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Review Article

A Systematic Review on Clinical Research and Approval Process

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ABSTRACT

Drug discovery is a key step or process by which lead molecule is been optimized for further preclinical and clinical trial studies. Drug development process involves target identification, target validation, lead identification, and lead optimization. Once the lead molecule is optimized the HIT compound is been analyzed further in preclinical trial in animals and clinical trial in human subjects. The development of a new drug till marketing authorization should gone through several stages in order to make the drug safe, effective and should posses best quality to get approve for applicable regulatory requirements. The overall theme of our article is to review and state the process from drug discovery to approval for marketing of drug. The process from drug discovery till marketing authorization is time taking, complex and expensive so each target should be consider for development of new drug and new research tools must be used for any new drug development process. It takes around 10-15 years and US\$ 1 billion for a new lead compound to make it as a medicine and to get marketing approval for general public use. On an average million lead molecules are been scrutinized to make a HIT compound, so that it can be use for further preclinical and clinical studies to make it available in market. This article provides a brief outline on stages from drug development to clinical research.

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INTRODUCTION

Clinical research is defined as a systematic investigation in human subjects for the evaluation of safety, efficacy and quality of a new drug. As now days various diseases are emerging and producing life threatening effects on humans, where as the treatment are limited to cure that disease, at this stage there is necessity of new drug development to cure various diseases. The global pharmaceutical organizations are taking steps to develop newer and better drug molecules to cure the diseases through clinical research. Clinical research involves three importance stages as: Drug discovery, Pre-Clinical testing and Clinical trials. The process from drug discovery till marketing authorization is time taking, complex and expensive so each target should be consider for development of new drug and new research tools must be used for any new drug development process. It takes around 10-15 years and US\$ 1 billion for a new lead compound to make it as a medicine and to get marketing approval for general public use. On an average million lead molecules are been scrutinized to make

a HIT compound, so that it can be use for further preclinical and clinical studies to make it available in market. This article provides a brief outline on stages from drug development to clinical research. ⁽¹⁾

Drug Discovery Process

Drug discovery involves comprehensive understanding about disease causing agent and its treatment. This in turn requires understanding of gene alteration, effects on proteins, interaction of protein with other cells and effects of disease on human subjects. The drug discovery process is detailed in step-wise manner further. Drug discovery involves major four steps: Target identification, Target validation, Lead identification and Lead optimization. ⁽²⁾

Target identification

This is the first step in drug discovery process, where the biological origin and potential targets of disease is been identified. The identified target is generally protein, gene, enzyme, ion channel, receptor etc in nature. Human contains

enormous of targets and their sub-products, as it is consider most challenging task in drug discovery process. ⁽³⁾

Target validation

After the target is been identified, it is important to understand the target that is involved in disease process, and altering that target is likely to have a therapeutic effect on human subject. Target validation is considered a process demonstrating the target that has been identified have a functional role in disease process. ⁽⁴⁾

It involves studies intact with animal models that can provide information about the organism response to pharmacological interventions. By this it will help to know whether the identified target is relevant to the disease that has been studied. It also helps in identifying biological molecular structure and conducting validation to show therapeutic effects i.e. predicted molecular target for example genes, proteins, ion channels, enzymes etc are been verified. If the identified target is not validated then it cannot further proceed in drug development, thus early validation of target with the help of biomarkers are specific metric for target validation. ⁽⁵⁾

Lead identification

Lead identification is a major step in drug discovery where a 'lead compound' or 'molecule' is been identified, that may act on identified target to alter the disease process in human subjects. The lead compound may be from natural (plant origin or animal origin) or synthetic (molecular modeling or biotechnology etc). After identification of lead compound, it is been scrutinized and extensive testing is done to form HIT compounds. Further HIT compounds are studied in detail for physical, chemical and biological properties. ⁽⁶⁾

Lead optimization

It is a process which includes refinement of chemical structure and determination of structural activity relationship (SAR) of identified HIT compound. These compounds are then confirmed about its pharmacological characteristic to obtain compound molecule with preferred pharmacodynamic and pharmacokinetic properties. Further the research is carried out in animals for preclinical testing. ⁽⁷⁾

Preclinical Research (Drug testing on animals)

The preclinical studies mainly involve obtaining data related to critical safety and pharmacology, which will help to test drugs in human subject in clinical trials. Objective of preclinical studies mainly involves: Support for human pharmacology, Support for human toxicology, Prediction of human pharmacokinetics, Screening new dosage forms and formulations. Preclinical testing is carried out in-vitro and in-vivo. The in-vitro studies are those studies that are performed in laboratories in test tubes and beakers. Preclinical testing is performed in accordance with SOP's and Good Laboratory Practices (GLP) guidelines. Various toxicity studies are been carried out in preclinical trials are as follows: Systemic toxicity, Local Toxicity, Hypersensitivity, Genotoxicity and Carcinogenicity. ⁽⁸⁾

Systemic toxicity

Systemic toxicity is referred as that toxic effect caused as an outcome of adsorption, distribution of a substance that may affect whole body but not any specific site or location. Systemic toxicity studies involve generalized biological effect to tissue or organs via any drug, molecule or their extracts. These occur by one route and the toxicity is carried out to various location causing adverse effects. ⁽⁹⁾

Local toxicity

Local toxicity is referred as that toxic effect caused at a local area, surface or organ that may affect a specific location or area of a body. Local toxicity studies involve generalized effect to surface via any drug, molecule or their extracts. These occur by one route and may be carried out to several other surfaces of the body or organs. It occurs at the site of first contact between biological system and toxic substance. ⁽¹⁰⁾

Hypersensitivity

Hypersensitivity can be defined as state where immune system is been altered and it response against an antigen which is determined hyperactivity leading to immune pathology, i.e. it refers to adaptive response from immune system that occur in exaggerated form and outcome as a disease. These reactions might be damaging, uncomfortable or occasionally fatal as it requires pre sensitized state of host. ⁽¹¹⁾

