A Comprehensive Review on Basic Concept and Requirements of Clinical Trials Study

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Abstract

A clinical trial is a research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are fastest and safest way to find treatment that work in people and way to improve health. Investigational trials determine whether experimental treatment or new ways of using known therapies are safe and effective under controlled environment. Observational trials address health issues in large groups of people or population in natural settings. Clinical trials aim to measure therapeutic effectiveness and constitute an important and highly specialized form of biological assay. In phase I pharmacokinetics, safety, gross effects are studied on human volunteers, by clinical pharmacologists. If the drug passes the test, it enters phase II testing's, where pharmacokinetics, safety, therapeutic efficiency is studied on selected patients by clinical pharmacologist, if passes hundreds of selected patients are now studied, primarily for safety and therapeutic effectiveness by clinical investigators in phase III. If this is passed the drug is now approved and marketed. Even after marketing, physicians from various hospitals and clinics send their opinion about the drug, regarding ADR (Adverse drug reaction), efficacy in phase IV [1].

Keywords: *Clinical trials, Therapeutic, Clinical pharmacologist, Pharmacokinetics, ADR (Adverse drug reaction), Efficacy.*

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1. Introduction

Clinical trials are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes. People volunteer to take part in clinical trials to test medical interventions including drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments and preventive care [2].

Clinical trials are carefully designed, reviewed and completed, and need to be approved before they can start. People of all ages can take part in clinical trials, including children.

Participants in a clinical trial receive specific interventions based on the research plan or protocol developed by the investigators. Medical products, such as drugs or devices, procedures, or changes in participant behavior, such as diet, are examples of interventions. Clinical trials may compare a new medical approach to an existing standard, to a placebo containing no active ingredients, or to no intervention. Some clinical trials compare interventions that are already on the market. When a new product or approach is being researched, it is not always clear whether it will be beneficial, toxic, or no different from existing alternatives. The investigators attempt to determine the intervention's safety and efficacy by measuring specific outcomes in the participants. For instance, researchers may administer a drug or treatment to participants with high blood pressure to see if their blood pressure drops.

Clinical trials used in drug development are sometimes classified according to phase. The Food and Drug Administration defines these stages (FDA).

Some people who are not eligible to participate in clinical trials may be able to obtain experimental drugs or devices through better accessibility [3].

2. Preclinical studies

Preclinical studies are performed in in vitro, in vivo, ex vivo, and in silico models to obtain basic information about the safety and biological efficacy of a drug candidate before testing it in a final target population, i.e., humans. Preclinical studies or tests are mainly performed in compliance with GLP/GSP guidelines (good laboratory practice and good scientific practices) to ensure reliability and reproducibility of results. The FDA/EMA require supporting basic preclinical data to IND application especially on toxic effects, safety profile, pharmacokinetics, and pharmacodynamics [4, 9].

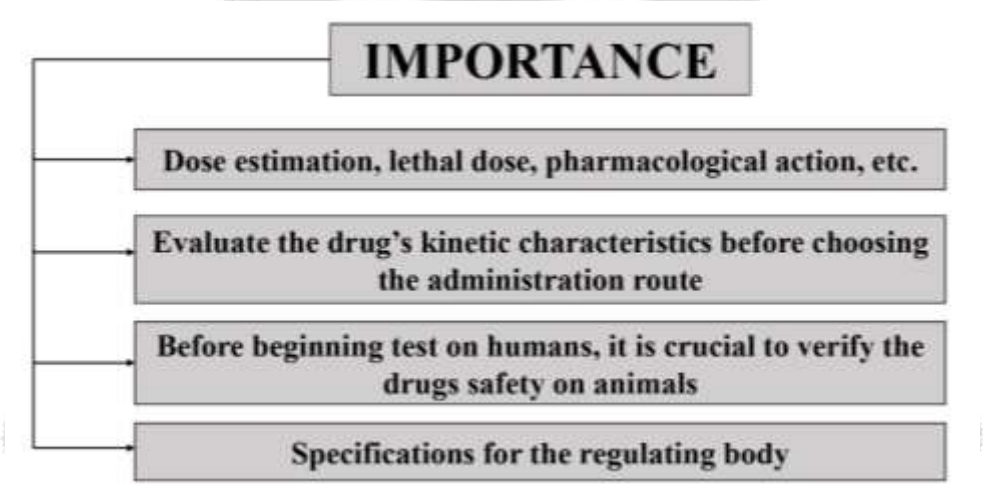


Figure 1: Importance of Preclinical studies

3. Phases of clinical trials [5]

STAGES	STUDY PARTICIPANTS	LENGTH OF STUDY	PURPOSE	DESCRIPTION	ESTIMATION
Phase 0	10 to 15 healthy volunteers	Low dose <1% of dose calculated fewer than seven days	The purpose of this phase is to help speed up and streamline the drug approval process. Phase 0 studies may help researchers find out if the drugs do what they're expected to do.	Phase 0 First in man an early trial to determine if drug engages its expected target.	Can be conducted with prior approval whole final IND review is pending
Phase 1	20 to 100 healthy volunteers or	Several months	SAFETY AND DOSAGE	Phase 1 studies are closely monitored and gather information about how a drug interacts with the	Approximately 70% of drugs move to the

	people with the disease/condition.		During Phase 1 studies, researchers test a new drug in normal volunteers (healthy people). In most cases, 20 to 80 healthy volunteers or people with the disease/condition participate in Phase 1.	human body. Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate and what its acute side effects are. As a Phase 1 trial continues, researchers answer research questions related to how it works in the body, the side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2 studies.	next phase
Phase 2	Up to several hundred people with the disease/condition.	Several months to 2 years	EFFICACY AND SIDE EEFECTS In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed.	Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols.	Approximately 33% of drugs move to the next phase
Phase 3	300 to 3,000 volunteers who have the disease or condition	1 to 4 years	EFFICACY AND MONITORING OFADVERSE REACTIONS Researchers design Phase 3 studies pivotal studies, these studies involve 300 to 3,000 participants.	It is possible that less common side effects might have gone undetected. Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side effects.	Approximately 25-30% of drugs move to the next phase
PHASE 4	Several thousand volunteers who have the disease/condition		EFFICACY AND SAFETY Phase 4 trials are carried out once the drug or device has	A kind of clinical research that examines long-term adverse effects brought on by a novel treatment after it has received regulatory approval and is available on the market. These studies may also	Approximate two years, minimum

			been approved by FDA during the Post-Market Safety Monitoring	examine the effectiveness of a novel medication over an extended period of time while searching for side effects that were not detected in earlier studies.	

Table 1: Informative detail on phases of clinical trial.

3.1 Different types of Phase 1 trials

3.1.1 SAD

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until recalculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up at which point the drug is said to have reached the Maximum tolerated dose (MTD) [10, 45].

3.1.2 MAD

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug [43].

4. Trial Design

4.1 Adaptive clinical trial

purpose of an adaptive trial is quickly identifying drugs that have a therapeutic effect done by adjusting dosing levels. This trial evaluates a medical device or treatment by observing participant outcomes on a prescribed schedule, and modifying parameters of the trial protocol in accord with those observations. Modifications parameters include dosage, drug undergoing trial, patient selection criteria, sample size and mix [29, 67].

