Conduct of Clinical Trials

Module 3 Topic 8

What is a Clinical Trial?

A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention

What is an investigational product?

'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form'

What makes Clinical Trial different from 'Standard of Care'

- Clinical research refers to studies in which people participate as patients or healthy volunteers.
- Trials are conducted on drugs, to compare their efficacy and safety with that of standard drugs.
- Only after the completion of the trials, a drug may be marketed for the particular indication in which it has been proved useful.

Clinical Trials

- Clinical Trials are conducted according to Good Clinical Practice, which is defined as:

  " a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected."

(ICH GCP)

Indian GCP

- It is a standard for clinical studies or trials that encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies. It ensures that the studies are implemented and reported in such a manner that there is public assurance that the data are credible, accurate and that the rights, integrity and confidentiality of the subjects are protected. GCP aims to ensure that the studies are scientifically authentic and that the clinical properties of the "Investigational Product" are properly documented.

Why Do Research Studies?

- To collect data on usual and unusual events, conditions, & population groups
- To test hypotheses formulated from observations and/or intuition
- Ultimately, to understand better – improve health outcomes with change

Types of Medical Research Studies

- Non-directed Data Capture
  - Vital Statistics
- Directed Data Capture & Hypothesis Testing
  - Cohort Studies, Case Control Studies

Why Do Research Studies?

- Clinical Trials
  - Investigation of Treatment/Condition
  - Drug Trials
- Some Examples of Trials....
  - They could be small investigator-led studies that are addressing a disease management question, or an investigation of academic interest.

Why Do Research Studies?

- They might be ward based….
  - Improving disease management in very sick patients such as severe malaria, malnutrition and management of seizures and in-patient trials for product development such as PK studies
- Or Community Based…
  - Phase II and III regulatory trials in drug and vaccines for tuberculosis and Hypertension. Academic proof of concept trials. Large phase IV surveillance studies.

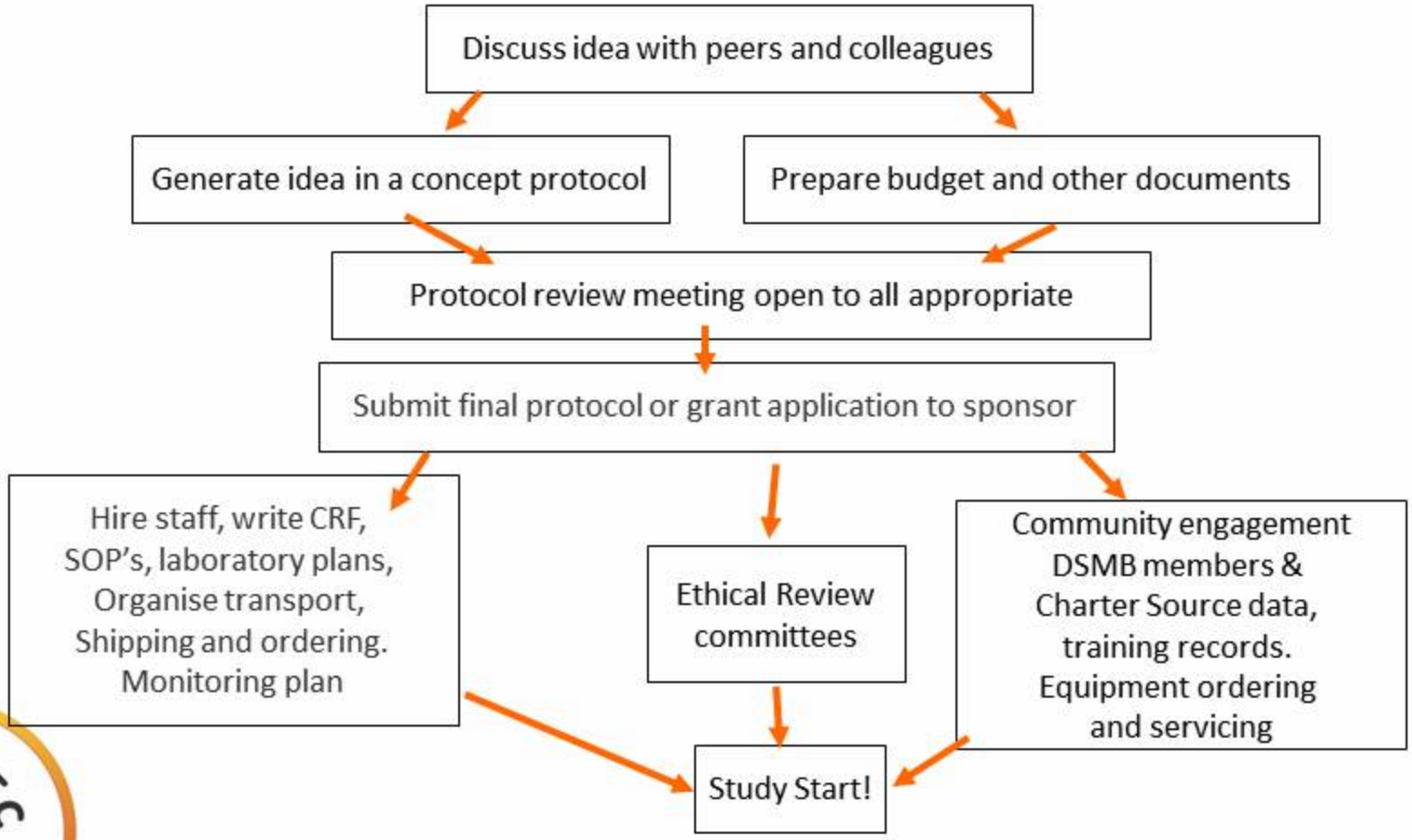
So why do trials?

