# CHAPTER 2.2

# VARIOUS PHASES OF CLINICAL TRAIL

## SHORT ANSWERS

### 1. Note on Randomized Clinical trail

A trail in which subjects are randomly assigned to two or more groups, with one group acting as a control or comparison group & other groups recieving the treatment under investigation.

### 2. Define Phase Zero

A study of new drug in micro doses to device PK information in human before undertaking Phase I studies is called "Phase Zero."

Micro dose = $\leq 1/100$ of the dose of a test substance calculated to produce pharmacological effect within a max dose $\leq 100$ micrograms

Objective:

To obtain preliminary PK data.

## 3. Note on open labelled clinical trails

It is a type of clinical trail in which both the researcher and participants know which treatment is being administered. This contrasts with single blind and double blind methods

It is appropriate for comparing two very similar treatments to determine which is most effective.

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## 4. Methods of Sample Size calculations in Clinical trails

Steps in deciding a sample size

i. Determine Goals
ii. Determine the desired precission of result
iii. Determine the confidence levels
iv. Estimate degree of variability
v. Estimate the response rate

$$n = \frac{\frac{P[1-P]}{\frac{A^2}{Z^2} + \frac{P[1-P]}{N}}}{R}$$

→ wherein: Sample size required

- N = No of people in population
- P = Estimate variance in ppl
- A = precision desired
- Z = Based on confidence level
- R = Estimate response rate

## 5. What are the Objectives of Phase 2 studies

- To evaluate the effectiveness of the drug for a particular indication in patients with the condition under study.
- To determine common short term side effect & risk associate with drug.
- Studies in phase II should be conducted in a group of patients who are selected by narrow criteria leading to a relatively homogenous population.
- To determine dose & regimen for phase III trails doses used in phase II trails are usually less than the highest dose used in phase I.
- Evaluation of potential study end point.

## 6. Use of Placebo in clinical trails

→ A placebo is a pharmaceutically inert substance, is the clinical researcher's analogue to the scientists control experiment.

→ A placebo controlled trail compare a new treatment with a placebo.

→ It is used to prove a new treatment effectiveness, belief in ability of drug to curve & ease allocating of subject in control & study groups.

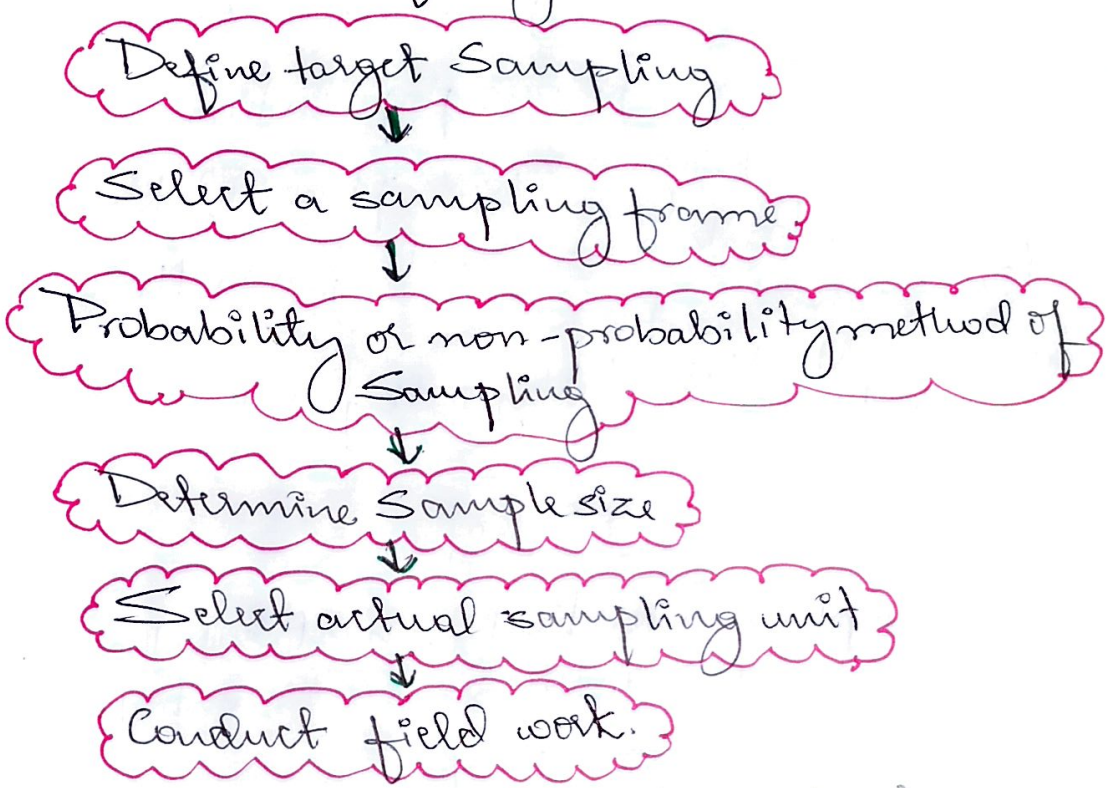
⇒ The placebo controlled trail is widely regarded as the gold standard for testing the efficacy of new treatments.