4.2 Randomized trial

The process of assigning clinical trial members to treatment groups is known as randomization. Randomization ensures that each participant has a known (usually equal) chance of being assigned to one of the groups. Randomization requires that group assignment cannot be predicted ahead of time. Purpose of Randomized trial is to reduce bias for testing new drug treatment. In this trial, each study subject is randomly assigned to receive either the study treatment or a placebo. Group receiving placebo is control group. Randomized trial is used to check effectiveness and efficacy of drug [7, 53].

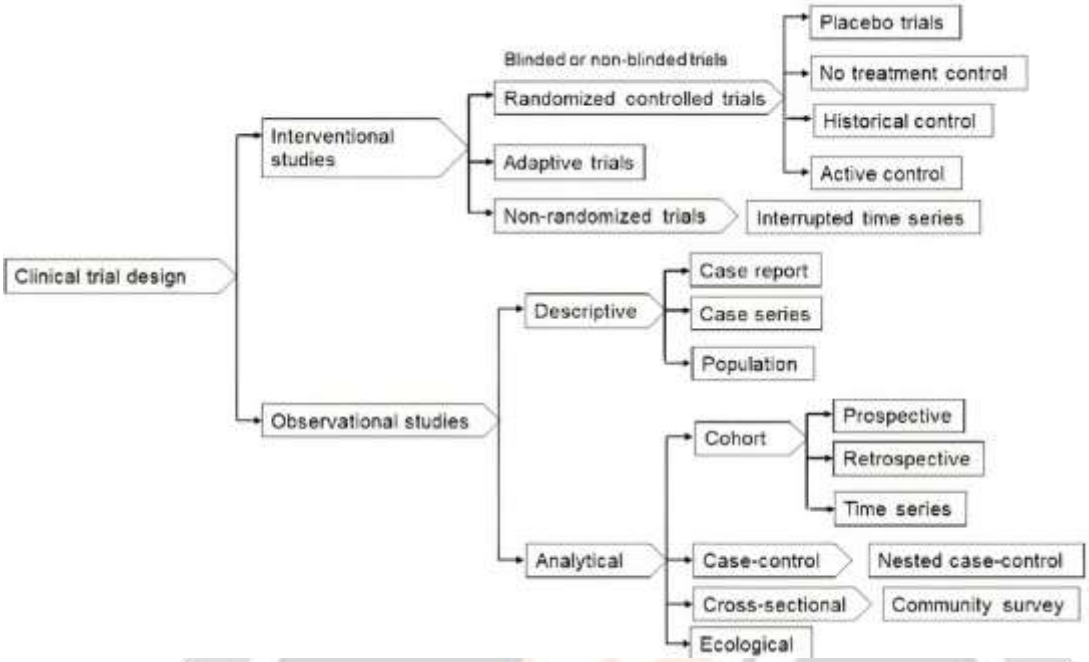


Figure 2: Classification of clinical trial design.

4.3 Blind trial

In blind trials, the subjects involved in the study do not know which study treatment they receive and for what purpose. In double blind trials, subjects and investigator / doctor do not know which medication is given. Neither the patients nor the researchers monitoring. The outcome know which patient is receiving which treatment, until the study is over. It is very effective to reduce bias. It is one in which the participants have no idea which treatment they are receiving. They could be a new treatment, a treatment modality, or a placebo. This is determined by the trial's design. Because all patients receive identical injections or tablets, they cannot tell which treatment they are receiving [8].

5. The investigational new drug process

Drug developers, or sponsors, must submit an Investigational New Drug (IND) application to FDA before beginning clinical research.

- In the IND application, developers must include:
- Animal study data and toxicity (side effects that cause great harm) data
- Manufacturing information
- Clinical protocols (study plans) for studies to be conducted
- Data from any prior human research
- Information about the investigator [19].

6. Asking for FDA Assistance [7]

Drug developers are free to ask for help from FDA at any point in the drug development process, including:

- Pre-IND application, to review FDA guidance documents and get answers to questions that may help enhance their research

- After Phase 2, to obtain guidance on the design of large Phase 3 studies
- Any time during the process, to obtain an assessment of the IND application
- Even though FDA offers extensive technical assistance, drug developers are not required to take FDA's suggestions. As long as clinical trials are thoughtfully designed, reflect what developers know about a product, safeguard participants, and otherwise meet Federal standards, FDA allows wide latitude in clinical trial design.

7. FDA IND Review Team [6, 21]

The review team consists of a group of specialists in different scientific fields. Each member has different responsibilities.

1. Project Manager: Coordinates the team's activities throughout the review process, and is the primary contact for the sponsor.

2. Medical Officer: Reviews all clinical study information and data before, during, and after the trial is complete.

3. Statistician: Interprets clinical trial designs and data, and works closely with the medical officer to evaluate protocols and safety and efficacy data.

4. Pharmacologist: Reviews preclinical studies.

5. Pharmakineticist: Focuses on the drug's absorption, distribution, metabolism, and excretion processes. Interprets blood-level data at different time intervals from clinical trials, as a way to assess drug dosages and administration schedules.

6. Chemist: Evaluates a drug's chemical compounds. Analyzes how a drug was made and its stability, quality control, continuity, the presence of impurities, etc.

7. Microbiologist: Reviews the data submitted, if the product is an antimicrobial product, to assess response across different classes of microbes.

7.1 Approval [3, 24]

The FDA review team has 30 days to review the original IND submission. The process protects volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials. FDA responds to IND applications in one of two ways:

- Approval to begin clinical trials.
- Clinical hold to delay or stop the investigation. FDA can place a clinical hold for specific reasons, including:
- Participants are exposed to unreasonable or significant risk.
- Investigators are not qualified.
- Materials for the volunteer participants are misleading.
- The IND application does not include enough information about the trials risks.

8. Types of clinical trial [24, 25]

1) Treatment trials Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
2) Prevention trials Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.
3) Diagnostic trials Conducted to find better tests or procedures for diagnosing a particular disease or condition.

4) Screening trials Test the best way to detect certain diseases or health conditions
5) Quality of Life Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

Statistical principles and methodology are also embedded within other ICH guidelines, particularly those listed below. The specific guidance that contains related text will be identified in various sections of this document [7, 62, 63].

9. GCP guidelines from ICH

The ICH GCP principles [13, 16]

1. Clinical trials should be carried out in accordance with the ethical principles derived from the Helsinki Declaration and that are consistent with GCP and the applicable regulatory requirements.

2. Before beginning a trial, the foreseeable risks and inconveniences should be balanced against the expected benefit to the individual trial subject and society. Only if the anticipated benefits outweigh the risks should a trial be initiated and continued.

3. The claims, safety, and well-being of the trial subjects should take precedence over the interests of science and society.