- Aim
  - To make human life more healthy through development of better medicines
- Objective
  - To develop drugs that cover diseases presently untreatable.
  - To develop better drugs for diseases, that will be more efficacious, safer, more economical or provide more convenience to patients.
  - To develop drugs to mitigate the suffering of the people.

Basic Concepts

- Establish the question - ideally has just one and this is the primary end point. Common failing is too many end points. The best designed trials keep it simple as this make a clear answer more likely and easier to achieve
- Secondary objectives; a few related, appropriate secondary questions are normal as long as they do not distract from the primary. Some might be exploratory.
- Trial is then designed around these. The protocol sets out how the question will be answered

Trial Process



How?

Protocol

- Carefully designed to protect the rights and well being of participants.
- The rationale for conducting the study
- The type and number of patients/ volunteers in whom the study is to be done
- Gives detailed schedule of tests, procedures, medications, dosages, and length of the study.
- Parameters of safety and efficacy to be measured and time of measurement
- Method of analysing the results

Trial Rationale

- There should be a scientifically valid reason to conduct the study.
- Generally the study should add knowledge that will help humanity.
- Any study that will eventually harm humans is unethical.
- Rationale should be explained in a relatively simple language, since the document is going to be examined by people who may not be experts in the field.
- Explain what is expected to be gained by the study and how the study results may change the practice.

Budget

- Every activity costs money, clinical trials need a heavy financial input from the sponsor.
- The sponsor with the help of a CRO/site makes a budget and makes arrangement to pay for the expenses.
- Budget and method of payment is mentioned in the clinical trial agreement signed between the sponsor, the investigator and the site.
- Generally payment is made on milestone basis, with a fixed amount being payable when a particular milestone is reached.

Insurance

- Every clinical trial has to be insured by the sponsor.
- The insurance company releases the insurance document on the payment of the premium.
- There is provision for payment of individual participants who suffer from SAEs, and there is limit for the total payment too.
- Most insurances are granted for a fixed period of one year or some such period.
- Medical reimbursement or compensation paid by the sponsor is recovered from the insurance by the sponsor.

Participants

- Studies may use participants of any age and sex, the range and selection must be decided.
- Generally pregnant and lactating women are not used, unless the drug under test has special relevance to them.
- They are described by Inclusion and exclusion criteria. IC being first applied to the population, then EC used to drop unsuitable members.

Participants

- Total number required to complete, and expected dropouts used to calculate the number to be screened.

- Each participant must understand and agree to being included in the study.

Proxy

- Participants may be vulnerable, and unable to decide whether to participate or not; in such a case Legally Authorized Representative may decide on behalf of the participant.
- Children are often able to take a decision, even though they are not legally allowed to consent, an assent process is then used.
- Participants may be unable to record their decision due to blindness or illiteracy, a witness may then be used in the consent process.
- In India certain trials, require Audio/Video recording of the consent process.

