CLINICAL TRAILS

Dr.RLC.SASIDHAR

Associate Professor, CHIPS

Clinical Trails

- Clinical trials are studies performed with human subjects to test new drugs or combinations of drugs, new approaches to surgery or radiotherapy or procedures to improve the diagnosis of disease and the quality of life of the patient.
- clinical trials are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol.

- **Meinert:** “ a planned experiment designed to assess the efficacy of a treatment in man by comparing the outcomes in a group of patients treated with the test treatment with those observed in a comparable group of patients receiving a control treatment, where patients in both groups are enrolled, treated, and followed over the same time period."

Clinical trials help physicians discover the answers to the following questions

- Is the treatment safe and effective
- Is the treatment potentially better than the treatments currently available
- What are the side effects of the treatment?
- Does the treatment have any possible risks?
- How well does the treatment work

- The first clinical trial of a novel therapy was conducted accidentally by the famous surgeon Ambroise Pare in 1537. In 1537 while serving with the Mareschal de Motegni he was responsible for the treatment of the battlefield wounded soldiers. As the number of wounded was high and the supply of conventional treatment – oil was not adequate to treat all the wounded, he had to resort to unconventional treatment. He describes,' at length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine
- One of the most famous clinical trials was James Lind's demonstration in 1747 that citrus friuts cure scurvy. He compared the effects of various different acidic substances, ranging from vinegar to cider, on groups of afflicted sailors, and found that the group who were given oranges and lemons had largely recovered from scurvy after 6 days.

Historical Events in the Development of Clinical Trials.

Date	Author	Event
1747	Lind	Experiment with untreated control group (Lind, 1753)
1799	Haygarth	Use of sham procedure (A Placebo Surgery)
1800	Waterhouse	U.S. based smallpox trial
1863	Gull	Use of placebo treatment

Classification of clinical trials

The U.S. National Institute of Health(NIH) organizes trials into five different types:

- **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 or minerals.

- **Screening trials**:

  Test the best way to detect certain diseases or health conditions.

- **Diagnostic trials**:

  Conducted to find better tests or procedures for diagnosing a particular disease or condition.

- **Treatment trials**:

  Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

- **Quality of life trials**:

  Explore ways to improve comfort and the quality of life for individuals with a chronic illness.

- **Compassionate use trials** :

  Usually, this involves a disease for which no effective therapy exists, or a patient that has already attempted and failed all other standard treatments and whose health is so poor that he does not qualify for participation in randomized clinical trials.

Primary responsibility for regulation of clinical trials rests with agencies of the U.S. Department of Health and Human Services (HHS).

- Office for Human Research Protections (OHRP)
- Office of Civil Rights (OCR)
- Food and Drug Administration (FDA)
- Office of Research Integrity (ORI)
- National Institutes of Health (NIH)
- Centers for Medicare and Medicaid Services (CMS)

Regulatory Agencies in INDIA

- Ministry of Health and Family Welfare
- Central Drug Standards Control Organisation
- Indian Council of Medical research
- Ministry of chemical and fertilizers

