Registry – India (CTRI) ensures mandatory pre-registration of all trials conducted in the country
- USA: ClinicalTrials.gov provides global visibility into trial protocols and results.
- EU: The EU Clinical Trials Register functions similarly for studies conducted in Europe.

Registries help reduce publication bias and strengthen public trust in clinical research.

5. Regulatory Inspections and Compliance
Regulators conduct periodic audits and inspections to ensure compliance with GCP, approved protocols, and national laws. Non-compliance can lead to trial suspension, rejection of data, or legal penalties. Sponsors and investigators must maintain detailed documentation, ensure proper monitoring, and uphold participant safety at all times.[23,24]

6. Role in Drug Approval
After clinical trials conclude, regulatory authorities evaluate safety, efficacy, and quality data to determine whether a drug can be approved for marketing. Post-marketing surveillance requirements ensure continued monitoring of safety, enabling authorities to detect rare adverse.

Effects and update guidelines or restrictions as needed.[25]

CHALLENGES IN CONDUCTING CLINICAL TRIALS

Clinical trials are the basis for evidence-based medicine, but they are a large and complicated undertaking. Despite being a vital part of the development of new treatments, clinical research has many scientific, logistical, financial, and ethical challenges. Each step from preparation to recruitment, data collection, and approval can face challenges that delay results, increase costs, and in some cases cause potential therapies from withstanding the test of time before they are able to help patients. In order to help researchers to design and conduct clinical research, it is essential to understand the challenges researchers face.[26]

1. Patient Recruitment and Retention
One of the major obstacles to conducting clinical research is the effort it takes to find and retain qualified participants. Finding sufficient volunteers who meet a series of eligibility criteria is often resource-intensive and time-consuming. In fact, many clinical trials never meet their target enrolment numbers, and as a result, studies either extend to a later finish date, or are ultimately stopped prematurely.

As the study design is weighted with low recruitment or high dropout rates, researchers and investigators cannot obtain adequate statistical power, as it becomes impossible to brief implications when less information exists. Scholars are now looking into digital outreach, decentralized or virtual models DCTs, and community model programs to address the lack of public awareness and experienced complexity for potential participants.[26]

2. High Cost and Long Duration
Performing a clinical trial is a costly endeavor that generally takes several years. The total cost of drug development, encompassing every stage of development and approval (including Phase III trials), is estimated to be in excess of 2 billion dollars and typically requires 10-15 years. A significant proportion of these costs are related to clinical trials.

Not surprisingly, any delays to participant recruitment, protocol deviations, or delays related to required regulatory approval can increase the bottom line significantly. If a drug fails during the latter stages of development, especially Phase III trials the loss is considerable. A key consideration for pharmaceutical companies and academic research institutions is trying to balance the need for sufficient review with financial viability is one of the most challenging logistical considerations.[27]

3. Complex Regulatory Requirements
Clinical research is subject to many rules and regulations, which are meant to keep participants safe and ensure high-quality data. Although such regulations are necessary, they can tend to be complicated and lengthy to work through. Each country, for example, has their own regulatory authority - e.g., the data regulatory agencies may be FDA (United States), EMA (Europe), CDSCO (India) - each agency/incorporating agency with their own rules and timelines for submitting information, documentation, responses, and approval of the study.

To remedy this in the research, various "harmonization" efforts have created discussions about running a single trial, the International Council for Harmonisation (ICH), and Good Clinical Practice (GCP).[19] Nevertheless, the inconsistency of compliance will continue to be a challenge moving forward, especially in low- and middle- income countries who have a developing infrastructure.[27]

4. Ethical and Safety Concerns
The protection of ethical integrity and participant safety is fundamental to every clinical trial while also presenting one of the greatest challenges. Trials must ensure participants understand the risks involved and freely provide informed consent. However, in reality, many participants may not fully comprehend the intricacies of the science that is reported, especially in populations with low literacy or access to the healthcare system.[28]

The increasing trend of utilizing digital technology and remote monitoring also creates ethical dilemmas surrounding data privacy, data security, and confidentiality. Protecting confidential and sensitive health data to avoid abuse or unauthorized access has become a contemporary ethical issues.

5. Data Management and Quality Control
One of the significant challenges in contemporary clinical research is the collection and management of large amounts of data, ranging from laboratory results and imaging studies to patient-reported outcomes and electronic health records, in a secure, accurate, and efficient manner. Meticulously entering this data

manually opens the door for human error, while electronic means of data collection introduce significant cost and time investments in both systems and training staff to use them properly. Even data collected by the same organization across multiple study sites can be inconsistent and hinder the reliability of results.[28]

6. Globalization of Clinical Research

Presently, numerous clinical trials are run in several countries to facilitate recruitment, ratio of patient population, and temporal generalizability of the study. While this approach may enhance external validity, it also comes with logistical and cultural challenges.

Importantly, international shipments of biological samples, or investigational drugs, are determined by international shipping and edibility standards while limiting the timeframe (ideally) with regions where each item is imported and exported to be used in the clinical trial. Any delays in receiving or shipping samples or investigational drugs may diminish the validity of data in the study or disrupt the timeline.[29]

7. Technological and Logistical Barriers

The emergence of technology has not only enhanced the efficiency of clinical trials but has also created new challenges. Advanced tools like electronic data capture (EDC) systems, wearable health sensors, and telemedicine platforms all require various levels of training, reliable internet access, and measures to mitigate cybersecurity.

In addition, researchers must consider whether the use of technology perpetuates an unintentional exclusion of populations without access to digital technology ensuring equity and inclusivity is just as vital to technology use as innovation.[29]

8. Post-Trial Challenges

Challenges remain even after a clinical trial concludes. Post-marketing surveillance (Phase IV) studies are necessary to assess long-term safety and identify uncommon side effects that may not have been detected in earlier stages. However, obtaining genuine real-world data necessitates collaboration with clinicians and patients.