Genotoxicity

Genotoxicity is defined as in-vitro and in-vivo ability of a compound that induces damage to genetic materials. This can happen being exposed to chemical, biological agents that can result into genomic instability or alteration in genes that can cause various diseases. They may bind to genetic material and damage them by affecting enzymes involved in replication, causing mutation that may led to defective conditions. ⁽¹²⁾

Carcinogenicity

A substance that causes cancer is termed as carcinogens from naturally occurring exposures (uv rays, radon gas, infectious agents, etc), medical treatments (radiation, chemotherapy, etc) or by other chemicals also. These may cause damage after repeated log term duration or may not have immediate harmful effects, with cancer developing only after a long period of time. These may cause alteration in cell cycle phases, where abrupt increase in cell count might be seen as an adverse effect. ⁽¹³⁾

In preclinical trials work falls in any four categories as:

- Safety pharmacology: These tests are performed to check that a drug does not produce any hazardous effects.
- Preliminary toxicology: These tests are performed to eliminate genotoxicity and to determine maximum effective dose of drug.
- Animal studies: These test includes pharmacokinetic studies (adsorption, distribution, metabolism, excretion in laboratory animals)
- Chemical and pharmaceutical development: This includes large scale synthesis and purification, stability of compound under different conditions, formulation development for further clinical studies. ⁽¹⁴⁾

- In preclinical trials, there are sets of limitations as:
- Time consuming and expensive toxicity testing requires 2-6 years.
- Ethical issues using large number of animals in preclinical trials.
- Therapeutic index and toxicity data may be productive but not for all toxicities.
- Adverse effects cannot be detected in preclinical testing's.
- Information obtains from preclinical testing are:
- Preclinical data including pharmacokinetic, pharmacodynamic and toxicological.
- Manufacturing data including process of manufacturing, stability, composition, etc.
- Protocol basis for clinical trials in human subjects.⁽¹⁵⁾

Clinical Trials (Trial on Human Subjects)

Clinical trials are the sets of procedure that are performed on human subjects by investigators to identify the safety, efficacy and quality of investigational product, or to study adsorption, distribution, metabolism and excretion of investigational product, or to identify adverse drug reaction and interactions of investigational product with adherence to subjects safety and applicable regulatory requirements.

Clinical trials are sets of procedures carried out in various phases, i.e. phase-I, phase-II, phase-III and phase-IV. Each phase has specific objective, time, money, population, methods and outcomes accordingly.⁽¹⁶⁾ The various phases of clinical trials are as:

Phase-I clinical trials (Humans experimentation Trial)

Phase-I clinical trials are referring to first introduction of investigational product into human subjects. Phase-I trials include assessment of investigational product's safety and effectiveness for further phase studies. These studies are carried out with among 20-100 health human subjects, and time required to complete this study is from 6 months to 1 year. Phase-I clinical trials are initiated with very minimal dose of investigational product ($1/10^{\text{th}}$ of the optimal animal dose) which is gradually increased to determine the tolerated dose of that particular investigational product.⁽¹⁷⁾

There are two types of phase-I studies, single ascending dose studies and multiple ascending dose studies. In single ascending dose studies small group of subjects are given single dose of drug and observed for period of time, where as in multiple ascending dose studies group of subjects are given multiple low doses of drug, which gives better understanding of pharmacokinetic and pharmacodynamics of the drug.⁽¹⁸⁾

Information obtained from phase-I studies

- Maximum tolerated dose
- Nature of adverse reaction
- Preliminary characterization of investigational product
- Accumulation of parent drug or metabolites
- Bioavailability of investigational product
- Drug-drug interaction
- Assessment of drug's safety profile

As phase-I clinical trial continues, investigators find out MOA, safety and effectiveness information, dose range. This is basis design of phase-II clinical trials, where almost 60-70% of drugs travel to next phase.⁽¹⁹⁾

Phase-II clinical trials (Therapeutic Exploratory Trial)

Phase-II clinical trials are conducted to evaluate efficacy of an investigational product in diseased human subjects. These trials are generally conducted among 100-500 diseased human subjects and it commonly takes 2-3 years for completion. Also, phase-II trials include evaluation of study endpoints, therapeutic regimens and target population for further studies in phase-III. It is been classified into two categories as Phase-II a (pilot clinical trial), in which the trials are feasible, small scale and often unblinded or open label trials. Whereas Phase-II b (pivotal clinical trials) are well planned, well controlled open or double blinded, placebo or controlled, may not randomized, i.e. conducted for most rigorous study of drug effectiveness.⁽²⁰⁾

Information obtained from phase-II studies

- Determine effectiveness of investigational product
- Optimal dose strength and schedules of dosing
- Therapeutic effect of investigational product
- Placebo and fixed treatment regimen

Phase-III clinical trials (Therapeutic Confirmatory Trial)

Phase-III clinical trials are generally considered to demonstrate or confirm the therapeutic benefits, safety and effectiveness of investigational products. Generally these trials are carried out in 1000-5000 diseased human subjects and it lasts for 2-10 years. Phase-III trials are longest and costliest trials, hundreds of sites participate to conduct these trials. Further it is been categorized into two parts as, phase-III a (confirmatory trials), in which the safety and effectiveness of an investigational product is been confirmed and act as basis for marketing approval (NDA application). Where as in phase-III b trials further dose-response relationship and in combination with others drugs is been studied in different stages of disease.⁽²¹⁾

Information obtained from phase-III trials

- To confirm the safety and effectiveness of an investigational product
- Basis for marketing approval (NDA application)
- Dose-response relationship
- Combination response with other drugs

Phase-IV clinical trials (Post Marketing Surveillance)

