PHASES OF CLINICAL TRAILS

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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.

CLINICAL TRIAL:

- Carefully and ethically-designed experiment, in which participating subjects are assigned to the different modes of intervention simultaneously (in the same period of time), at random and are also supervised in a simultaneous way.

OPEN CLINICAL TRIAL:

- Confusing term, used to indicate that a clinical trial does not have any specific methodological characteristic.
- An open clinical trial is a clinical trial without a control group, as opposed to a controlled clinical trial.
- It can also be a non-blinded clinical trial, as opposed to a single-blind or double-blind clinical trial.

SINGLE-BLIND CLINICAL TRIAL:

- Trial in which the subject, but not the observer, does not know which of the possible treatments he is receiving.

DOUBLE-BLIND CLINICAL TRIAL:

- Trial in which neither the subject nor the observer know which treatment is being administered.

TRIPLE-BLIND CLINICAL TRIAL:

- Clinical trial in which the participating subject, the observer-researcher and the researcher who analyzes the data do not know which treatment is being received.
- This is done when the clinical variables examined are soft, that is, they can be interpreted in different ways.

CROSSOVER CLINICAL TRIAL:

- Clinical trial in which each individual consecutively receives each of the treatments under study.

UNICENTER CLINICAL TRIAL:

- A trial carried out by a single researcher or research team in one hospital or another type of centre.

MULTICENTER CLINICAL TRIAL:

- According to Royal Decree 561/1993, “A trial carried out in two or more centres with the same protocol and a coordinator who is responsible for processing all the data and for analysing the results”.

PARALLEL CLINICAL TRIAL:

- Clinical trial in which each group of patients receives a single treatment simultaneously.

Randomized Controlled Clinical Trial (RCT):

- A prospective, analytical, experimental study using primary data generated in the clinical environment. Individuals similar at the beginning are randomly allocated to two or more treatment groups and the outcomes the groups are compared after sufficient follow-up time. Properly executed, the RCT is the strongest evidence of the clinical efficacy of preventive and therapeutic procedures in the clinical setting.

Randomized Cross-Over Clinical Trial:

- A prospective, analytical, experimental study using primary data generated in the clinical environment. Individuals with a chronic condition are randomly allocated to one of two treatment groups, and, after a sufficient treatment period and often a washout period, are switched to the other treatment for the same period. This design is susceptible to bias if carry over effects from the first treatment occur.

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 I

- Objectives
  1. To assess a safe & tolerated dose
  2. To see if pharmacokinetics differ much from animal to man
  3. To see if kinetics show proper absorption, bioavailability
  4. To detect effects unrelated to the expected action
  5. To detect any predictable toxicity
- Inclusion criteria
  - Healthy volunteers : Uniformity of subjects: age, sex, nutritional status [Informed consent a must]
  - Exception: Patients only for toxic drugs Eg AntiHIV, Anticancer
- Exclusion criteria
  - Women of child bearing age, children.

- Methods:
  - First in Man : Small number of healthy volunteers
  - First in a small group of 20 to 25
  - Start with a dose of about 1/10 to 1/5 tolerated animal dose
  - Slowly increase the dose to find a safe tolerated dose
  - If safe → in a larger group of up to about 50 –75
  - No blinding
  - Performed by clinical pharmacologists
  - Centre has emergency care & facility for kinetics study
  - Performed in a single centre
  - Takes 3 – 6 months [70% success rate]

- **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 II

- First in patient [different from healthy volunteer]
- Early phase [20 – 200 patients with relevant disease]
  - Therapeutic benefits & ADRs evaluated
  - Establish a dose range to be used in late phase
  - Single blind [Only patient knows] comparison with standard drug
- Late phase [50 – 500]
  - Double blind
  - Compared with a placebo or standard drug
- Outcomes
  - Assesses efficacy against a defined therapeutic endpoint
  - Detailed P.kinetic & P.dynamic data
  - Establishes a dose & a dosage form for future trials
- Takes 6 months to 2 years [35% success rate]

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 III

- Large scale, Randomised, Controlled trials
- Target population: 250 – 1000 patients
- Performed by Clinicians in the hospital
- Minimises errors of phases I and II
- Methods
  - Different patient subgroups Eg: pediatric, geriatric, renal impaired
  - Randomised allocation of test drug /placebo / standard drug
  - Double blinded:
  - Cross over design
  - Vigilant recording of all adverse drug reactions
  - Rigorous statistical evaluation of all clinical data
- Takes a long time: up to 5 years [25% success]

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
- Helps to detect
  - rare ADRs
  - Drug interactions
  - Also new uses for drugs

- *Venlafaxine* a popular antidepressant whose misuse is possibly related to the increase it produces in dopamine neurotransmission mainly at the prefrontal cortex level
- The abuse of *tropicamide*, an ophthalmic anticholinergic compound which, when injected, may be associated with hallucinations, dysphoria, psychomotor agitation, tachycardia and suicidal ideation.
- The abuse potential of the above molecules is not mentioned in the medications' package leaflet/patient information leaflet

Hydromorphone

- The FDA approved this molecule in 2004 for the management of moderate/severe pain Eventually, a sponsor's study identified that, compared to taking hydromorphone alone, when co-administered with alcohol the blood hydromorphone concentrations were significantly higher. FDA's Role in Preventing Prescription Drug Abuse. Eventually, sales and marketing of the drug were suspended.

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.

- India emerged as a global hub for clinical research. According to a report by Mc Kinsey the global Clinical trial outsourcing opportunity in India in the pharmaceutical industry is estimated to be around $2 billion by 2010 and there will be the demand for more than 10,000 investigators trained in Good Clinical Practice (GCP) and 50,000 clinical research professionals.
- According to records collected by the Indian Council of Medical Research and the Drug Controller General's office, between July-December 2007, only 11 trials were registered. The number increased to 137 between Jan-Dec 2008 and then to an all-time high of 546 between Jan-Dec 2009. This year, while January saw 58 trials registered, February recorded 60.

- Top multinational pharmaceutical companies like Pfizer, Glaxo Smith Kline, Aventis, Novartis, Novo Nordisk, Astra Zenica, Eli Lilly are conducting clinical trials in India apart from the Indian companies like Dr. Reddys, Nicholas Piramal, Cipla and Lupin. Currently, there are more than 150 CROs in India, out of which 20 comply with ICH-GCP guidelines.