Phases of Clinical Trial

By
Swarnakshi Upadhyay
Assistant Professor
School of Pharmaceutical Sciences
CSJM University, Kanpur

Overview

- Introduction: Clinical research
- Drug development phases
- Pre-Phase 1 activities
- Phases of Clinical trial
- Regulatory approvals: IND & NDA
- Summary of Clinical trial phases

Introduction

- Clinical trial is a systematic investigation in human subjects for evaluating the safety & efficacy of any new drug.
- Clinical trials are a set of tests in medical research and drug development that generate safety and efficacy data for health interventions in human beings.

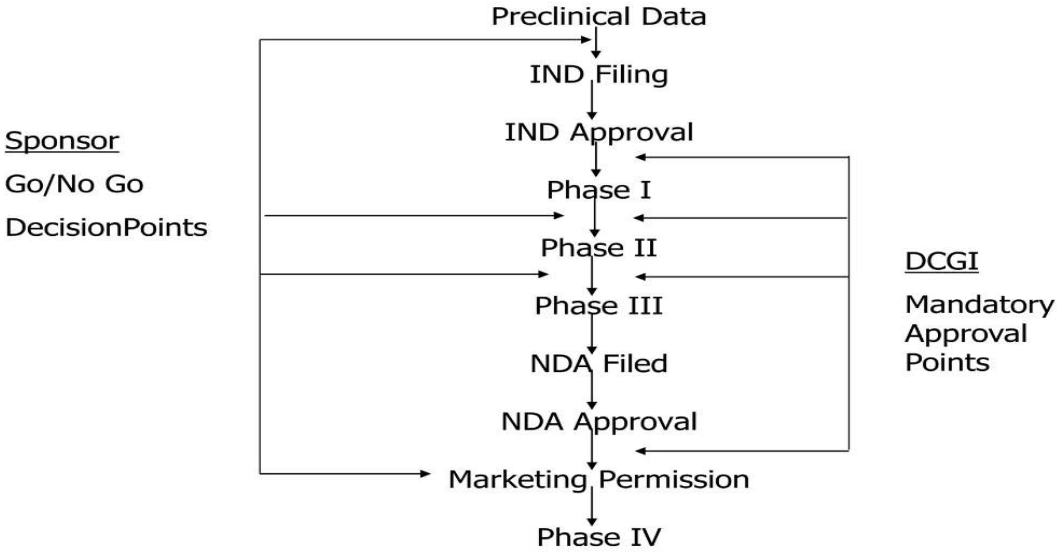
Introduction

- Clinical trials are conducted only when
  - satisfactory information has been gathered on the quality of the nonclinical safety
  - health authority/ethics committee approval is granted in the country where approval of the drug is sought.
- Clinical Trial is the mainstay for bringing out New Drugs to the Market.

Drug Review Steps

- 1. Preclinical (animal) testing.
- 2. An investigational new drug application (IND) : outlines what the sponsor of a new drug proposes for human testing in clinical trials.
- 3. Phase 1 studies
- 4. Phase 2 studies
- 5. Phase 3 studies
- 6. Submission of New Drug Application (NDA) is the formal step asking the FDA to consider a drug for marketing approval.
- 7. FDA reviewers will approve the application or find it either "approvable" or "not approvable."
- 8. Phase 4 studies