Ethics of Clinical Trials

- **Respect for Persons:** Treatment of person as autonomous

- **Beneficence:** conflict between good of society vs. individual

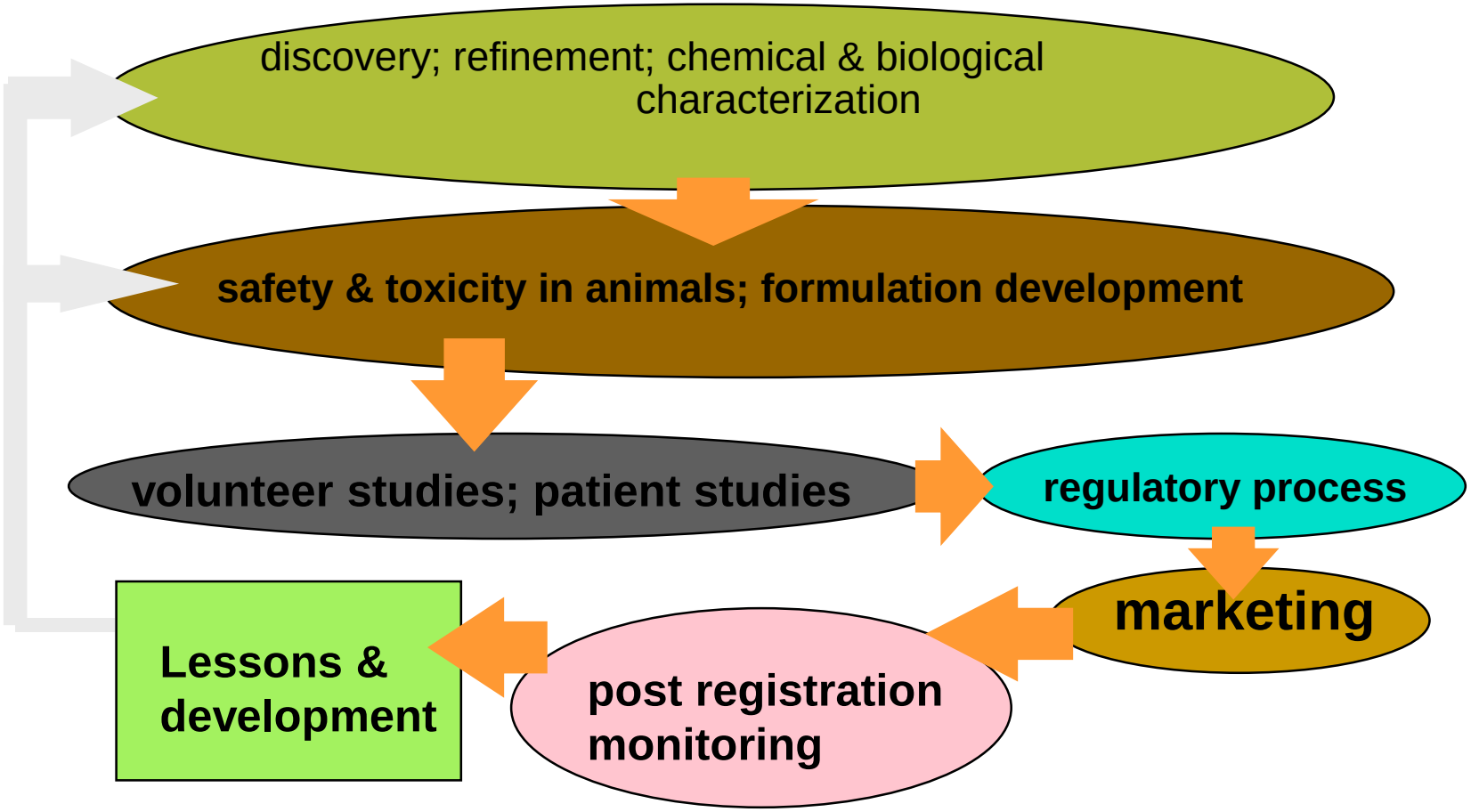
- **Justice:** Treatment of all fairly & all equally share benefits & risks

How are patients benefited and protected?

