Stake Holders
in Clinical Research

Module 1 Topic 5

Stake Holders

Major or Essential

- Participants
- Regulator
- Investigator
- Ethics Committee
- Monitors
- Statistician

Minor or Supportive

- Accountants
- Auditors
- Medical Writers
- Clinical Research Coordinators
- Regulatory Managers
- Vendors

Participants

- These are probably the most important persons in clinical research.
- It is because of their volunteering, that any progress can be made in research. The protection of their rights and well being is the most important concern.
- Clinical trial participants are usually patients who suffer from a diseases, for which a new therapy is under development.
- In phase I trials and BA/BE studies, usually healthy volunteers are the participants. Though for studies on toxic drugs, patients are used.
- Different types of participants are required for each type of study.

Participants for Phase I

- The objective of these studies is to study the safety of the new drug, it is the first time humans are exposed to the drug.
- A small number of healthy participants is exposed to the drug in this study.
- Healthy, means persons who have no disorder that will interfere with the testing of the drug or will put them at an increased risk of harm.
- Only when the drug is expected to be harmful to healthy people, patients suffering from the disease are used in Phase I.

Bioavailability/Bioequivalence Studies

- Drug kinetics is usually studied in a small number (often 24) of healthy volunteers.
- An essential feature is that their liver function and kidney function should be normal, since these organs are responsible for metabolism and excretion of most drugs.
- Volunteers with normal physiological vales ensure least harm due to a new drug.
- For anticancer drugs patients are used, and not normal healthy volunteers.