## 7. Principles of trail Subject Sampling

The subject should be representative of target population hence inclusion & exclusion criteria are considered in subject sampling

**Size:** It should be not too large & not too small

**Principle:**
- Statistical regularity
- Inertia of large numbers




Subject Sampling flow chart

# Discuss in detail the various phase of clinical trial

10M, 5M

## 1) phase I :

human Pharmacology phase

1. phase I trials are the first stage of testing in human subjects
2. conducted in healthy volunteers.
- number of subj : 20-80
3. Duration of trial : up to one-month
4. these experiments determine the maximum tolerated dose (MTD) or non-toxic effect level.
5. the MTD in animal is converted to a dose considered equivalent in man. (HED)
- once the highest dose is established 4-5 fractions are selected to complete the dose range to the tested in the first phase I study.
- The starting dose is always much lower than the highest one
- The subjects are divided into groups & experimentation start with group assigned to the lowest doses

objectives: SA

1) obtain indication on the safety & tolerability of the drug over a wide range of doses.

2) study the p'kinetic & p'dynamic properties of drug

3) a sequence of single dose is used. the selection of the dose range to test is usually obtain from animal toxicology test.

4) maximum tolerated dose: to determine the tolerability of the dose range expected to be need for later studies & to determine the nature of adverse reaction that can be expected.

5) p'kinetic: that is characterisation of a drug A, D, M, E & determine p'kinetic parameters in diff age group to support dosing recommendation.

6) bioavailability & bioequivalence studies

## Types of phase 1 Trials

- SAD : Single assending dose
- MAD : multiple assending dose

## SAD Single Assending dose

- sad studies are those in which small groups of patient are given a single dose of drug, while they are observed & rested for a period of time.

- if they don't exhibit ADR, the therapeutic data is roughly in line with predicted safer values, the dose is escalated & a new group of patient is given a higher doses.

## MAD Multiple Assending dose.

- mad studies are conducted to better understand the p' kinetic & p' dynamic of multiple doses of the drug.

- in these studies, a group of patient recives multiple low dose, while samples are collected at various time

## 2) phase II (~~therapeutic exploratory~~ therapeutic Exploratory trail)

-are the initial safety of the therapy has been conformed in phase I trials, phase II are conducted.

2) They are controlled clinical studies to access the clinical efficacy of the therapy.

3) These phase II trials are called ~~therap~~ exploratory trial

- performed on larger group (50-300)

- Duration : several months

objective

1) - to evaluate the effectiveness of the drug for a particular indication or indication in patients with the condition under study.

2) - to determine common short term side effect & risk associate with drug.

3) - studies in phase II should be conducted in a group of patient who are selected by narrow criteria leading to a relatively homogenous population.

4) to determine dose & regimen for phase III trials

doses used in phase II are usually less than the highest dose used in phase I.

5) - evaluation of potential study end point

## Types of phase II

i. Phase II A → design to assess dosing requirment

ii. Phase II B → " " study efficacy.