Rationale of Clinical Trials

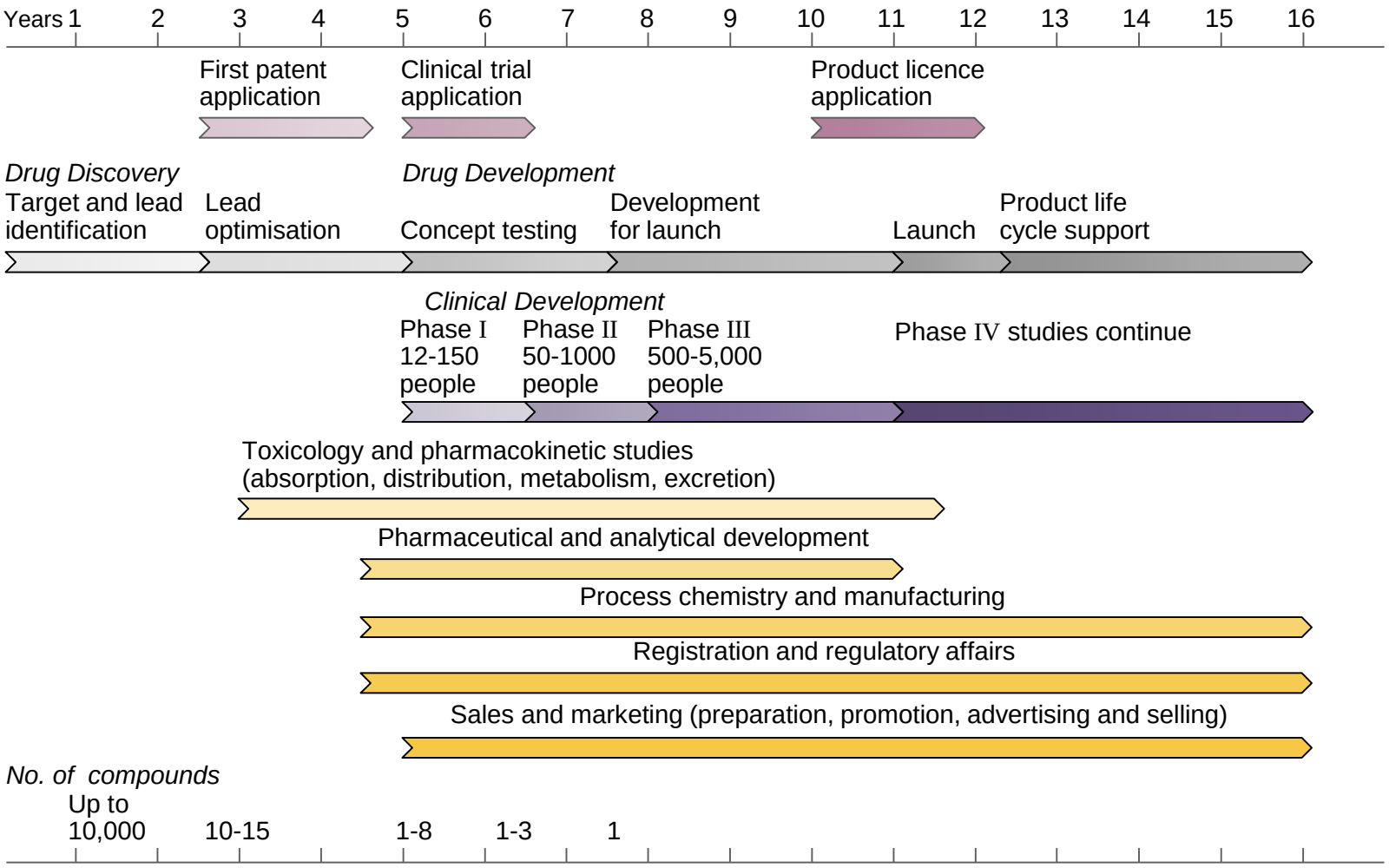
- Clinical trials are the method for determining whether an intervention has a postulated effect.
- Clinical trials develop scientific evidence with acceptable levels of risk and sufficient scientific defensibility.
- Variability in measurement and subjects is inherent but accounted for in such studies.
- Bias, which may exist in observational studies, is avoided through randomization and other techniques.

Drug discovery/development process



Discovery=find new active structure : Development=convert it to a useful drug

The path to a new medicine



PRE-CLINICAL TRIALS

As described earlier, a preclinical trial involves in vitro (test tube or cell culture) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information.

Steps involved in designing a Pre-Clinical Trial/Study:

• **Identifying a Drug Target:** All drugs target specific points in biochemical pathways. Almost all illnesses except infectious diseases are caused by problems associated with specific biochemical pathways. Identifying the appropriate target step in the biochemical pathway is critical and can determine the chances of success of the prospective drug molecule.