Clinical Drug Development Phase

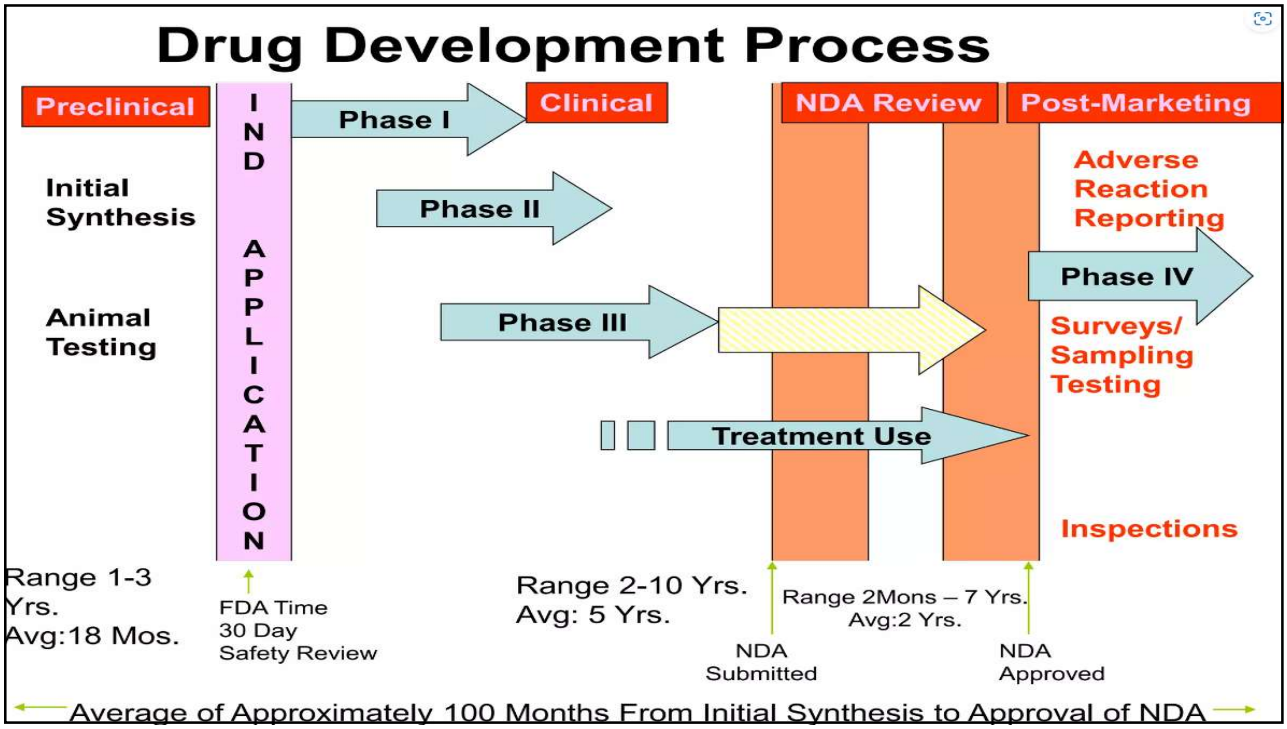


Phases of clinical trial

- Exploratory CT's (Proof of Concept) — Phase 0, Phase I, Phase II
- Definitive CT's (Pivotal) — Phase III, Phase IV

Phase 0, Phase I, Phase II, Phase III → Developmental CT's (Premarketing Phase of Clinical Drug Development)

Phase IV → Post marketing Phase



Preclinical evaluation phase (animal studies)

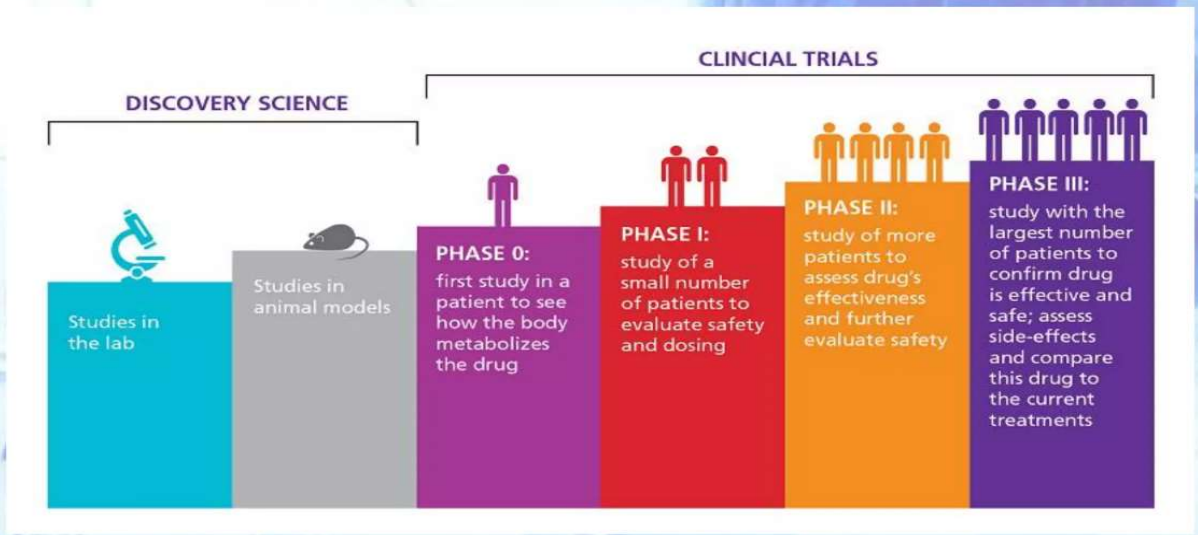
Major areas are:

- Pharmacodynamic studies in vivo in animals, In vitro preparation
- Absorption, distribution , elimination studies (pharmacokinetics)
- Acute ,sub acute, chronic toxicity studies (toxicity profile)
- Therapeutic index (safety & efficacy evaluation)