Research on any new drug continues even after marketing approval by regulatory bodies. As after marketing, large number of people/patients with different gender, age, diet, etc uses the drug, it is mandatory for manufacturing company to monitor it carefully and submit the data to applicable regulatory authorities. Sometimes regulatory authorities require a company to conduct additional research on marketed drug in phase-IV trials to evaluate long term safety, efficacy and quality of marketed drug. Commonly conducted studies include drug-drug interaction, dose-response or safety studies, mortality/morbidity studies, epidemiological studies, etc.⁽²²⁾

Features of phase-IV clinical trial

- Study long term side effect
- Interaction with drugs not tested earlier
- Ongoing technical support of drug
- Competitive reason to find new market for drug
- Inclusion and Exclusion criteria for wider patient population
- Real life examination of drug

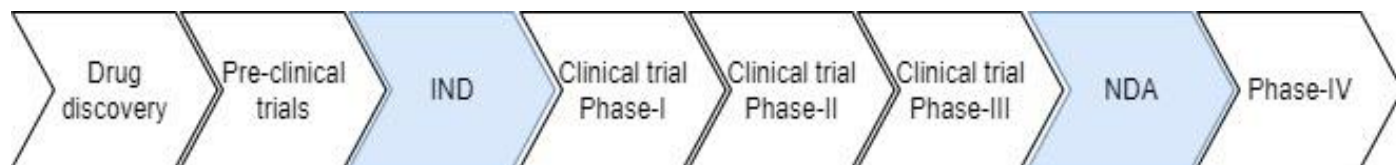


Figure 1: Drug development to Phase-IV trials process

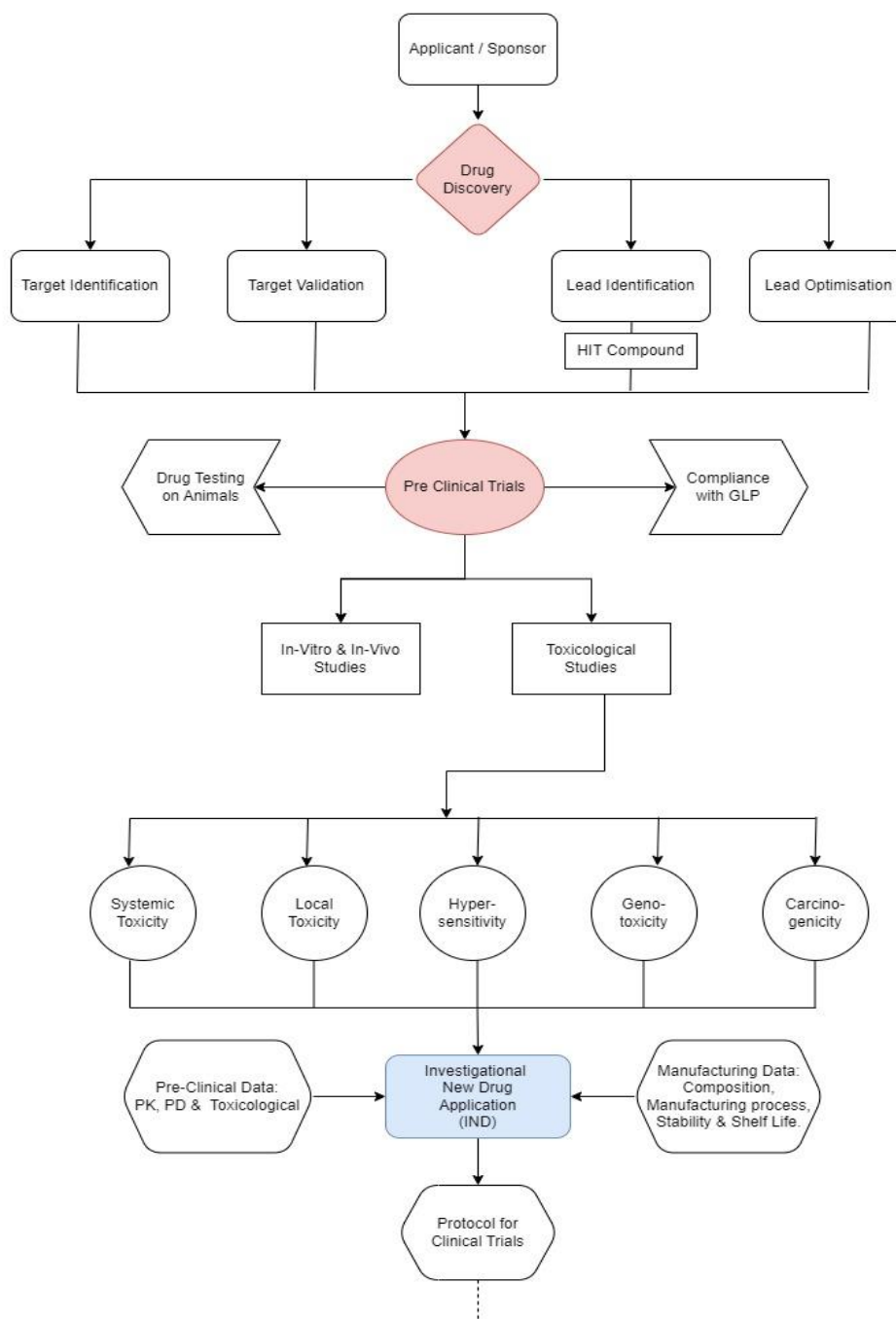
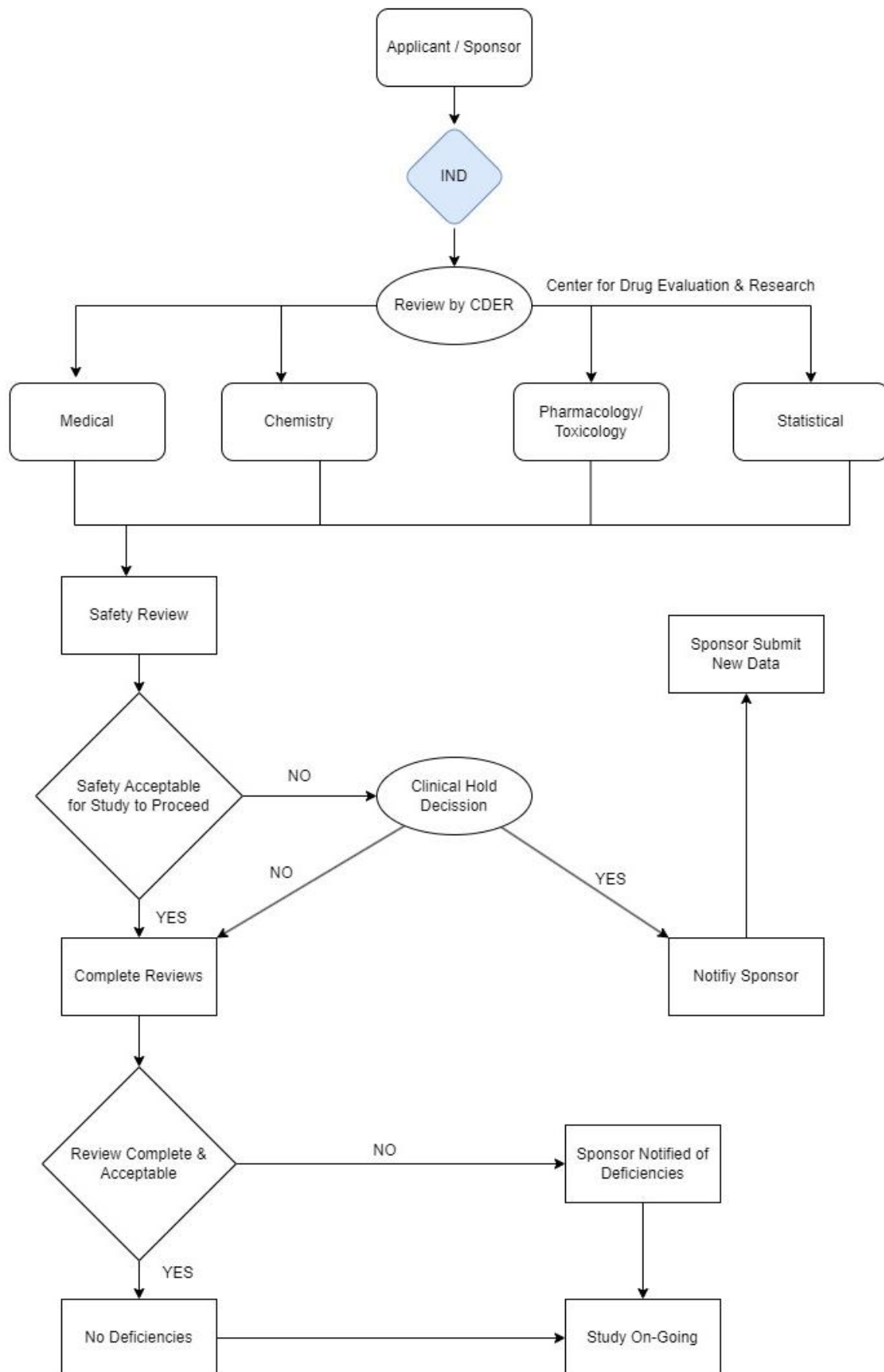