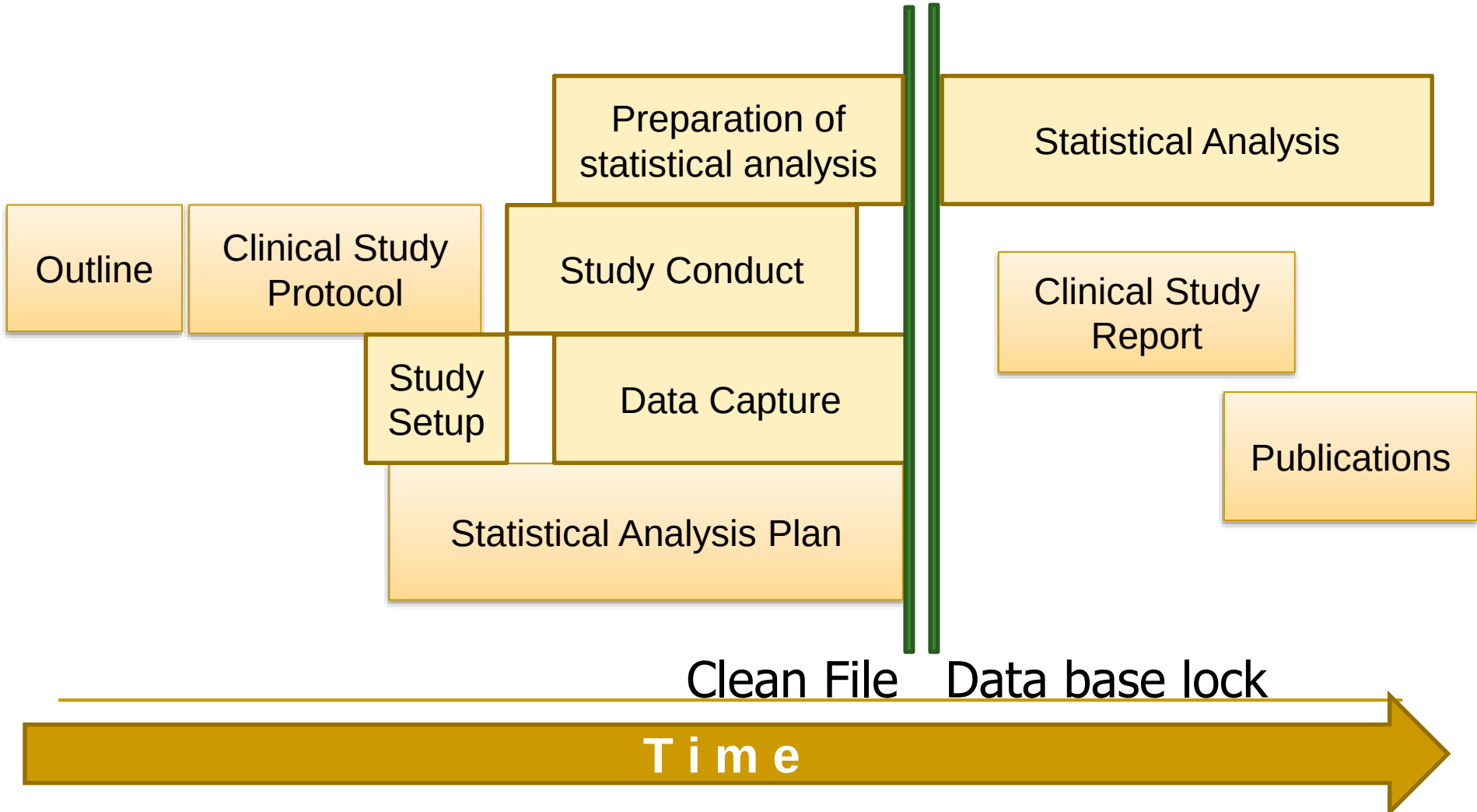
• **Developing a Bioassay:** A bioassay is a "live" system that is devised to measure the effects of a drug. It varies from a cell or tissue culture system to organs or even a whole living being. For example, a zebra fish embryo can be used to observe the effects of drugs on bone density, blood vessel growth, among other systems.

•**Screening the drug in the Bioassay:** This is a screening test done with the bioassay to determine the safety and effectiveness of the molecule. The drug must clear this step.

•**Establishing effective and toxic doses**: This step involves establishing the safe and toxic dose ranges. Future studies take cues from here about the dose ranges to be tested in humans.

•**Filing for an approval as an IND (Investigational New Drug):** After all these steps are cleared the drug is fit for an application to the FDA as an IND.

The Clinical Study Process



Essential elements

- Human subjects
- Intervention
- Prospective in nature with follow-up observations
- Inclusion and exclusion criteria
- Risks and benefits for patients
- Informed consent required
- High cost
- Limited number of subjects
- Cannot completely control a subject's environment

Clinical Trial Protocol

- A **clinical trial protocol** is a document that describes the objective, design, methodology, statistical considerations, and organization of a clinical trial.

1 **General Information**

1.1 Protocol title, protocol identifying number, and date.

1.2 Name and address of the sponsor and monitor

1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert for the trial.

1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

1.6 Name, title, address, and telephone number(s) of the qualified physician, who is responsible for all trial-site related medical decisions (if other than investigator).

1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

2. **Background Information**

2.1 Name and description of the investigational product(s).

2.2 A summary of findings from non clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

2.6 Description of the population to be studied.

2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

3 **Trial Objectives and Purpose**.