4. Nonclinical and clinical data on an investigational product should be sufficient to fund the proposed clinical study.

5. Clinical trials must be scientifically valid. Outlined in a clear and detailed protocol

6. A trial should be carried out in accordance with the protocol that has undergone prior institutional scrutiny independent ethics committee (IRB) (IEC) approval / positive interpretation

7. Medical care provided and medical decisions made subjects should always speak on their behalf. When it is the responsibility of a qualified physician, or when suitable for a qualified dentist

8. Every individual involved in the trial should be qualified to do so through education, training, and experience carry out his or her responsibilities

9. Consent should be freely given and informed prior to clinical trial participation from each subject

10. All preclinical and clinical data should be recorded, handled, and stored in such a way that it can be accurately reported, interpreted, and verified.

11. The confidentiality of records that could identify subjects should be protected, while adhering to the applicable regulatory requirements for privacy and confidentiality.

12. Investigational products must be manufactured, handled, and stored in accordance with best manufacturing practices (GMP). They must be used in accordance with the protocol for approval.

13. It is necessary to install systems with operations that ensure the quality of every aspect of the trial.

'Guidelines on the Statistical Analysis of Clinical Studies' (March, 1992) from the Japanese Ministry of Health and Welfare and the U.S. Food and Drug Administration document entitled 'Guideline for the Format and Content of the Clinical and Statistical Sections of a New Drug Application' (July, 1988). Some topics related to

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

E2C: 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 Pharmaceuticals [32, 48, 60].

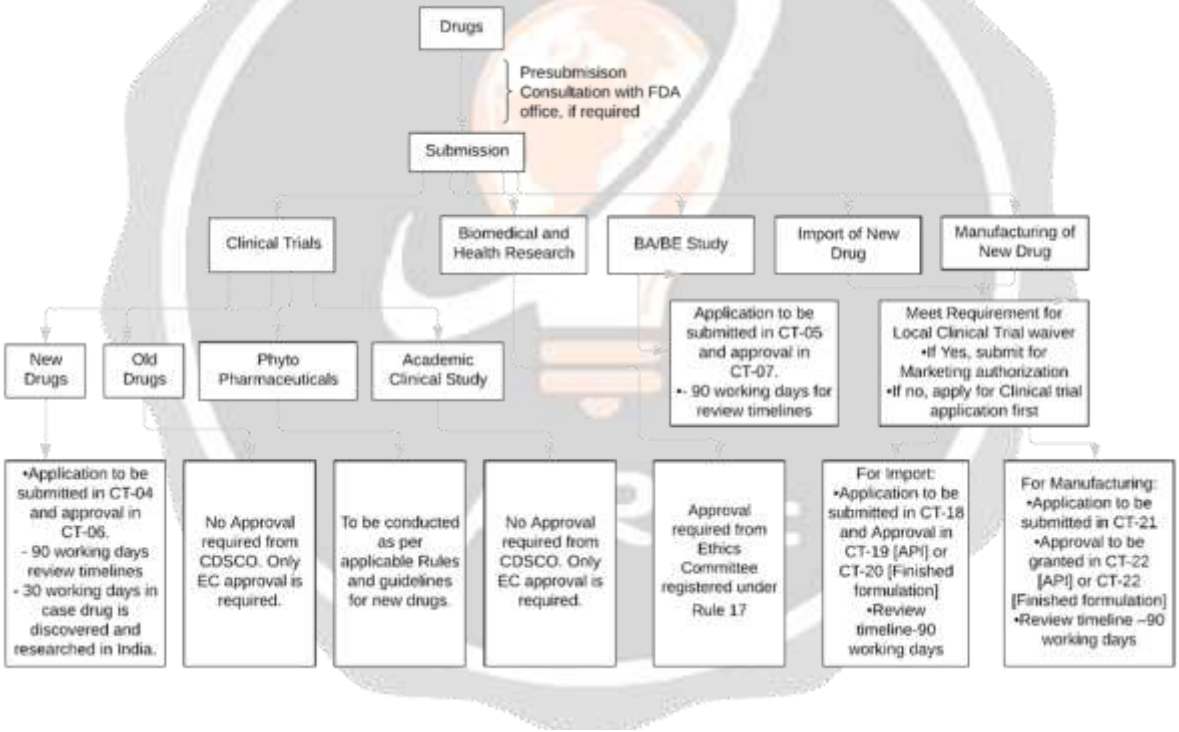


Figure 3: Regulatory Pathway for Product Registration.

10. Evaluation of safety and tolerability

In all clinical trials evaluation of safety and tolerability constitutes an important element. In early phases this evaluation is mostly of an exploratory nature, and is only sensitive to frank expressions of toxicity, whereas in later phases the establishment of the safety and tolerability profile of a drug can be characterized more fully in larger samples of subjects [26]. Later phase controlled trials represent an important means of exploring in an unbiased manner any new potential adverse effects, even if such trials generally lack power in this respect. Certain trials may be designed with the purpose of making specific claims about superiority or equivalence with regard to safety and

tolerability compared to another drug or to another dose of the investigational drug. Such specific claims should be supported by relevant evidence from confirmatory trials, similar to that necessary for corresponding efficacy claims [27].

11. Regulatory Framework in India

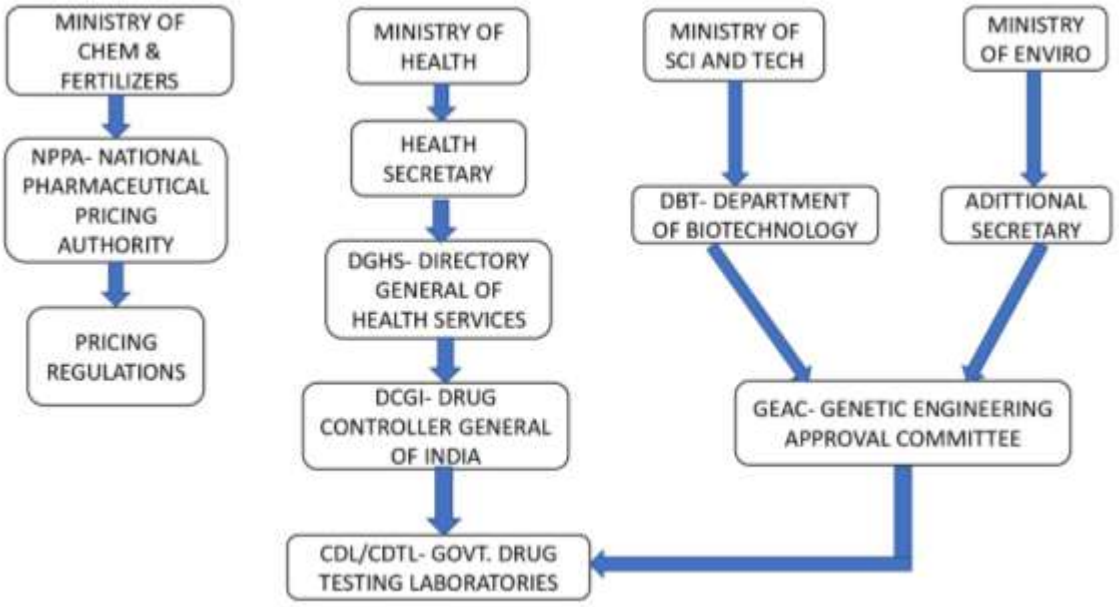


Figure4. Flowchart of Regulatory Framework in India

12. Ethical conducts [40, 54]

Trials are closely supervised by appropriate Regulatory authorities. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. The local ethics committee has discretion on how it will supervise observational studies or those using already collected data. Conference of Harmonization Guidelines for Good Clinical Practice (ICH GCP) is a set of standards used internationally for the conduct of clinical trials. The guidelines aim to ensure that the "rights, safety and wellbeing of trial subjects are protected". The declaration of Helsinki of the World Medical Association (1964) codifies recommendation for guidance of doctors in clinical research.