### i. Phase II A : (Assess dosing requirement)

- proof of concept studies II A is useful for dealing with innarative compound.
- Aim to confirm mechanism of action.
- it is based only in proofs in vitro & animal models.
- the sample is rigorously selected in that subj with a pure text book like clinical picture are included.
- the proof of concept stidies are generally small & complex.

ii. Phase IIB: (Study efficacy).

- Dose finding or dose ranging studies.

- it includes:

1) Studies in elderly patient.

2) " comparing diff races

3) " in patient with hepatic or renal insufficiency

## 3) Phase III Therapeutic explor Confirmatory Trail.

- phase III are randomized controlled multicenter trials on large patient group (300-3000) or more depending upon the disease

- Duration → several years

objective

1) - to definite assessment of the efficacy of the new then in comparision with current gold standard treatment

2) - to conform therapeutic benefit.

3) - to conform the preliminary evidence accumulating in phase II that the drug is safe & effective

4) to gather additional info about efficacy & safety that is needed to evaluate the over all benefit-risk relationship of the drug.

## Phase IV

post marketing trials

- are studies performed after approval & related to the approval indication.
- go beyond the prior demonstration of the drug safety, efficacy & dose definition.
- include additional drug-drug introduction, dose-response or safety studies & trials designed to support use under approved indicate

ex objective

1) comparision b/w the new treatment & frequently used current treatment
2) p' economic assessments, intended to extend the info obtaine in phase I.
3) Safety assessment via clinical trials & studies pharmacovigilanc
4) p' dynamic assessment

Q. Methods of Randomization.

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## Randomization Methods

→ it is a procedure that introduce chance into the assignment of subject to particular Treatment grp.

→ It is an effective way of reducing the selection bias bcz it gurantees that Treatment assignment is not based on pt's characterization.

→ Benefits of Randomization :

- Eliminate selection bias
- Forms basis for statistical Tests
- Balance arms c respect to prognostic variables.

→ Criteria for randomization :

- unpredictability
- Balance
- simplicity

→ Methods : 1, Simple Randomization
2, Constrained randomization by Blocking
3, Constrained randomization by stratification
4, Blinding

## 1) Simple Randomization

1, This method is equivalent to tossing a coin for subject that enters a Trial, such as heads = Active, Tail = placebo.

2, Generally the Random number generator is used.

3, It is simple & easy to implement

4, However it can get imbalanced in Treatment assignment especially in smaller Trials,
large imbalance can reduce the credibility of Trial result & ↓ statistical power

## 2) Constrained Randomization by Blocking

1, This is restricted Randomization process that improve balance in number of subjects assigned to each Treatment group

2, A block size is selected & contains a pre specified number & proportion of Treatment assignment.

3, the patients are randomized ε a forced balance of Treatment within each block

4, A sequence of block's make up the randomization Trial.

5, This method ensure equal Treatment allocation within each block if the complete block is used.

## 3) Constrained Randomization by stratification

1, If there are important factors (prognostic factors) ≤ are known to influence Treatment effects, it is desirable that the Treatment group are as similar as possible ≤ respect to Those factors
(eg: gender : M & F , Age : ≤65 ≥ = 65)

2, There may be an imbalance within Treatment group with reguard to These factors, ≤ ↓ statistical power, this Can be avsided by using a statistified randomizatio

3, Each situation Corresponds to a level of one factor or to a Combination of levels of several factors.

## 4) Blinding

1, Treatment Blinding or masking is an effective way to ↑ the objectivity of the person observing experimental outcomes

2, when the Treatment are masked, the bias or expectation of observe do not influence the measurement Taken.

3, Blinding is intended to minimize the potential bias resulting from difference in measurement, Treatment of pts or interpretation of results.
that could arise as result of investigator knowledge of the assigned Treatment.

→ Single Blind :

- The patients are unaware of Treatment receive,
- The experimentor is aware of who or what belongs to the control grp & the experimental grp.

→ Double Blind :

- Both the patients & investigator are unaware of ≤ Treatment is being administered.

→ Triple Blind :

- The subject, researcher & person administering the Treatment (often a pharmacist) are unaware to what a is being given.

→ unblinding :

- individual may only be unblinded in the event of a serious advese evets.