IND APPLICATION FILING

- Once preclinical studies have indicated the safety and efficacy of a drug an IND application has to be filed with the regulatory authorities.
- For obtaining regulatory Approval for Phase I, phase II and Phase III clinical evaluation.
- Contents of IND application:
  - Preclinical Data (All data from animal studies)
  - Information on composition and source of drug
  - Chemical and manufacturing information
  - Proposed clinical plans and protocol
  - Ethical Committee Clearance

PHASES OF CLINICAL TRIALS



PHASE 0 STUDY/MICRODOSING

- Study of new drug in micro doseS to derive PK information in human before undertaking phase I studies is called PHASE O
- *Micro dose:* Less than 1/100 of the dose of a test substance calculated to produce pharmacological effect with a max dose ≤100 micrograms •
- *Objective:* To obtain preliminary Pharmacokinetic data.
- *Preclinical Data:* Sub acute toxicity study in one species by two routes of administration.

PHASE 0 STUDY/MICRODOSING

- **Advantages:**
  - ♣ Less chances of adverse effects
  - ♣ Short duration
  - ♣ Less no. of volunteers
  - ♣ Reduced cost of development
  - ♣ Reduced drug development time
- **Limitations:**
  - ♣ Study mainly based on PK parameters - not efficacy and safety based
  - ♣ Agents having different kinetic characteristics between micro dose and full dose are not evaluated by phase 0 trials
  - ♣ Of Limited use for agents having Non linear PKs
  - ♣ The laboratory parameters are very limited and expensive, researchers have to depend on BA/BE labs

PHASE 1

- First stage of testing in human subjects.
- Designed to assess the safety, tolerability, PK and PD of drug.
- 20-25 healthy volunteers; Duration: 6-12 months.
- *Patients:* Anticancer drugs, AIDS therapy.
- The aim of a Phase I trial is to determine the maximum tolerated dose (MTD) of the new treatment.
- Kinds of Phase I:

  SAD: Single ascending dose studies.

  MAD: Multiple ascending dose studies.

  Food Effect: Investigates differences in absorption caused by food.

PHASE 1

SUBJECTS:

- Healthy human volunteers: Commonly used.
- Patient Volunteers: Cytotoxic drugs, AIDS therapy

-Patients in advanced stage of disease.

LIMITATIONS:

- Trial restricted to homogenous subjects.
- Performance extrapolated to heterogeneous market place.

PHASE 2

- It is a Therapeutic Exploratory Trial consists of 20-300 Subjects.
- To confirm effectiveness, monitor side effects, & further evaluate safety.
- First in patients (who have the disease that the drug is expected to treat).
- Duration: 6 months to several years.
- **Optimum dose finding:**
  - *Dose efficacy relationship*
  - *Therapeutic dose regimen*
  - *Duration of therapy*
  - *Frequency of administration*
  - *Therapeutic window*

PHASE 2

- For New Actions of a marketed drug, start with Phase II (Phase I exemption obtained).
- **Phase II Study Types:**
  - *Phase IIA*: Designed to assess dosing requirements.
  - *Phases IIB*: Designed to study efficacy.

PHASE II CLINICAL TRIALS:

Phase IIa	Phase IIb
EARLY PHASE	LATE PHASE
Pilot clinical trials	Pivotal clinical trials
20-200 PATIENTS	50-300 PATIENTS
Not multicentric	Multicentric
SINGLE BLIND comparison with a standard drug	DOUBLE BLIND compared with a placebo or standard drug

PHASE 3

- It is a Therapeutic confirmatory trial.
- Target population: several 100's to 3000 patients.
- Duration: Takes a long time, up to 5 years.
- To establish efficacy of the drug against existing therapy in larger number of patients, method of usage, & to collect safety data etc.
- • To assess overall and relative therapeutic value of the new drug Efficacy, Safety and Special Properties

PHASE 3

- Subtypes:
  - • Phase IIIA: to get sufficient and significant data.
  - • Phase IIIB: allows patients to continue the treatment, Label expansion, additional safety data.
  - • Phase III B studies are known as "label expansion" to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing.

Phase III

- **Phase IIIa**
- Prior to NDA
- Generates data on safety and efficacy

- **Phase IIIb**
- After the NDA but prior to the approval and launch.
- These may supplement or complete the earlier trials or may be directed to Phase IV trials.