Figure 2: Drug development and Pre-clinical trial process

**Figure 3:** Investigational New Drug Application process

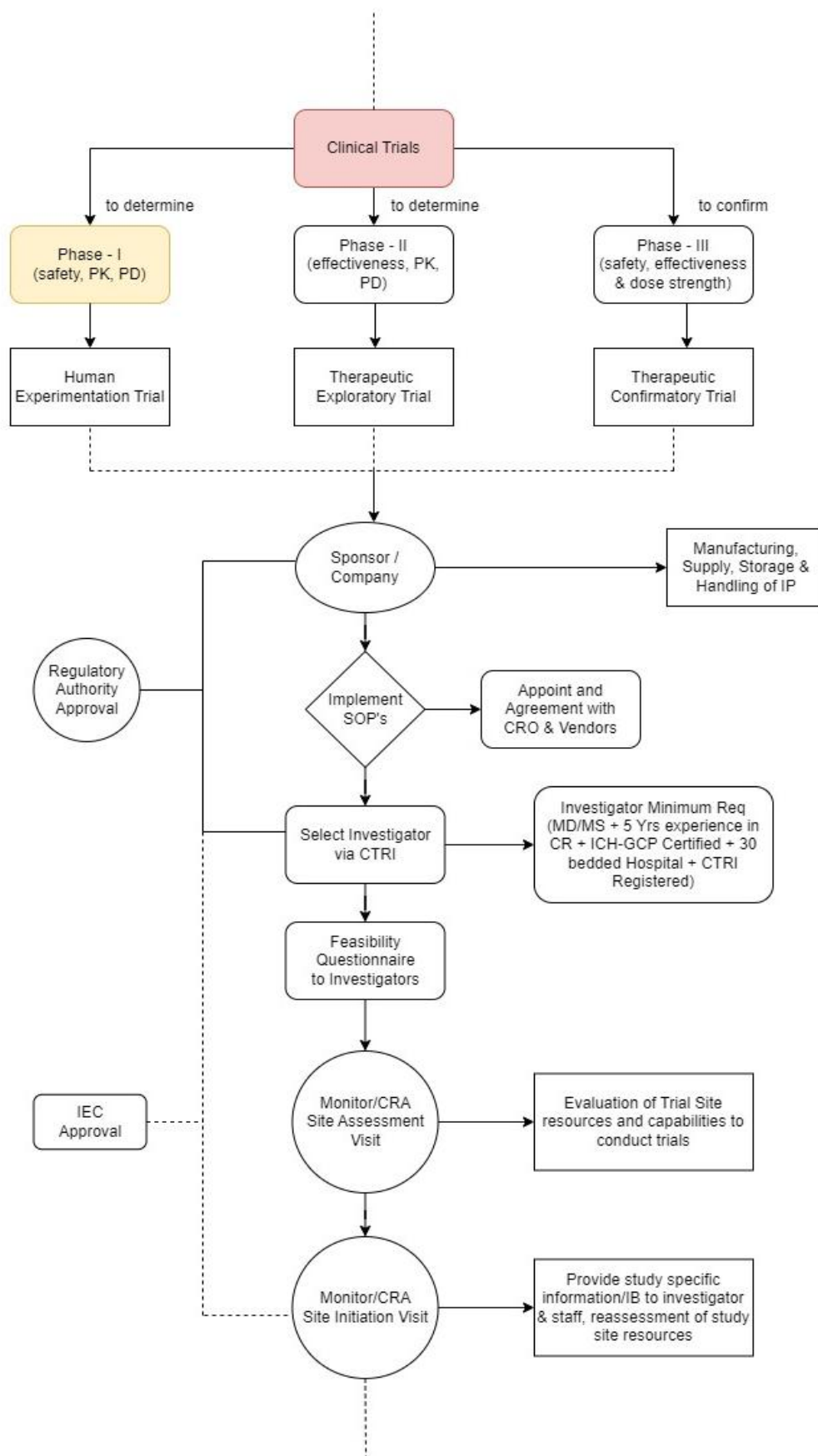
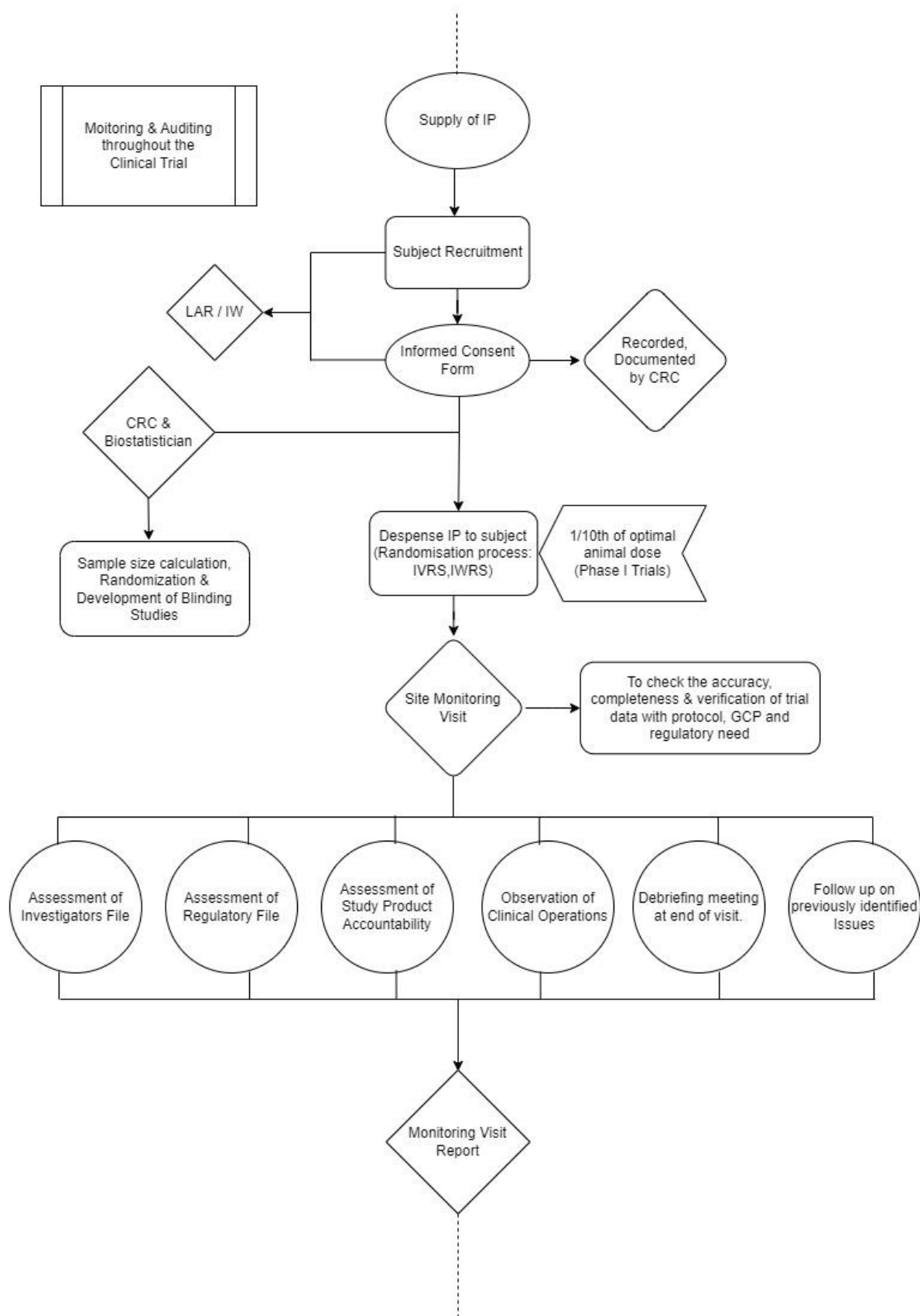