# CLINICAL TRIALS



## 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

## DRUG REVIEW

- Before one can initiate testing in human beings, extensive pre- clinical or laboratory research is required
- Research usually involves years of experiments in animal and human cells.
- If this stage of testing is successful, the sponsor then provides this data to the FDA requesting approval to begin testing in humans. This is called an Investigational New Drug (IND) Application
- If approved by the FDA, testing in humans begins. This is done through a formally written and approved protocol.





## 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)





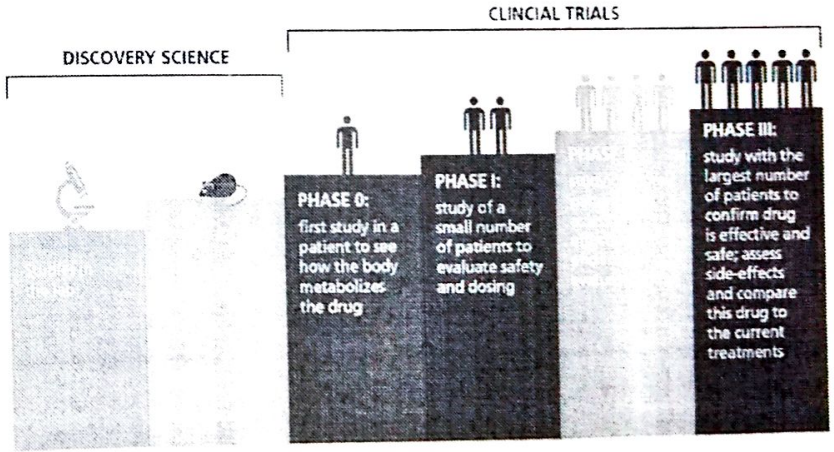
## IND APPLICATION FILING

- 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 0
- *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 StudyTypes:**
  - *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.
- 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:

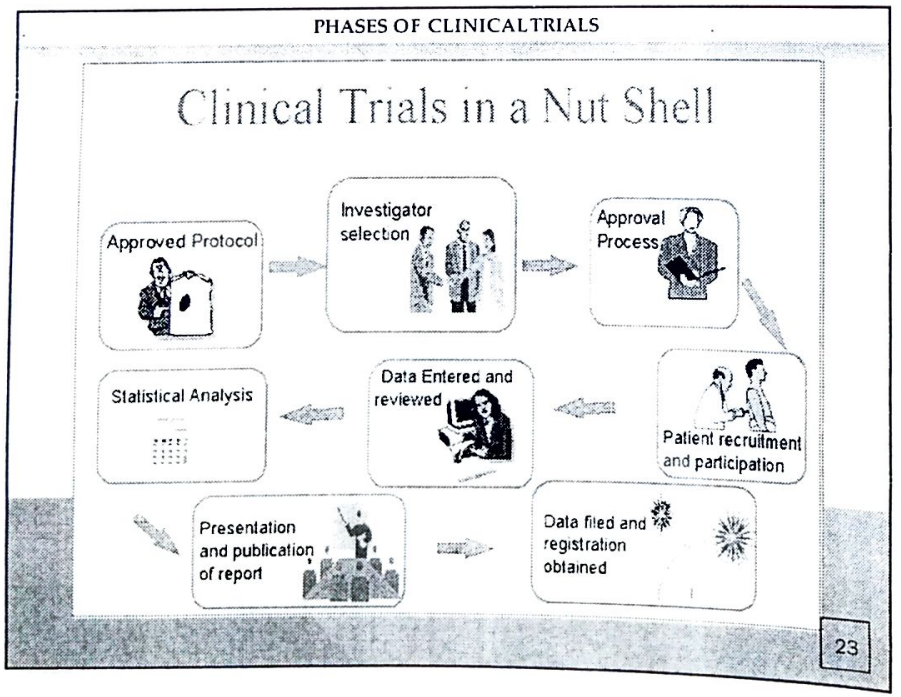
- Confirm the efficacy and safety profile in large populations during practice.
- Detect the unknown/rare adverse drug reaction/s.
- Evaluation of over-dosage.
- Identifications of new indications.
- Dose refinement: Evaluation of new formulations, dosages, durations of treatment.

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)












## 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