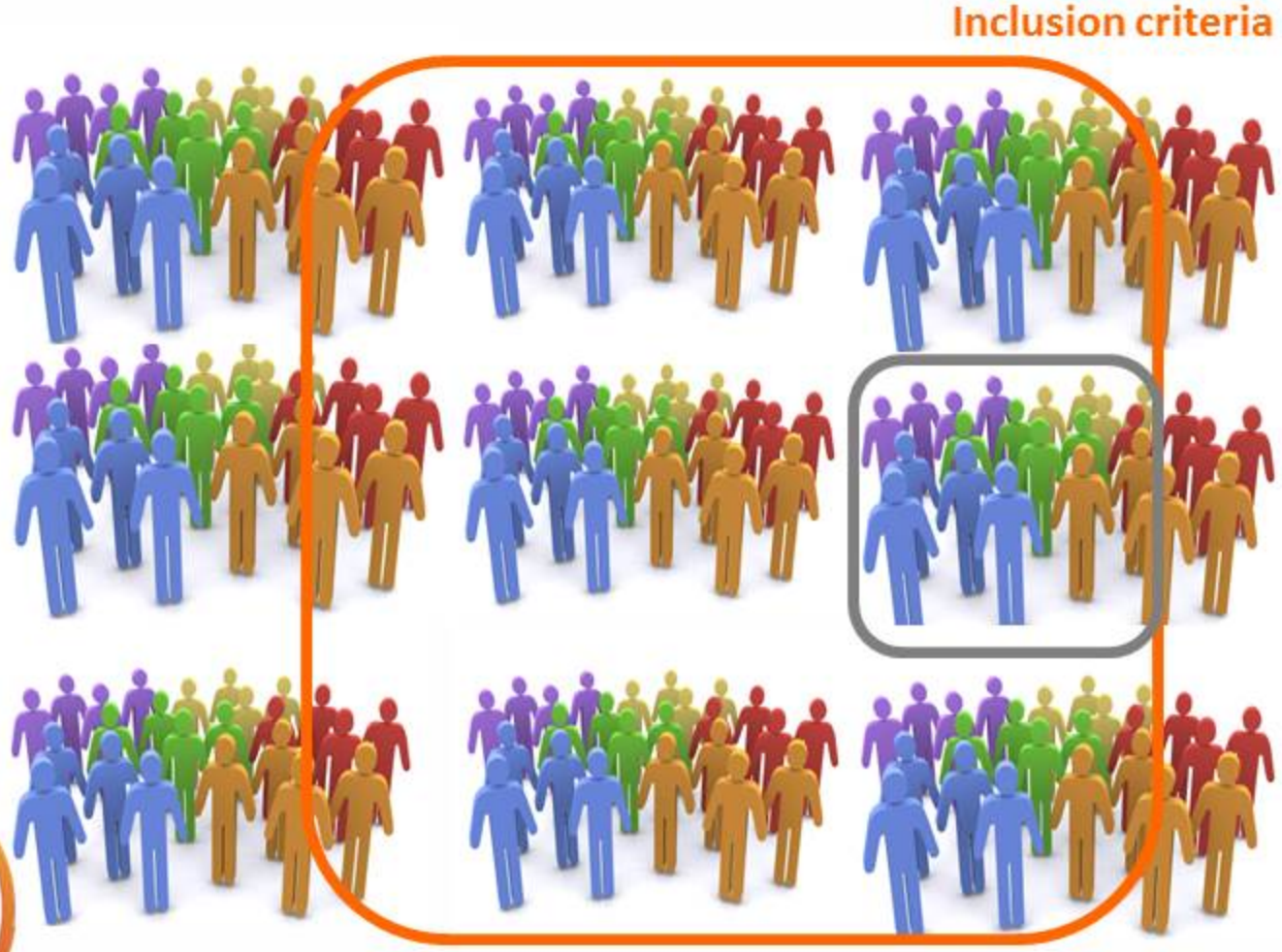
Participants for Phase II

- The objective of Phase II studies is to explore the therapeutic potential of new drugs.
- Most drugs do not affect healthy individuals, hence patients suffering from disease (which the drug is intended for) are chosen.
- Usually volunteers are chosen from a small range of age, weight etc., so that they are a homogenous group.
- Patients with co-morbidities are usually avoided, since they complicate the measurement of drug efficacy.

Participants for Phase III

- Phase III are confirmatory trials, usually comparing the new drug with the best available treatment for the disorder.
- Participants should resemble those that are seen in routine clinical practice.
- For the sake of safety, pregnant subjects are avoided and women with reproductive potential required to practice contraception.
- A set of inclusion and exclusion criteria define who can be included and who cannot.

Participant selection



Participant age

Investigator

A person responsible for the conduct of the study at the trial site. Investigator is responsible for the rights, health and welfare of the study subjects. In case the study is conducted by a team of investigators at the study site then the designated leader of the team should be the Principal Investigator.