Figure 4: Clinical Trial Phases process

**Figure 5:** Clinical Trial Phases process (continue)

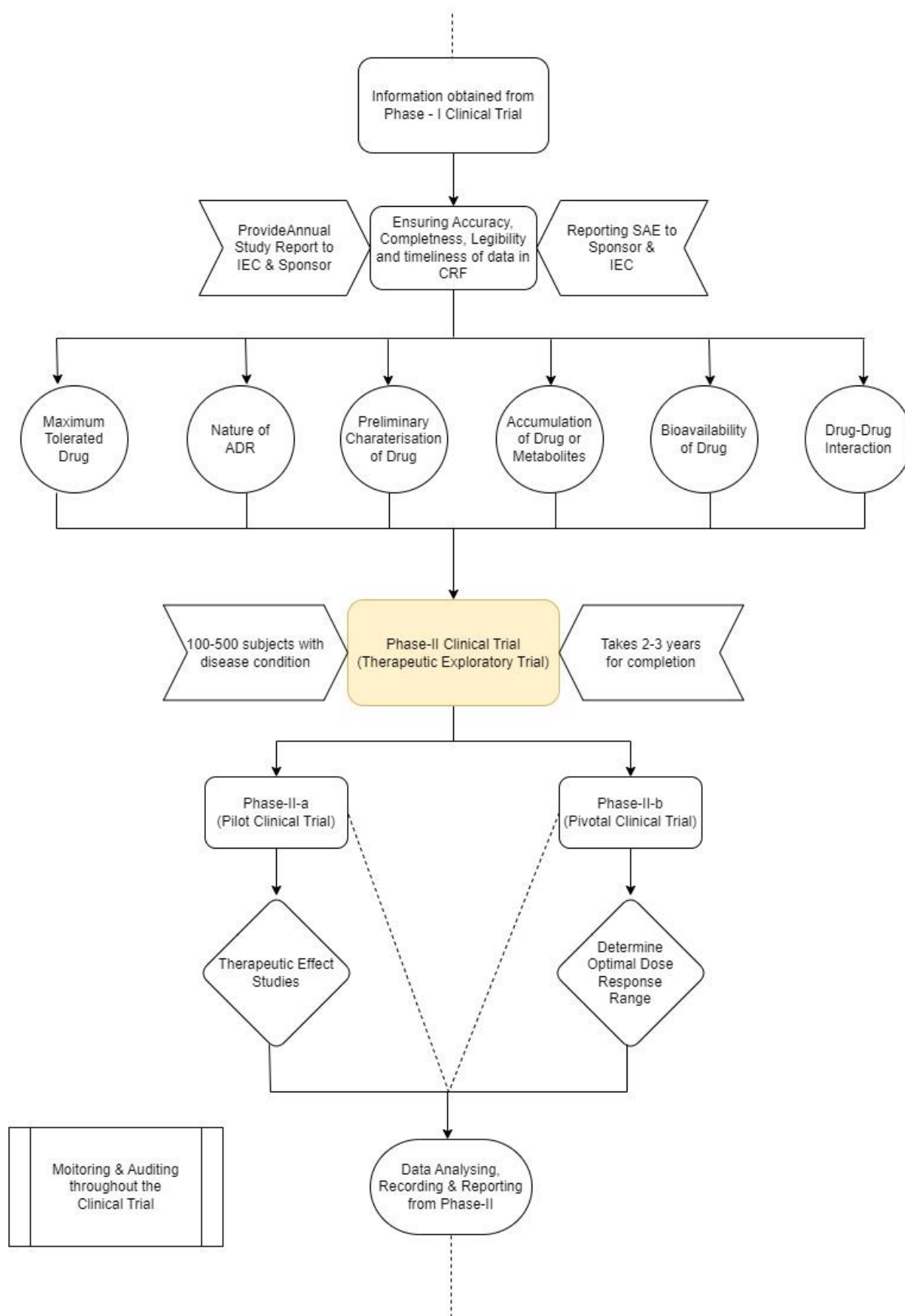
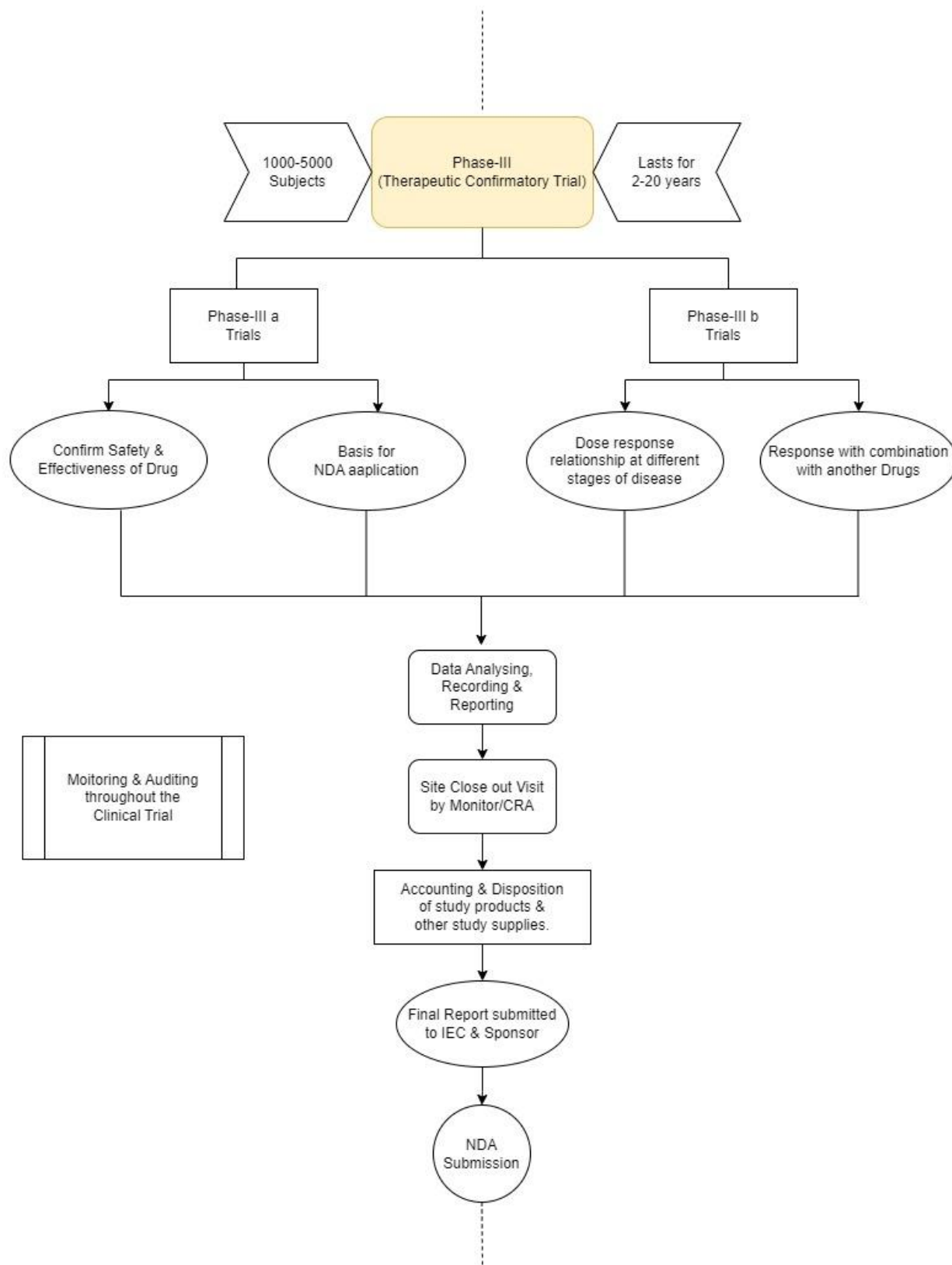