4 **Trial Design**. The scientific integrity of the trial and the credibility of the data from the trial

A description of the trial design, should include:

4.1 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

4.2 A description of the measures taken to minimize/avoid bias.

4.3 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

5 **Selection and Withdrawal of Subjects**

5.1 Subject inclusion criteria.

5.2 Subject exclusion criteria

5.3 Subject withdrawal criteria

6 **Treatment of Subjects**

6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s),

6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.3 Assessment of Efficacy

6.4 Assessment of Safety

6.5 Statistics

6.6 Procedure for accounting for missing, unused, and spurious data.

7 Data Handling and Record Keeping

Study Participant Recruitment

Identify eligible participants

Explain study

Provide informed consent

Reassess eligibility

Assign to one group

Participants should be told

May have side effects (adverse effects)

Time commitment

Benefits & risks

May withdraw at any time

Enrollment 100% voluntary

Institutional Review board

- Participants' rights are protected by Institutional Review Boards [IRBs]
- An IRB is defined as any board, committee or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects"

Informed Consent

Objectives of Informed Consent

To Ensure

- Voluntaries
- Comprehension
- Information

To Demonstrate That

- Person freely gave consent to participate
- Consent given by a competent person
- Person has been given all information
- Person knows this is research – not treatment

The Possible World of Clinical Trial Designs

- Randomized/blinded trial
- Randomized/double blinded trial
- Non-randomized concurrent controlled trial
- Placebo trial
- Parallel group design
- Crossover design
- Withdrawal trial

- **Randomized:** Schemes used to assign participant to one group. o Ex: Every 3 gets higher dose
- **Blinded:** Participants do not know if in experimental or control group
- **Double Blinded:** Participants and staff do not know group assignment
- **Placebo:** Inactive pill w/ no therapeutic value

Parallel group design

- The most common trial design in which subjects are randomized to one or two or more arms, each arm being allocated a different treatment.
- These treatments include the investigations at one or more doses and one or more control treatments such as placebo and or active comparator.

Cross over design

- Each subject is randomized to a sequence of two or more treatments and hence acts as his own control for treatment comparisons.
- In the simplest 2 X 2 cross over design each subject receives each of two treatments in randomized manner in two successive treatment periods.

PHASES OF CLINICAL TRAILS

Phase 0

- It is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.
- Phase 0 trials are also known as human micro dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies and pharmacodynamics (how the drug works in the body).

- Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug)

- A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect.

- **Phase I** - The first studies in humans are Phase I trials. They are performed with small numbers of patients or healthy volunteers and are used to answer questions such as what dose of the drug is likely to be effective and what side effects might occur.

- **Phase II** - The trials with larger numbers of patients and focus on how well the treatment or procedure works, perhaps in particular situations or groups of patients.

Phase III

- The trials enroll large numbers of patients and are used to compare the effectiveness and safety of the new treatment with that of the standard existing treatment.

- Information obtained from Phase III trials that demonstrates the benefits a new drug over the existing treatments are presented to regulatory authorities in order to obtain a licensee to market and sell the drug.

Phase IV trial

- Also known as **Post Marketing Surveillance Trial**.
- Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold.
- Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons

- The safety surveillance is designed to detect any rare or long term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials.
- Recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

Documents for the conduct of clinical trial

- The list of documents to be maintained and submitted in the clinical research study are grouped in to three sections according to the stage of the clinical trial.

1. Before the clinical phase of the trial commences.
2. During the conduct of the trial.
3. After completion of the trial.

Before the clinical phase of the trial commences

- Investigators brochure.
- Signed protocol and amendments and sample case report form.
- Information given to the trial subject.
  1. Informed consent form
  2. Advertisement for subject recruitment.
  3. Any other information.
- Financial aspects of the trial.
- Insurance statement.
- Signed agreement between involved parties.
- IRB/IEC composition.
- Regulatory authority approval
- Meical/ laboratory procedures certification.
- Sample of label attached to investigators drug containers.
- Trial initiation monitoring report.

During the conduct of the trial

- Investigator brochure updates
- Any revision of protocol, informed consent form.
- Regulatory authority approvals.
- Cirriculam vitae for new investigators or sub investigators.
- Updates of Meical/ laboratory procedures certification.
- Monitoring visit reports.
- Signed informed consent forms.
- Notification of investigator or sponsor of serious adverse events & reports.
- Notification by sponsor or investigator to authority & IRB /IEC of unexpected serious ADR.
- Subject screning and enrollment log.

After completion of the trial

- Investigational product accountability at site.
- Documentation of investigational product destruction.
- Completed subject identification list.
- Audit certificate.
- Final trial close out monitoring report.
- Final report by investigator to IRB/ IEC where required and applicable to authority.

How a trial is started...?