12.1 Plans included in clinical trials are: -

12.1.1 Double Blind Trials [29, 60, 65]

A double blind trial is one in which neither the researchers nor the patients are aware of the outcome. Each patient is assigned a code number by the computer. The code numbers are then assigned to treatment groups. Your code number will be printed on your treatment. Neither you nor your doctor discover whether or not it is the new treatment.

The list of patients and their code numbers are kept confidential until the trial is completed. In a case of emergencies, researchers could determine which trial group a patient was assigned to. However, no one knows until the trial is over.

12.1.2 Open Trials [1, 7, 10]

An open-label trial, also known as an open trial, is a type of clinical trial in which participants' data is not withheld. Both the researchers and the participants are aware of which treatment is being administered. In contrast, in a double-blind trial, information is deferred from both the researchers and the participants in order to reduce bias.

- Open-label trials may be appropriate for comparing two similar treatments to see which one is more efficacious, such as considering multiple prescription anticoagulants or possible relief from symptoms of some disorders when a placebo is given.
- A randomized open-label trial is still possible. Untreated open-label trials may also be conducted, with all participants receiving the same treatment (no placebo group).

12.2 Approval from the ethics committee for review and approval for clinical trials [11]

The sponsor must obtain confirmation of EC analysis and approval for the clinical trial. Before beginning a clinical trial, the sponsor should obtain the following:

1) A profile of each member of the ethics committee, including their name, address, qualifications, and experience.
2) GCP compliance confirmation from the ethics committee.
3) Ethics committee approval was documented.
4) Copy of Ethics Committee approvals in the event that its approval is contingent on changes, if any.
5) Copy of any Ethics Committee documents involving re-evaluations/re-approvals with favorable suggestions, as well as any removals or suspensions of favorable opinion.

13. Serious adverse events that occur during a clinical trial must be reported

- An adverse medical event (SAE) is one that occurs throughout a clinical trial that is linked to a patient's death or hospitalization. (If the study was performed as an outpatient) hospital stay was extended (assuming the study was performed with patients), ongoing, or severe impairment, a congenital condition typicality, birth defect, or something else life-threatening. Within 24 hours of the incidence of any SAE, the investigator must notify the DCGI for regulatory studies, the sponsor, and the IEC. If this is not possible, the DCGI should be informed of the delay in reporting the SAE along with the report [46, 48].

After thorough analysis, provide the SAE report to DCGI.

- Additionally, send within 14 calendar days of the event to the Chairman of the IEC and the Head of the institution where the trial was conducted. (These should be reported in academic studies) Just within 24 hours to the IEC [52, 53]. Within 30 calendar days of the event, IEC must send its report on the SAE to the DCGI, along with a thorough analysis and its recommendation for any monetary support that the sponsor or his agent should provide [12, 13].

14. Schedule Y

Schedule Y defines the clinical trials as the requirements and guidelines for import and manufacture of new drugs for sale or for clinical trials. It describes the details of application process for conducting clinical trials; responsibilities of the sponsor, investigators and the Independent Ethics Committee. T-License and NOC (no objection certificate) are granted within two to four weeks after approval of the study [14, 18]. Clinical Trials can only

be initiated after obtaining written permission from IEC and DCG. Clinical Trials for a new drug/investigational new drug, whether for clinical investigations, or any clinical experiment by an institution shall be conducted except under, in accordance with, the permission, in writing of the Licensing Authority designated by Central Authority while Rule 122 E of Schedule Y clearly defines 'new drug' as new molecules as well as drugs used abroad but to be introduced for the first time in the country. New indication or new dosage form of an already approved drug is also considered as a new drug. Even fixed dose combinations of drugs already in use are considered as new drugs. Clinical trials have been defined in Rule 122DAA of the D and C Act in India as "Systemic study of new drugs in human subjects to generate data for discovery and/or verifying the clinical, pharmacological including pharmacodynamics and pharmacokinetics and/or adverse effects with the objective of determining safety and/or efficacy of the new drugs [18, 19].

In the field of clinical research, large pharmaceutical companies and distinct multinationals' needs changed, and a revised version of Schedule Y in accordance with the ICH-GCP (International Council of Harmonization and Good Clinical Practice) standard was put forth in 1995. Several revisions to Schedule Y have occurred since then in order to provide a safe environment for clinical research to be conducted in India [19, 22].

DCGI (Drugs Controller General of India) has taken numerous steps to steer the clinical research industry in the right direction with recent innovations in its operations [14].

Steps such as registering contract research organizations (CROs) with DCGI, auditing clinical trials while they are being conducted, developing guidelines for ethics committees to operate ethically, and many other future prospects and competitive analysis will undoubtedly benefit Indian clinical research to help the industry [39].

It has to be a responsibility of all stakeholders viz., Investigators, Ethics Committee, Sponsor, Regulatory authority to ensure the safety and wellbeing of subjects and obtaining the quality data. New revised schedule Y of D and C act is step of Indian Government towards harmonizing with the guidelines of international bodies such as World Health Organization (WHO) and ICH guidelines based on 'Declaration of Helsinki'. For conducting a Clinical trial in India, it is necessary to apply in prescribed Form '44' along with requisite fees [22, 57].

The drugs and Cosmetics Act of 1940 and its Rules of 1945 are implemented at the federal and state levels in order to regulate clinical trials and ensure the efficacy and safety of all drugs imported or manufactured in India and marketed there. The Drugs Controller General (India) (DCGI) is in charge of enforcing these rules and acts as the head of the Central Drugs Standard Control Organization (CDSCO). They ensure that the data produced is authentic, efficient, and feasible, and they serve as the foundation (if relevant) for approving to market the drug [39, 57].

Important forms of D and C Act	
Form 44	Application for grant of permission to import or manufacture a New Drug or to undertake clinical trial
Form 12	Application for license to import drugs for the purposes of examination, test or analysis
Form 11	License to import drugs for the purposes of examination, test or analysis (Validity is one year)
Form 4	Issue of import certificate (Validity is six months)
Form 1	Application form for issue of import certificate for import of narcotic drugs and psychotropic substance
Form 4	Issue of import certificate (Validity is six months)
Important rules of D and C Act	
Rule 34	Application for license for examination, test or analysis
Rule 122-A	Application for permission to import new drug
Rule 122-D	Permission to import fixed dose combination
Rule 122-DA	Application for permission to conduct clinical trials for new drug/investigational new drug
Rule 122-DAA	Definition of clinical trial
Rule 122-E	Definition of new drug
Rule 55	Application for import certificate
Rule 56	Issue of Import certificate
Rule 122 DAB	Draft guidelines for registration of all clinical research Organizations involved in clinical trial in India. (valid for five years)

Fig 5: Rules of D and C Act (1940-1945).

