2. CLINICAL TRIALS

PART III

CLINICAL PHARMACOLOGY

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Objectives:

- At the end of practical class the student shall be able to:
    - Understand the phases of clinical trial in order to evaluate drugs in man.
    - Appreciate ethical requirement for conducting a clinical trial.
    - Understand components of informed consent form.

- The ultimate aim of pharmacological studies in animals is to find out therapeutic agent suitable for clinical evaluation in man.

- Administration of a biologically active agent is associated with an element of risk which cannot always be predicted by even the most careful and exhaustive animal experiments.

- Hence, the drug has to be carefully evaluated in man himself for its safety and efficacy before it is accepted for therapeutic use.

- The process of evaluation of a drug in human beings to determine its efficacy, toxicity etc. is known as clinical trial.

Methods:

To govern the stepwise evaluation of new pharmaceutical products in man, the Food and Drug Administration has categorised clinical trials in to following phases.

Phase	Description
I.	**First exposure in man** ◦ To establish tolerability, dose, duration of action, other preliminary information on pharmacodynamics & pharmacokinetics ◦ Conducted in ***healthy human volunteers*** (n = 25-50)
II.	**Further evaluation** ◦ The drug is studied for the first time ***in patients*** at limited centres ◦ Detailed assessment of efficacy and safety in relatively small number of patients with specific indications (n = 100-200) ◦ To determine final dosage form of drug
III.	**Controlled clinical trial** ◦ The drug is evaluated in large number of patients (n=250-500) at various centres simultaneously (multi-centric study) ◦ Comparison against standard therapy or a placebo
IV.	**Post marketing surveillance for efficacy and safety** ◦ Wider exposure to large number of patients (minimum n = 3000) under actual conditions of use ◦ Constitutes monitoring the safety of drug

Design:

The clinical trial is designed to ensure precise, informative and convincing comparison made between the test drug and standard drug or placebo. So the treatments may be compared:

A. **Between groups of patients (parallel group studies) -** where the drug is given to one group and results are compared with those from other group (control group).

B. **Within a group of patients crossing over from one treatment to other (crossover studies) -** where the drug is alternated with a placebo or previously established drug, in all patients under the study.

Sample size:

- A sufficient number of patients must be studied to give realistic chance of detecting a clinically important difference.

Randomization:

- In order to balance the control and treatment groups and to avoid any selection bias, allocation is carried out by randomization by a person who is completely unaware of therapy allotted to individual group.
- Individuals may be paired for important factors like age or sex.
- Order of treatment can be randomised if patient acts as his own control.
- Simple randomization can be done by toss of coin, throw of dice or by table of random numbers.
- The last method is most practical.

Ethical requirements:

- Ethics is the study of right behaviour of an individual in a civil society.
- Two important components of ethics are:
  - **Ethics committee:** The Institutional/Independent ethics committee (IEC) reviews the submitted research plans (protocol), study design, confirms risk/benefit assessment, safety of the volunteers etc. and approves/disapproves initiation and conduct of the trial.
  - **Informed Consent Form (ICF):** Informed consent is a process whereby volunteer/patient willingly (voluntarily) gives consent to participate in study/trial after being adequately informed about objective, nature, procedure, duration, associated risk and benefits, inconvenience that may be caused by participating in study.
    - ICF is a medico-legal document printed in simple, understandable and non-technical language known to participant (subject), signed and dated personally by participant and investigator.
    - If the participant is illiterate, an impartial witness (not related to trial) should be present during entire discussion and should sign ICF.
    - The volunteers should be given freedom for questions, discussion and allow refusing or withdrawing from study without penalty.

Bias:

- There are two types of bias: **1) Participant bias** and **2) Observer bias.**
- The patients who tend to respond to any treatment positively are known as placebo responders.
- **The subject bias** is usually controlled by single blind study design.
  - This involves administration of an inert material with same physical appearance, colour, shape, odour etc.
  - as active dosage form known as placebo or dummy medication.
- **The observer's bias** can be discounted by using double blind study design in which the evaluating physician and the subject both are unaware of the nature of drug being administered.
  - The codes are allotted to each medication packet and the code is not broken until all of the clinical data have been collected.

Statistical test:

A well executed trial should be backed up by accurate statistical analysis, adopting appropriate methods and proper interpretation of significant or non-significant findings.

Assignments:

What are the aims and objectives of research in human beings?

What do you mean by a double blind trial?

What is the role of placebo in controlled clinical trials?

How will you eliminate bias while conducting clinical trials?

What are the two important components of ethics in clinical trials?