Figure 6: Clinical Trial Phases process (continue)

**Figure 7:** Clinical Trial Phases process (continue)

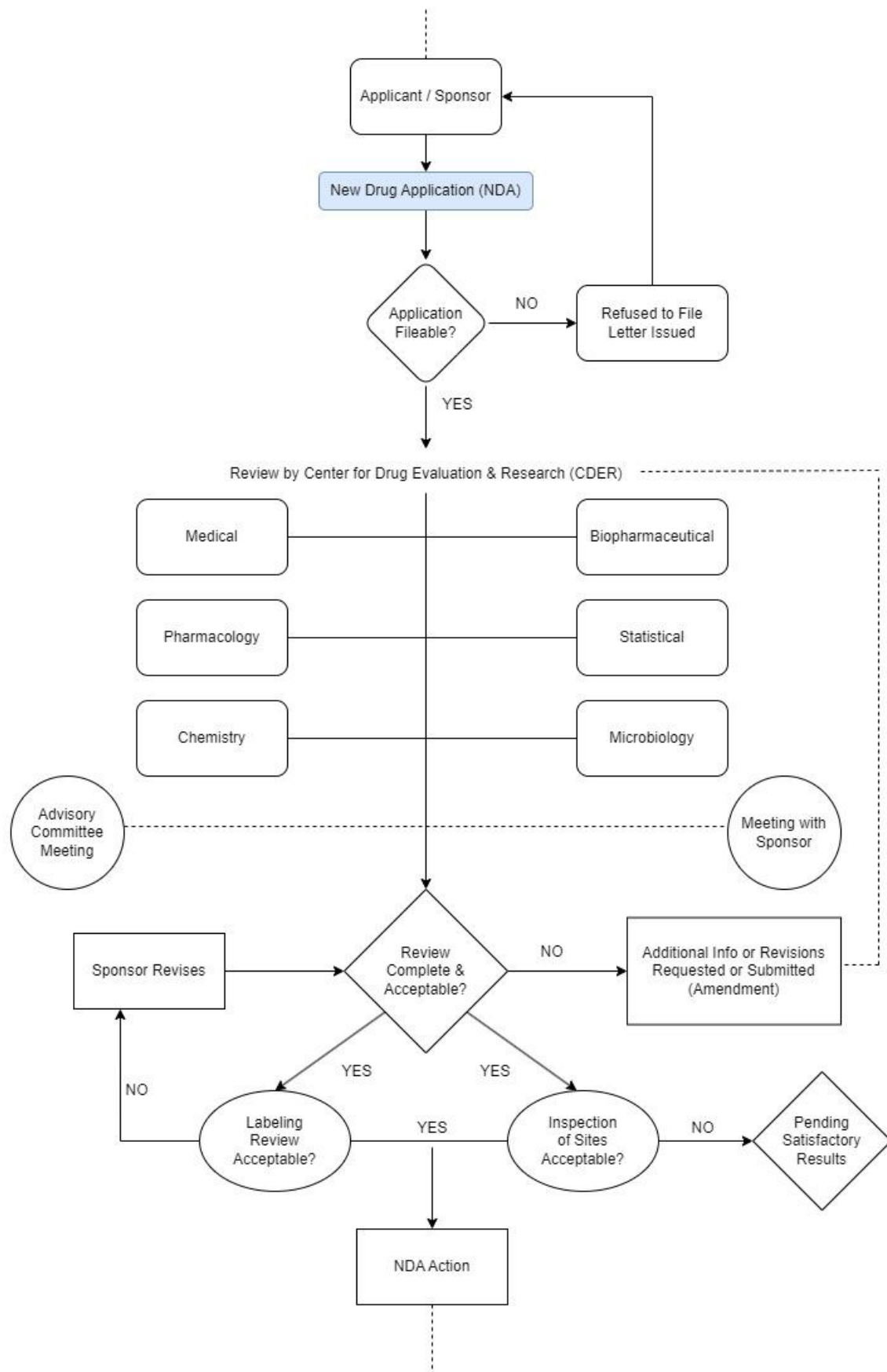


Figure 8: New Drug Application process

Roles and responsibilities of stake holders engaged in successful trials

Important stake holders involved in clinical trials are:

Sponsor/Manufacturing company/Contract Research Organization (CRO)
 Investigator/Principle investigator (PI)
 Institutional/Independent Ethics Committee (IEC)
 Clinical Research Associate (CRA)
 Clinical Research Coordinator (CRO)
 Regulatory Authority
 Study/Subject/Patient
 Biostatistician
 Clinical Data Manager (CDM)
 Responsibilities of Sponsor/CRO
 Manufacturing/supply and storage of investigational product
 Implement and maintain quality control, SPO's to ensure that the trials are conducted, documented, reported in compliance with protocol, GCP guidelines and applicable regulatory requirements
 Investigator selection via CTRI
 CRO, central lab appointment to carry out different trial related activities
 Study staff training
 Legal agreements with all parties taking part in clinical trials (CRO, lab, vendors, etc)
 Study management, data handling and record keeping
 Approval from regulatory authorities
 Clinical trial monitoring and auditing
 Compensation to subject taking part in clinical trial in accordance with guidelines
 Publication of trial results if required
 Preparing and submission of study related reports
 Reporting of SAE to all concerned authorities (IEC, regulatory authority)
 Ongoing safety evaluation of investigational product
 Sponsor can premature terminate the study ⁽²³⁾

Responsibility of Investigator

Adequately qualified, trained and experience to conduct clinical trial (MD/MS, 30 bedded hospital, ICH-GCP certified, CTRI registered)
 Have knowledge of IB, GCP and applicable regulatory regulations
 Permit monitoring and auditing at site
 Must provide medical care to subjects during and after the trials
 Declare appropriate conduct of study according to protocol, GCP guidelines and applicable regulatory requirements
 Obtain informed written, recorded consent form from each subject prior to study participation
 Handling, dispensing of investigational product to subject at site
 Maintain source data on care provided to subject at site during the trials
 To ensure accuracy, completeness, timeliness data reporting to sponsor in the CRF's
 Report all SAE's to sponsor and ethics committee as per given guidelines
 In case of premature termination of study, investigator should inform patient, sponsor and ethics committee

Provide annual report of study progress to sponsor and ethics committee
 Selection and recruitment of study subjects
 Documentation of deviation or violation of all protocol to sponsor and ethics committee
 Filling of essential documents ⁽²⁴⁾

Responsibility of IEC

Review all ethical aspect of clinical trial and execute aspects of same free from bias
 IEC should inform in written the terms of reference, condition of appointment, quorum requirement, i.e. should have specific SPO's to carry out the functions
 Review all trials related documents and provide approvals to conduct clinical trial in human subjects
 Review various SAE's and annual study reports
 Ensure compliance with GCP and applicable regulatory requirements
 To ensure the protection, well-being of subjects participating in clinical trial
 To terminate, hold clinical trial for reason that could affect rights and well-being of subjects participating in clinical trials ⁽²⁵⁾

Responsibility of CRA/Monitor

To verify that the investigator have adequate qualification, experience and trained
 To ensure that the site have adequate facilities and resources to conduct clinical trials
 To ensure that IP are supplied only to subjects who are eligible to receive at specified dose and time
 Reporting unwanted deviation or violation from protocol to sponsor
 To keep a record of monitoring visit with investigator and involved parties
 Study specific training to staff, if required
 Ensuring that all CRF's are correct, complete, signed and dated
 Should submit a written report after each visit to the sponsor in correspondence to investigator ⁽²⁶⁾

Responsibilities of CRC

Reviewing and completion of feasibility questionnaires received from sponsor or CRO
 Have adequate knowledge of trial protocol, IB, GCP guidelines and applicable rules and regulation
 Submission of trial proposal to IEC
 Evaluation of trial subjects
 Enrollment of trial subjects
 Completion and maintenances of trial related documents (source documents, essential documents)
 Report SAE to sponsor and IEC
 Archiving all trials related documents ⁽²⁷⁾

Responsibility of regulatory authority

Implementation of rules and regulations
 Review of trial proposal to conduct clinical trial
 Inspection, auditing of site, CRO, lab anytime
 Review protocol, AE, SAE or violations
 Terminate/Suspension of trial
 Approvals for conducting clinical trial and marketing authorization (IND, NDA) ⁽²⁸⁾

Responsibility of Biostatistician

Calculation of sample size
Implementation of specific trial design
Randomization of trial subject (using IVRS or IWR method)
Blinding method development
Interim data analysis
Interpretation of clinical trial data
Preparation of statistical report ⁽²⁹⁾

Responsibility of CDM

Design forms for tracking data/ data management
Generate data queries
Compliance with protocol, GCP guidelines and applicable regulatory requirements
Perform quality control audits
Train staff on technical procedures or software's
Prepare data analysis and progress report
Analyze clinical data using appropriate statistical tools ⁽³⁰⁾

Responsibilities of study subject

Read carefully informed consent form and other documents, ask question if they are not understand
Evaluate risk and benefits when deciding wheatear to participate or not in the trial
Do not sign the consent from until it is understood or feel comfortable to participate in trial
Follow rule and direction for medication and contraindication
Respect all staff and other participants participating in clinical trial
Be available at appointment date on time and inform staff if not present
Provide appropriate answer during trial screening
Inform immediately about any pain, discomfort or other problem during clinical trial
Keep information about trial confidential
If decided to withdraw from study, inform staff and follow the prescribed procedure for withdrawal ^(31, 32)

Abbreviation used

AE: Adverse Event
CDER: Center for Drug Evaluation and Research
CTRI: Clinical Trial Registry India
CRA: Clinical Research Associate
CRO: Contract Research Organization
CRC: Clinical Research Coordinator
CRF: Case Report Form
CDM: Clinical Data Management
GLP: Good Laboratory Practices
GCP: Good Clinical Practices
IND: Investigational New Drug
IVRS: Interactive Voice Responsive System
IWRs: Interactive Web Responsive System
IW: Impartial Witness
IP: Investigational Product
IEC: Independent/Institutional Ethics Committee
IB: Investigator Boucher
ICH: International Council for Harmonization
LAR: Legally Acceptable Representative
NDA: New Drug Application
MOA: Mechanism of Action
PI: Principle Investigator

PK: Pharmacokinetic
PD: Pharmacodynamic
SAE: Serious Adverse Event
SPO: Standard Operating Procedure

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