CDSCO GCP Guideline

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

ICH GCP E6 R2

Investigator

Qualified in the relevant field by

- Education
- Training
- Experience

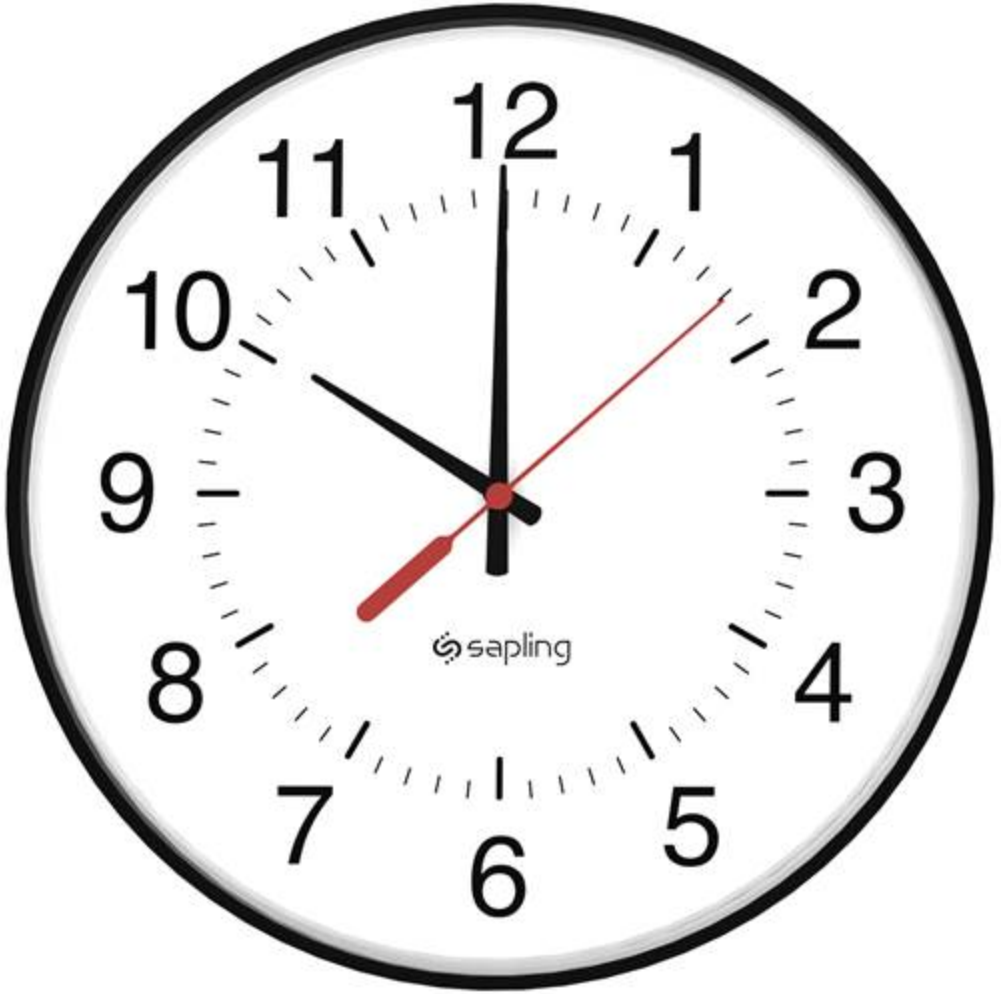
Evidenced by

- Curriculum vitae
- Certificates of domain training
- Certificates of GCP training

Physicians, Surgeons, Dentists

Resources

- Men
- Machines
- Money



Investigator

- Choose an investigator by reputation, a good doctor is more likely to be a good investigator.
- Previous experience in clinical research, as a team member or as a leader is preferable.
- Do not go by the recommendation of the sales team, an honest scientist is needed, not a loyal one.
- Do not choose the most famous or those heading large organizations, they rarely have time to devote to research.

Very personal recommendations, based on experience

Sponsor

An individual or a company or an institution that takes the responsibility for the initiation, management and / or financing of a Clinical Study. An Investigator who independently initiates and takes full responsibility for a trial automatically assumes the role of a Sponsor.

CDSCO GCP Guideline

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

ICH GCP E6 R2

Sponsor

Pharmaceutical or Biotechnology Companies, like

- Pfizer
- Novartis
- Glaxo SmithKline
- Sanofi Aventis
- Cipla, Lupin, Cadila

Government or Semi Governmental Organizations Like

- Indian Council of Medical Research
- World Health Organization
- Indian Dental Association
- Indian Association of Pediatrics

Individual Investigators

Requirements

- Should have
  - the legal rights to the compound under study (IPR)
  - have the resources to finance the study
  - pay for expenses agreed upon in agreement
  - take up all responsibilities as per law of the land

- Roles and responsibilities of the sponsor are described in detail in all guidelines, ICH GCP, CDSCO GCP and Drugs and Cosmetics rules.

Ethics Committee

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/ providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

ICH GCP E6 R2

Indian Rules

Institutional Ethics Committee → Clinical trials, academic trials, biomedical and health research, bioavailability and bioequivalence studies

Independent Ethics Committee → Bioavailability and bioequivalence studies

New Rules

EC for Clinical Trials, Bioavailability and Bioequivalence Studies

Registered with CDSCO

→ Clinical trials, academic trials, biomedical and health research, bioavailability and bioequivalence studies

EC for Biomedical and Health Research

Registered with Department of Health Research
Min. Health and Family Welfare

→ Biomedical and health research

KLINTEC Academy

EC Composition

EC Member	Affiliation	Qualifications
Chairperson/ Vice Chairperson	Non Affiliated	• A well-respected person from any background with prior experience of having served/serving in an EC

EC Composition

EC Member	Affiliation	Qualifications
Member Secretary/ Alternate Member Secretary	Affiliated	• Should be a staff member of the institution • Should have knowledge and experience in clinical research and ethics, be motivated and have good communication skills • Should be able to devote adequate time to this activity which should be protected by the institution

EC Composition

EC Member	Affiliation	Qualifications
Basic Medical Scientist(s)	Affiliated/ Non affiliated	• Non-medical or medical person with qualifications in basic medical sciences • In case of EC reviewing clinical trials with drugs the basic medical scientist should preferably be a pharmacologist

EC Composition

EC Member	Affiliation	Qualifications
Clinicians	Affiliated/ Non affiliated	• Should be individual/s with recognized medical qualification, expertise and training

EC Composition

EC Member	Affiliation	Qualifications
Legal expert	Affiliated/ Non affiliated	• Should have a basic degree in Law from a recognized university, with experience • Desirable: Training in medical law