PHASE 3: End Of Clinical Trial Activities

- Sponsor: Expert Committee review of Efficacy, safety and potential sales (Profit).
- Go-No Go decision to file new drug application with DCGI.
- Expert review by DCGI's Committee
- DCGI approval.
- NCE marketed ⇨ Phase IV begins

NDA: New Drug Application

- NDA Refers to New Drug Application.
- Formal proposal for the FDA/DCGI to approve a new drug for sale.
- Sufficient evidences provided to FDA/DCGI to establish:
  - Drug is safe and effective.
  - Benefits outweigh the risks.
  - Proposed labeling is appropriate.
- NDA contains all of the information gathered during preclinical to phase III.

PHASE 4

- Post Marketing Surveillance (PMS).
- No fixed duration / patient population.
- Helps to detect rare ADRs, Drug interactions and also to explore new uses for drugs [Sometimes called Phase V].

PERIODIC SAFETY UPDATE REPORTS :

To be submitted by the manufacturer every 6 months for 2 yrs and then annually for next 2 yrs after marketing approval.

- Harmful effects discovered may result in a drug being no longer sold, or restricted to certain uses

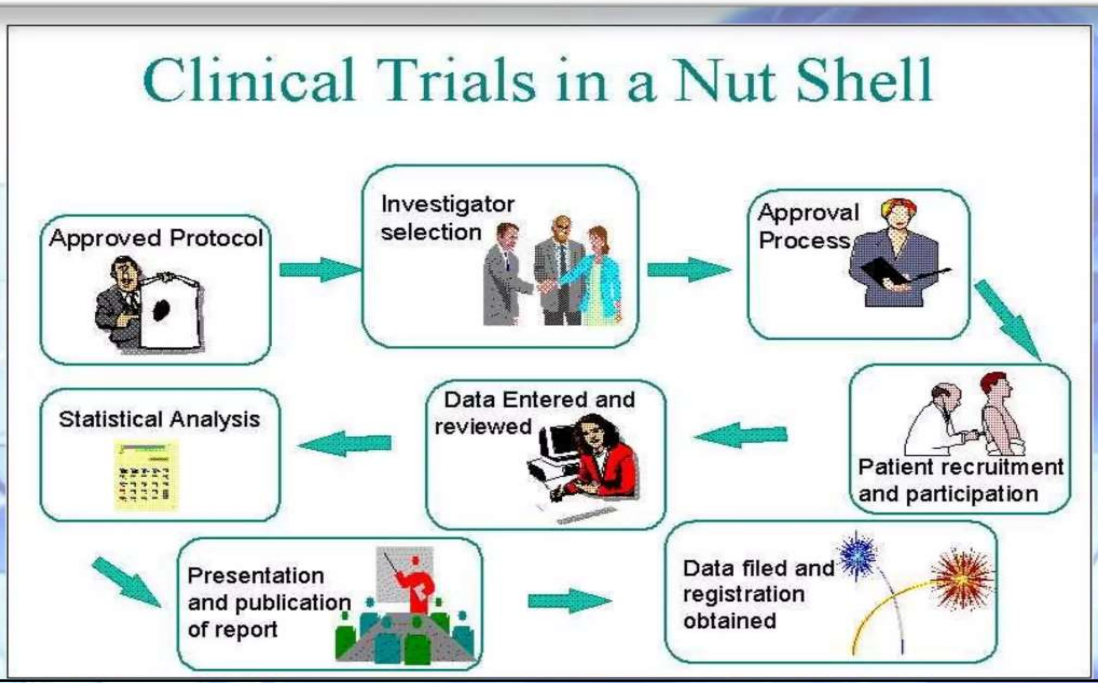
OBJECTIVES OF PHASE 4:

- Confirm the efficacy and safety profile in large populations during practice.
- Detect the unknown/rare adverse drug reaction/s.
- Evaluation of over-dosage.
- Identifications of new indications.
- Dose refinement: Evaluation of new formulations, dosages, durations of treatment.

REPORTING OF ADR:

- The ADR can be reported to a formal reporting system such as:
  - WHO International System
  - USFDA- Medwatch
  - UK- Yellow card system
  - INDIA- National Pharmacovigilance Programme (CDSCO)

PHASES OF CLINICAL TRIALS



CONCLUSION

- Clinical trial is a human experiment designed to study the efficacy and safety of a new drug/intervention.
- Involves Phase 1-4 with specific objectives and end results.
- Application to Regulatory authority:
  - IND – Permission to conduct CT
  - NDA – Permission to Market New drug.
- Well designed and effectively executed clinical trials form the base of therapeutic decisions.
- CT must follow guidelines & protocol to ensure well-being of participants.
- Ultimate Goal of Drug Development - Drug Approval