15. Application for permission

Application is made in FORM 44 accompanied with following data in accordance with appendices, namely

- Chemical and pharmaceutical Information
- Animal pharmacology data
- Animal toxicology data
- Human clinical pharmacology data
- Regulatory status in other countries
- Prescribing Information
- Complete testing protocol for quality testing

Fig 6: Requirements and guidelines for permission to import and manufacture of new drugs for sale or to undertake clinical trials.

Major Clinical Trials Challenges in Asia include while the globalization of clinical research is driving growth across Asia, there are some obstacles to overcome, including regulatory complexities, infrastructure and legal issues, and language and cultural barriers.

15.1 Essentials documents for clinical trials

The following are the crucial records for clinical trials [37]:

- Investigator's Brochure
- Clinical Study Protocol
- Subject Information and Informed Consent Form
- Clinical Study Reports
- Case Report Form (CRF)

15.1 1 Investigator's Brochure

Contains pre-clinical and clinical details on a medicine under research. The material must be presented in a clear, straightforward, objective, and balanced manner, with the translation process taken into consideration [37].

The Title Page of the Investigator's Brochure includes information about the Sponsor, the name of the investigational product(s), the edition number and date, as well as the edition number and date it supersedes. Insisting that the IB be treated as a confidential document, the Sponsor may want to insert a Confidentiality Statement. The following sections are often seen in a typical investigator's brochure [35-38]:

- Abbreviations list
- Contents

- Summary: A succinct explanation of the investigational product's significant physical, chemical, and medicinal features as well as pharmacological, toxicological, pharmacokinetic, metabolic, and therapeutic data pertinent to the relevant stage of the clinical study.
- The investigational product's chemical name (and generic and trade names, if approved), all of its active ingredients, pharmacological class, the justification for conducting additional research with the investigational product, and anticipated indications for its use are all provided in the introduction. The general strategy to be used in evaluating the investigational product should be described in this section.
- The medical product's physical, chemical, and pharmaceutical characteristics and formulation
- Non-clinical studies - This section presents information gleaned from animal studies about the experimental drug's non-clinical pharmacological, pharmacokinetic, metabolic, and toxicological properties.
- Clinical studies: If the medicine under research has already received approval for use in other indications, this part will give data on post-marketing experience as well as information on pharmacokinetics, biotransformation, safety, and effectiveness in humans.
- Conclusions and Guidance for the Investigator.
- References (the references should be included at the conclusion of each section) (the references should be provided at the end of each section).
- According to standardized practices set by the drug development business, the Investigator's Brochure should be evaluated at least once a year and updated as appropriate.

15.1.2 Clinical study protocol

These concerns should be included in the Trial Protocol when the goals and layout of a clinical study have been decided. The Study Protocol is a document that contains instructions for all parties engaged in the clinical research. It sets precise goals for each participant and stipulates how they should go about achieving those goals [41].

The study protocol should guarantee that clinical trials are conducted properly and that data are collected, analyzed, and then submitted to regulatory authorities for evaluation and consideration [41].

The Study Protocol should have the following sections [38, 41, 42].

- Introduction (short explanation of the issue and recommended course of action)
- Ethics Committee Opinion
- number of participants
- Goals and aims of the research
- study period
- Informed Consent

- **Selection standards for subjects**
  - inclusion standards
  - Exclusion standards

- **Methodology**
  - Study Evaluations and Procedures
  - Effectiveness endpoints definition
  - the study timetable

- Study Tours
- Study Plan
- rounds of treatment

- **Reporting on Safety**
  - Retraction from the Study
  - abnormal results from laboratory tests
  - Adverse events (AEs)
  - deviations from the standard for other safety parameters
  - Serious adverse events (SAEs)

- **Criteria for clinical laboratories**
  - Appendixes
  - Additional safety measures
  - data evaluation
  - concurrent pharmaceuticals

The Study Protocol may include the following appendices: Patient Information Sheet, written details, and/or a form of informed consent (ICF). Detailed instructions (e.g., for study subjects or study site staff) [42].

It is best to avoid using phrases (both medical and legal ones) that may be challenging for research participants to grasp when translating the aforementioned papers that include patient information. Special terminology should be defined or explained if they are used in the papers [44].

Protocol amendment [44]

Major modifications to the original Study Protocol are described in the protocol amendment. The Ethics Committee must once more approve any modified protocol.

15.1.3 Informed consent

One of the most crucial components of the system assuring the morality of medical research and the preservation of study subjects' rights is informed consent.

Having been fully informed about the research, informed consent is the procedure by which a subject voluntarily affirms his or her desire to participate in one or more clinical trials. A written, signed, and dated Informed Consent Form should be used to record informed consent (ICF) [44, 47].

Potential study participants should be made aware of the goals and procedures of the study, the drug product and recommended course of treatment, any available alternative therapies, any potential risks and advantages, as well as any potential complications and discomforts that might result from taking part in the study [47].

The potential subject voluntarily consents to take part in a research based on the information that he or she has received and comprehended. Inducement or coercion should not be used to acquire the informed consent [64]. The participant should be informed that he or she has the right to withdraw from the research at any moment and that doing so will have no impact on how they will be treated in the future [49].

Main principles of informed consent [49]

The following things should be explained to the subject:

- The goals of the trial.
- The trial's procedures.
- The treatment plans and trial drug(s).
- Alternative therapies that are offered (s).
- The probable advantages, drawbacks, and discomforts.
- The subject should understand:
- That at any point, he or she may stop participating in the study.
- That his or her future medical treatment will not be impacted by withdrawing from the research.
- Consent should be freely provided after being fully informed.
- That compulsion or incentive should not be used to get consent.

15.1.4 Clinical Study Reports

The Ethics Committee shall receive written updates from the Investigator about the status of the study. These may be the Interim report on the study's interim findings and an evaluation of them based on the analysis done throughout the study, or the Final report, which provides a complete, detailed account of the study, including a description of the materials under investigation, the study's design, and the presentation and evaluation of the findings of statistical analysis [50]. The Investigator should also write up reports on all significant changes that might impact research execution or put study participants at risk. These include the Adverse Event Report (also known as an Adverse Drug Reaction Report), Patient Entry Form (also known as a Patient Notification Form or Patient Entry Card), Patient Withdrawal Form, Protocol Deviation/Violation Report, Study Termination Report, etc. [51].

The Investigator is responsible for reporting on research progress; however, the Study Monitor should also submit written reports following each Study Monitoring Visit (Monitor Report). The Expert Report, which includes several facets of medication development, is written for the regulatory authorities by an expert in the relevant subject (a business executive or an independent individual) [51].

15.1.5 Case record form

A case record form is a written or digital record intended to capture all the details for a specific research subject needed by the study protocol.

There are various uses for the case record form, including [55]:

- To encourage the safe sharing of data between the study team and other departments of the institution, as well as to permit efficient, thorough data processing and analysis, results reporting, and data sharing.
- To make sure that data gathering follows the study protocol.
- To make sure the requirements for data gathering set out by the regulatory bodies are met.