Transparency and non-bias in the reporting of trial results is another critical ethical consideration. Selective reporting, where only the positive outcomes of a trial are published, could mislead patients and/or healthcare providers. A focus on open sharing of data as well as trial transparency is important in order to maintain trust of the public in science.[30]

9. Impact of COVID-19 on Clinical Trials

The COVID-19 pandemic brought about many shortcomings in the conventional clinical trials system. Lockdowns and travel restrictions, as well as patients who were wary of attending hospitals during the pandemic, hindered ongoing trials and cycled in delays for initiating new trials. Many participants would miss data collection due to visits not occurring, due to closures, travel restrictions and patients not wishing to attend the hospital.

The ultimate net effect was a substantial push towards innovations (virtual trials, remote monitoring, following-up through telemedicine) that could demonstrate that adaptable patient-centred trial designs can operate safely in a time of crises. The future challenges are merging these innovations with ethical and scientific rigour in trials.[30]

Fig. no. 3: Challenges in Clinical Trials.

RECENT ADVANCES IN CLINICAL RESEARCH

Clinical research has evolved significantly in the past decade, driven by rapid technological progress, global collaboration, and a stronger focus on patient-centric approaches. Modern clinical trials are now faster, more efficient, and more adaptable than ever before. These advancements aim to overcome longstanding challenges such as high costs, slow recruitment, limited diversity,

and issues of data accuracy. Innovations in digital technology, artificial intelligence, biomarker-driven studies, and regulatory modernization are reshaping how clinical trials are designed, conducted, and monitored

1. Artificial Intelligence and Machine Learning in Clinical Trials

Artificial intelligence (AI) has become one of the most transformative developments in modern clinical research. AI tools are now used to analyze complex datasets, predict patient outcomes, optimize trial design, and automate monitoring. Machine learning models can rapidly identify potential drug targets, simulate biological responses, and increase the accuracy of early-phase decision-making.[31]

2. Advanced Data Analytics and Real-World Evidence

The availability of large-scale digital health records, insurance databases, and wearable-generated data has made real-world evidence (RWE) an important part of modern clinical research. RWE complements traditional trials by providing insights into how treatments work in diverse populations and real-life conditions.

Regulatory authorities increasingly use RWE to support drug approvals, post-marketing surveillance, and decision-making. Sophisticated data pipelines now allow continuous data capture, automated cleaning, secure storage, and rapid analysis — all aligned with international GCP and ethical standards.[31,32]

3. Decentralized and Digital Clinical Trials (DCTs)

Digital health tools — such as remote monitoring devices, mobile apps, ePRO systems (electronic patient-reported outcomes), and digital consent platforms — make it easier to collect real-time data and improve patient engagement. DCTs have become especially popular after the COVID-19 pandemic, which highlighted the need for more flexible and resilient trial structures. Regulatory bodies in India and worldwide have updated guidelines to support virtual monitoring and digital documentation, improving transparency and participant safety.[32]

4. Biomarker-Driven and Precision Medicine Trials

Advances in genomics, proteomics, and molecular diagnostics have enabled precision medicine trials, where treatments are tailored to the specific biological characteristics of each patient. Biomarkers help researchers identify which individuals are most likely to benefit from a particular therapy, improving efficacy and reducing unnecessary exposure to ineffective treatments.

This approach is especially valuable in oncology, where biomarker-based early-phase trials are growing rapidly across BRICS nations and globally. Adaptive trial designs allow researchers to modify protocols based on interim results, making trials more efficient and ethically responsive.[32]

5. Improved Early-Phase Trial Designs

Early-phase studies (Phase 0, I, and II) have undergone major modernization to improve safety and speed. Microdosing studies, adaptive dose-escalation models, and innovative pharmacokinetic modeling tools have made early phases more predictive and informative. These advancements reduce participant risk, shorten development timelines, and help quickly identify whether a drug has real therapeutic potential.[33]

6. Strengthening of Ethical and Regulatory Frameworks

Recent years have seen major improvements in ethical oversight and regulatory harmonization, ensuring trials remain safe and transparent even as technology evolves.

In India, the New Drugs and Clinical Trials Rules (2019) and updated CDSCO policies have streamlined approvals, strengthened ethics committee oversight, and mandated compensation for trial-related injuries. These reforms have made India a competitive and trusted location for global clinical research while ensuring high protection for participants.[34,35]

7. Global Collaborative Research Networks

International collaborations are increasing rapidly, allowing researchers to conduct large, multi-country, multi-center trials. Global oncology networks, BRICS research partnerships, and cross-continental regulatory harmonization contribute to faster recruitment, more diverse data, and stronger scientific conclusions.[35]

CONCLUSION

Clinical trials play an integral role in how we currently view modern medicine; they act as a bridge between scientific discovery and real-world application to provide the data necessary to ensure that new medications, vaccines, and medical devices are safe and effective. Each step in the clinical trial process contributes to protecting the safety and interests of patients: from Phase I (the first time a new product will be administered to a human) through Phase IV (long-term follow-up). The ethical principles of respect for persons, beneficence, and justice, along with scientific rigor, support patient protection and build trust with the public for these types of studies. Important historical documents, such as the Nuremberg Code, Declaration of Helsinki, and the ICH-Good Clinical Practices, have changed clinical trial operations to one that is accountable, transparent, and compassionate.

While clinical trials provide critical data for the advancement of medical science, the current operational structure includes many challenges, such as high cost; long timeframes; participant recruitment; complex regulatory requirements; and data management issues. The continued application of integrity, transparency, and empathy will allow clinical research to remain a driver of medical advancements while providing protection to humankind.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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