Investigators/Personnel

- The name(s) of the hospitals/clinics where the study will be conducted.
- The name(s) of the investigators involved in the study
- The full CVs of the investigators, and senior members of the team
- The name of the Ethics Committee and its registration, accreditation details.
- The names of the other members of the investigational team.
- The organization responsible for data management.

Investigator's Meeting

- When there are more investigators, it is easier to have an investigators meeting to explain the trial to investigators in a single meeting.
- The Protocol and the all other documents are explained to the investigators
- The procedures are discussed threadbare, so that there is n difference in the study conducted at different sites.
- Investigators' feedback is taken and if any changes are required, they are carried out.

Ethics Committee

- Documents concerning the trial are to be submitted for EC approval
- They include
  - Protocol
  - Investigator's CV
  - Investigator's Brochure
  - Informed consent Forms
  - Case Record Forms
  - Clinical Trial Agreement
  - Insurance Certificate
  - Any other document asked for

Initiation Meeting

- Some times there is a gap between investigators' meeting and start of the trial.
- When all permissions are in hand, documents, medications are sent to the site, then initiation meeting can be held.
- Retraining of site staff if required, is done during this meeting.
- This meeting is to ensure that the site is fully ready to recruit the first subject.

Informed Consent

- Every potential participant has to provide a written informed consent
- This process is conducted by the Principal Investigator or a member of the team, who can answer all queries and clear all doubts of participants.
- This document must contain all the essential elements as described in Appendix V to the Drugs and Cosmetics Rules 1945.
- This document reveals the identity of the participate, hence shall be securely stored.

Study Duration

- Can be estimated but not accurately stated.
- From the first patient first visit to the last patient last visit, may last for years.
- In some cases, includes a run in period before the intervention begins.
- Has an observation period after the last dose being administered to the patient.
- This is the time during which the sponsors and investigators are responsible for the participant.

Monitoring/Auditing

- The trial site will be visited by representatives of sponsor and independent parties.
- The aim is to ensure that the rights and the well being of the subjects are protected.
- To assess the progress of the study and to ensure compliance with the protocol, SOPs, guidelines and regulations.
- For cause audits conducted when there is a specific need or information that something is not going on right at the site.

The Case Record Form

- This document is the data capture system.
- Collects only the data listed in the protocol and nothing else, and is filled with the help of source documents.
- Differs from the source data - patient notes and lab reports. This is a central concept in GCP that data is always verifiable.
- Designed so that transcription to the software becomes easy and automated.
- Data taken from here and entered into a database and then exported to statistical package. Important to keep CRFs to allow you to go back and resolve data queries

Database and Statistics

- Likely to need stats advice right at the start to help you decide on the all important 'n'…. How will you randomize, maybe you don't need 1:1. Keeping the numbers down is helpful. Time, cost and ethics – but you still need to answer the question
- Protocol needs to explain statistical objectives of your trial but it is the report and analysis plan that sets out how you will analysis the data. Must be finalized before database close to avoid risk of manipulating the data
- Database should be secure and have an audit trial. Currently difficult in non-commercial trials

Statistical Analysis

- Statistical help should be taken right from the time of designing the trial.
- Statistician should advice the sample size, method of randomization during the planning stage.
- May conduct an interim analysis if required.
- Perform all analysis as laid down in the protocol after the completion of the trial.
- Must provide opinion whether the objective of the trial was met or not.

Reconciliation

- On the completion of the trial, a complete reconciliation of the documentation and material is done.
- At the close out visit all financial payments are completed, documents and medications accounted for, and unused material returned to the sponsor.
- A formal letter of reconciliation is prepared and signed by the investigator and sponsor representative, and signals the end of the trial.

Clinical Study Report

- At the end of study and the completion of the data analysis, a comprehensive report is prepared on the trial.
- This is a detailed document about the methods and results of a **trial**. A CSR is a scientific document addressing efficacy and safety, not a sales or marketing tool; its content is similar to that of a peer-reviewed academic paper.
- The format of the report is as per Appendix II to the Drugs and Cosmetics Rules 1945.