The information gathered at the research site over the course of the investigation should be thorough and give a genuine and accurate account of what happened to each study participant. The research will only provide a trustworthy response to the queries about the safety and efficacy of the experimental medicine if the aforementioned requirements are satisfied [55, 56].

The information below should be included in every CRF [58]:

- Study Subject/Patient ID (number and initials).
- A thorough explanation of the dose guidelines for the experimental medicine.
- Title and number of the study.
- Named the investigator.
- Health conclusion for the subject.
- Criterion for inclusion and exclusion.
- Date and signature of the investigator.
- Demographic information.
- Concurrent medical care.
- Adverse events (side effects and undercurrent diseases).

The CRFs should also have specific pages for logging the following data [58]:

- Diagnoses, both primary and secondary.
- Past medical history.
- Baseline traits, the outcomes of interim analyses, the assessment of effectiveness endpoints, laboratory testing, the explanation of research methods, etc.
- Physical examination results.
- Relevant previous treatment.

Each CRF must be readable, duplicate able, and perhaps shareable further.

16. Registration of Clinical Trials

Before beginning a clinical trial, the sponsor is required to register for it. The clinical trial has been registered with the Clinical Trials Registry of the Indian Council of Medical Research in India. Once the sponsor has registered with the CTRI, the designated REF number indicates that the clinical trial has been successfully registered [12, 14].

Indian council of medical research (ICMR) has started an online registration system of clinical trials in 2007 known as 'Clinical Trial Registration-India (CTRI). Mainly western and southern cities in India are involved in clinical trials related activities such as Mumbai, Pune, Ahmedabad, Hyderabad, Bangalore and Chennai [14]. Clinical Research activities by pharmaceutical firms are generally outsourced to cs (CROs). There are many issues associated with clinical trials like inadequate informed consent, weaknesses of IRB/IEC, inadequate compensation and lack of post-access treatment by these CROs. CDSCO has put up a registration criterion and has issued a draft rule for these mushrooming CROs registration [15-17].

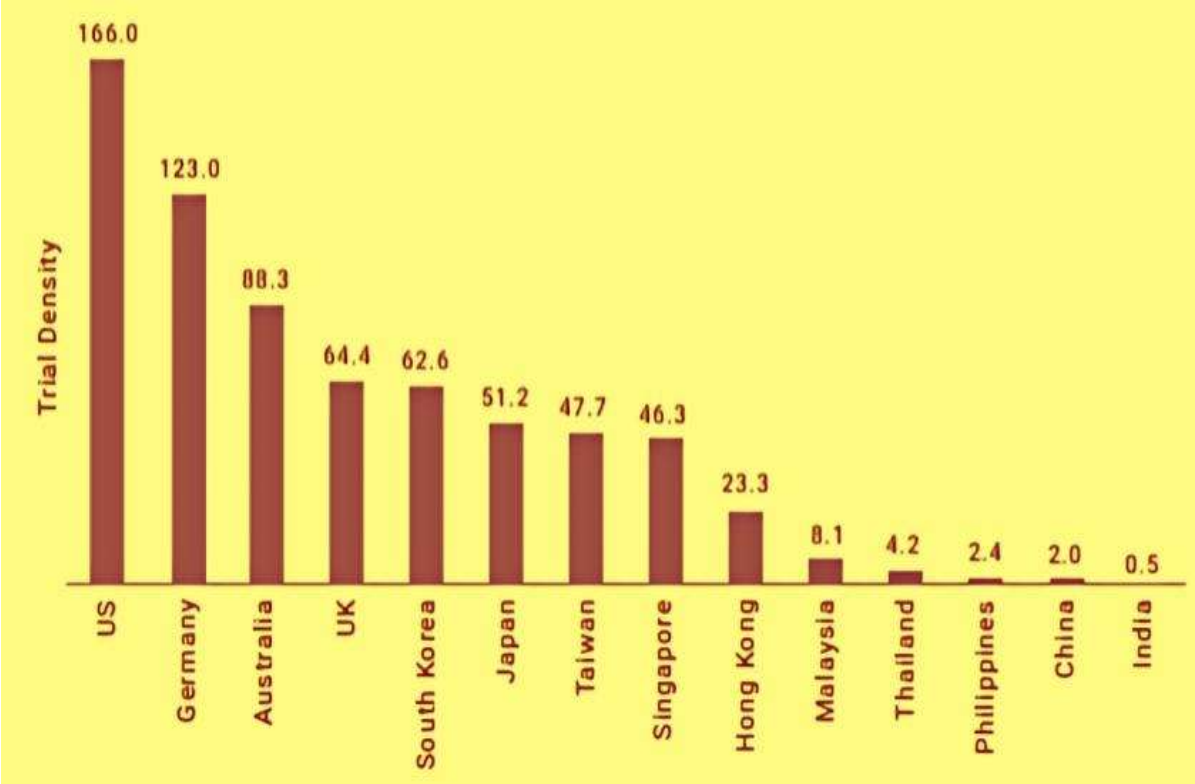


Fig 7: Clinical trial density of different countries in 2016.

16.1 Information required for registration [20]

• Public title of study

• Scientific title of study

• Secondary IDs, if any

• Principal Investigator's name and

• Contact person (Scientific Query)

• Contact person (Public Query)