EC Composition

EC Member	Affiliation	Qualifications
Social scientist/ philosopher/ ethicist/ theologian	Affiliated/ Non affiliated	• Should be an individual with social/behavioural science/ philosophy/ religious qualification and training and/or expertise and be sensitive to local cultural and moral values. • Can be from an NGO involved in health-related activities

EC Composition

EC Member	Affiliation	Qualifications
Lay person	Non affiliated	• Literate person from the public or community • Has not pursued a medical science/ health-related career in the last 5 years • May be a representative of the community from which the participants are to be drawn

EC Composition

EC Member	Affiliation	Qualifications
Lay person	Non affiliated	• Is aware of the local language, cultural and moral values of the community • Desirable: involved in social and community welfare activities

Accreditation

- The EC should be constituted and function according to written SOPs as per the Drugs and Cosmetics Rules 1945.
- All EC members should be trained initially and there should be evidence of continued training.
- The EC should hold a registration that is current, with the appropriate authorities.
- It should be accredited by NABH, or any other body as per prevailing rules.

Regulator

- The drug law has specified that the the regulator for Drugs and Cosmetics in India is the Drugs Controller General (India).
- The office of the DCGI is also bound by the Drugs and Cosmetics Act and Rules, and functions according to the same.
- In case the results of the drug trials are to be submitted to another regulatory authority, then the rules and regulations of that authority will have to be followed.
- In general trials conducted as per ICH GCP, are acceptable in most parts of the world.

Monitors

- Most trials will need to be monitored during their conduct, the monitor may be an employee of the sponsor or may be an independent person by the sponsor.
- The monitor will ensure that the rights and the well being of the trial participants are protected, and the trial is conducted according to the protocol, the SOPs and the governing rules and regulations.
- The monitor will submit his/her report to the sponsor who may share it with the investigator and the site authorities.

Statistician

- The statistician will be responsible for the calculation of the sample size before the trial protocol is finalized.
- He/she will be responsible for randomization, preparation of the statistical analysis plan (SAP).
- After the trial he/she will be responsible for all statistical analysis according to the SAP.
- He/she will ensure that all graphs and tables in the final report truly represent the results obtained.

Auditors

Auditors will conduct audits of trials, which are defined as:

"A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

ICH GCP E6 R2

Accountants

- Accountants are not specifically mentioned in any guideline as stakeholders of clinical research. However it is doubtful if any trial can be conducted without the support and oversight provided by accountants.
- During the trial, a number of vendors are involved and their accounts need to be settled in a timely fashion, staff will have to be paid and monies received by different sources. A variety of taxes may have to be paid and accounts maintained, this makes the role of an accountant very important and crucial to the proper conduct of a trial.

Medical Writers

- Clinical trials require the generation, maintenance and archival of a variety of documents. Many of them are simple, but there are complex ones that demand the expertise of a medical writer.
- Documents prepared by medical writers include but are not limited to:
  - Protocol
  - Informed consent forms
  - Investigator's Brochure
  - Clinical Study Report
  - SAE reports

Clinical Research Coordinators

- Most investigators are busy physicians or surgeons, and they do not have much time to devote to the paper work and other formalities.
- In all these functions the investigators are aided by the clinical research coordinators (CRC).
- CRCs are trained in clinical research and manage the myriad functions in the trial under the supervision of the investigator.
- Senior CRCs may work as quality managers and ensure that the quality of all clinical work is maintained.

Regulatory Managers

- Many organizations sponsoring multiple trials have regulatory managers (RMs) to liaise with the Drug Control Authorities.
- RMs manage functions like submission of documents to the regulators, taking appointments with them, tracking the progress of their applications etc.
- RMs are not defined by any guideline as stakeholders, but perform very important functions to ensure smooth and timely conduct of studies.

Vendors

- In addition to the stake holders described, there are a variety of services that need to be performed during the trials, they are collectively known as vendors.
- Vendors include but are not limited to:
  - Couriers
  - Suppliers of stationery
  - Insurers
  - Laboratory staff
  - Housekeeping staff

Team Approach

- Successful conduction of clinical research requires a team approach. A very large number of professionals are required to run clinical trials, and it would be wrong to classify them as major or minor.
- Each stake holder brings some specific skill or service on the table without which trials cannot be conducted smoothly.
- Today more than ever, timely completion of trials has become an important mechanism for ensuring financial health. One day's delay in the completion of trials may make a difference of a few million dollars to a major sponsor.