• Sources of monetary or material support

• Primary and Secondary sponsor

• Countries of recruitment

• Name of Ethics Committee and approval status

• Regulatory durance obtained from DCGI

• Health condition/problem studied

• Study type

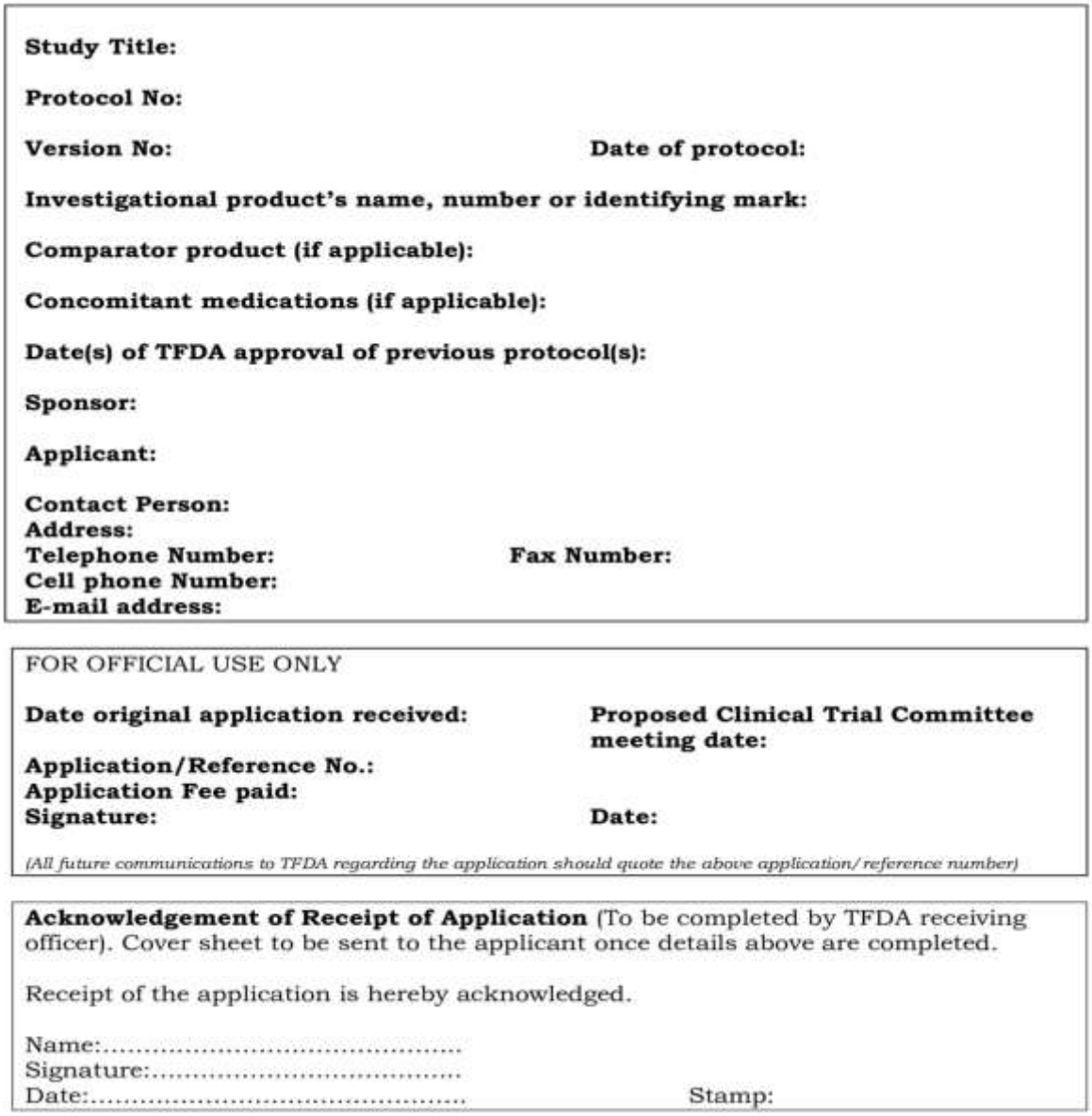
- Intervention and comparator agent
- Inclusion/Exclusion criteria
- Method of generating randomization sequence
- Method of allocation concealment
- Blinding/masking
- Target sample size
- Phase of trial
- Date of first enrollment
- Estimated duration
- Recruitment status
- Brief Summary

16.2 Basic procedure for conducting clinical studies in India [59]

Step 1: Get approval from India's Drugs Controller General.

Step 2: Obtain permission from the Ethics Committee for the specific clinical study.

Step 3: Register on the ICMR website at www.ctri.in.



Study Title:

Protocol No:

Version No: **Date of protocol:**

Investigational product's name, number or identifying mark:

Comparator product (if applicable):

Concomitant medications (if applicable):

Date(s) of TFDA approval of previous protocol(s):

Sponsor:

Applicant:

Contact Person:
Address:
Telephone Number: **Fax Number:**
Cell phone Number:
E-mail address:

FOR OFFICIAL USE ONLY

Date original application received: **Proposed Clinical Trial Committee meeting date:**

Application/Reference No.:
Application Fee paid:
Signature: **Date:**

(All future communications to TFDA regarding the application should quote the above application/reference number)

Acknowledgement of Receipt of Application (To be completed by TFDA receiving officer). Cover sheet to be sent to the applicant once details above are completed.

Receipt of the application is hereby acknowledged.

Name:.....
Signature:.....
Date:..... Stamp:

Fig 8: Clinical trial application form (CTA)

17. A typical CRO clinical trial budget

A CRO (Clinical Research Organization) is a private company that works with pharmaceutical companies to develop novel chemicals, drugs, or medical devices. Planning and carrying out clinical trials to evaluate the safety and efficacy of recently discovered drugs and medical devices in humans is the core duty of a CRO [57].

Asia Is a Popular Location for Clinical Trials Asia has emerged as a popular investment location due to its large treatment-naïve population, highly skilled investigators, robust clinical infrastructure, and faster time to recruit patients, enhanced profitability, and the same high-quality output [23].

- Regulatory affairs
- Site identification and selection

- Site contracting and payments
- Site initiation and activation
- Site management
- Onsite monitoring
- Drug safety management
- Drug logistics
- Biological sample logistics
- Clinical supplies logistics
- Medical writing
- Site close-out
- Project management
- Study files/document management
- Data management
- Statistics
- Quality control
- Communication with central CRO/sponsor
- Pass-through costs

17.1 Regulatory affairs [28]

Clinical trial regulatory affairs include the issuance of insurance policies in each country where the trial is conducted, ethics committee (EC) and regulatory authority (RA) initial submissions, study amendments, EC/RA reporting/communication, as well as the development and distribution of annual progress reports.

Total: $64,350

17.2 Site identification and selection [28]

Each selection visit includes time dedicated to scheduling, preparation, travel, the visit itself, post-visit report, and follow-up tasks.

Total: $46,200

17.3 Site contracting and payments [28]

These tasks involve contract negotiation and execution with each hospital and site payment management

Total: $64,350

17.4 Site initiation and activation [30]

CRAs and Clinical Project Managers of the CRO explain the goals and procedures of the trial to the site's research team After the initiation visit, the activation process involves local document verification/signatures and providing sites with access to the different trial systems (EDC, etc.).

Total: $42,700

17.5 Site management [30]

CRA's research team provides documents (e.g., Protocol, Patient Information Sheet / Informed Consent Form).

Total: $950,400

17.6 Onsite monitoring [30]

Monitoring plan visit includes time devoted to scheduling, preparation, recruitment, travel, the visit itself, post-visit report, and follow-up. A reasonable monitoring strategy can be one onsite monitoring visit per site every 2 months.

Total: $1,069,670

17.7 Drug safety management [31]

From the CRO's side, drug safety requires the receipt, review, listing, reporting, and follow-up of serious adverse events (SAEs).

Total: $29,820 (not including Medical Monitor)

17.8 Drug logistics [31]

The selection and contracting of a drug depot in charge of receiving, labelling, storing, and distributing the drugs, stock availability, shipments from depot to sites.

Total: $55,790 (CRO cost not including depot subcontracted service).

17.9 Biological sample logistics [30]

CROs coordinate the shipment of biological samples from sites to central laboratories for e.g.: - (blood samples for translational/biomarker or pharmacokinetics (PK) studies)

Total: $74,620 (not including shipping costs, which are listed as pass-through costs)

17.10 Clinical supplies logistics [33]

The supplies as such are listed apart, as pass-through costs.

Total: $22,575

17.11 Medical writing [28]

Review study protocol, Informed Consent Form, final clinical study reports, and scientific publications (abstracts, posters, and manuscripts), among other documents.

Total: $24,960

17.12 Site close-out [31]

An onsite close-out visit includes time for scheduling, preparation, travel, visit, post-visit report, and follow-up.

Total: $40,950

17.13 Project management [33]

Clinical project managers supervise the project, including financial, clinical, technical, and administrative aspects.

Total: $1,021,120

17.14 Study files/document management [28]

CROs have Clinical Trial Assistants (CTAs) encompass Investigator Site File (ISF) preparation and shipments, electronic Trial Master File (eTMF) maintenance, and final eTMF reconciliation.

Total: $148,993

17.15 Data management [34]

The CRO's Data Managers develop the data management plan and take care of the electronic Case Report Form (ECRF) or Electronic Data Capture (EDC) system specification, configuration, development, clinical databases, testing, and validation.

Total: $435,851

17.16 Statistics [34]

Biostatisticians and statistical programmers will work on the development of the randomization code, mapping, programming and the statistical analysis plan.

Total: $150,518

17.17 Quality control [28]

In order to ensure the quality of the study, the following activities will be conducted by the CRO's Quality Managers.

Total: $70,460

17.18 Communication with central CRO/sponsor [30]

Onsite meetings

Teleconferences.

Total: $89,100

17.19 Pass-through costs [61]

- Blood tubes
- Shipping packages
- Office supplies
- Payments to sites per enrolled patient
- Publication fees
- Ethics committee evaluation fees
- Site contract fees
- Regulatory authority evaluation fees
- Travel costs for selection, initiation, routine monitoring, and close-out visits
- Central pathology and radiology reviews
- Biomarker studies
- Coordinating investigators
- Drug manufacturing and testing
- Drug distribution services
- EDC license and service fees
- Web tools
- Document translations
- Data and Safety Monitoring Board (DSMB)

Total: $8,526,728

CLINICAL TRIAL BUDGET TOTAL: $12,929,155

The phase 3 clinical trial budget example discussed in this article adds up to $12.9 million.

18. Concept of Quality Based Design (QbD) in Clinical research

In the manufacturing, QbD is an idea that has been successfully applied having the main emphasis over building quality into a process from the beginning. Applied in clinical development, this approach would prospectively define critical factors (trial processes such as randomization and key data) and examine the objectives of a trial to meet their objectives [34]. It is essential to understand the processes and data required for a successful trial in order to subsequently manage and identify vital and possible risks to the quality of the trial. Through tailoring trial design, these risks would then be managed [35]. Focusing on important aspects of a trial could also considerably decrease the burden of clinical trial conduct by relieving sponsors of a supposed commitment to moderate every possible risk happen by a trial, particularly for those activities that minimally affect human subject protection and data quality. However, the existing models for clinical trial design, implementation and oversight may have become unsustainable in a clinical trial environment [34, 35].

A researcher Cook (2012) reported that the relationships between pharmacokinetic parameters and CQAs can be established in healthy volunteer during clinical trials which can be further useful in establishing relationships between pharmacokinetics and efficacy and safety [36].

19. Technology advancement in pharmaceutical industry

With the introduction of big data analytics in the pharmaceutical world and life sciences industry, the complex business processes were streamlined, and the efficiency of the process was improved. Thus, various investors from the healthcare and pharma domain have invested around $4.7 billion in big data analytics [35, 36].

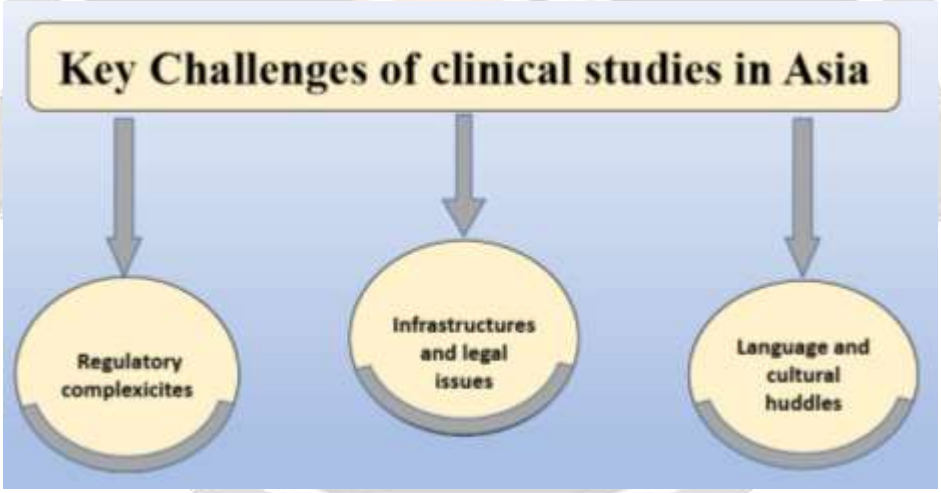


Fig 9: Key challenges of clinical studies in Asia.

19.1 Applications

19.1.1 Reduces Research and development cost

Medicines to fight diseases like ALS (Amyotrophic Lateral Sclerosis) are not being developed because the cost of developing the medicines outweighs the demand. Big data can help in fast-tracking the research work with the help of artificial intelligence to minimize the time needed for clinical trials [28].

Machine-learning algorithm was developed at Carnegie Mellon University to test and analyze the interaction of different drugs with protein structure [58]. The accuracy of the results obtained through the machine learning algorithm has saved valuable time, thus getting the drug from the clinical to the market at a faster rate [28].

19.1.2 Better Clinical trials

Machine learning techniques like association rules and decision tree helps in determining trends relating to patient acceptance, adherence, and various other metrics [13]. Big data can help in designing flowcharts to match and recruit more patients in clinical trials, which will, in turn, increase the success rate of the drug. Machine-learning algorithms have reduced manual intervention by 85% thus leading to cost and timesaving during large trials [28].

19.1.3 Escalated Drug Discovery

With the help of big data analytics, researchers use predictive modeling to analyze the toxicity, interactions, and inhibition of the drug [66].

19.1.4 Controlling Drug Reaction

Data mining on social media platforms and medical forums are performed along with sentiment analysis to gain insight into adverse drug reactions (ADRs) [28].

19.1.5 Precision Medicine

A combination of customized medicine can be created for individual patients who show different symptoms [66]. The predictive model developed from the patient's historical data can also help in detecting diseases much in advance [68].

19.1.6 Focus on Sales and marketing

Big data can help the pharma companies predict the sale of a particular medicine owing to the various demographic factors. This will help companies predict customer behavior and build advertisements accordingly to reach out to these consumers [69].

19.1.7 External and Internal Collaboration

Streamlining of drug discovery, clinical trials, and medical affairs will help in improving internal collaboration [70]. It will help in creating customizable medicine plans for each patient owing to their unique blend of diseases [71].

Whether it is the application of big data in precision medicines, or to decrease the rate of drug failures or to lower the cost of research and drug discovery, there is a bright future for big data analytics in the pharma world [13].

Fig 10: Reasons for which Asia is Preferred Destination for Clinical Trials.

India accounts for 16% of the world's population and 23% of the global disease burden expressed as disability adjusted life years [72]. The potential for clinical research in the country is thus immense, given the country's dual burden of communicable and no communicable diseases [73]. A recent study also found that the regulatory studies conducted in the country are not proportionate to the country's health-care needs. The researcher's understanding of both the disease burden and the regulatory requirements will go a huge way toward mitigating disease-related financial strain and suffering in the country [73, 74].

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