Foundation To GCP Guidelines

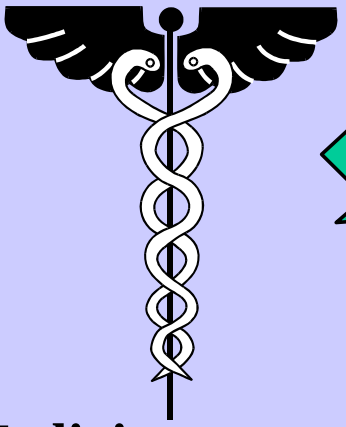
Society for the Promotion of Ethical Clinical Trials

What are GCPs ?

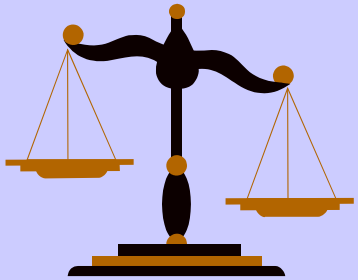
International ethical and scientific quality standards for,

- designing
- conducting
- recording
- reporting

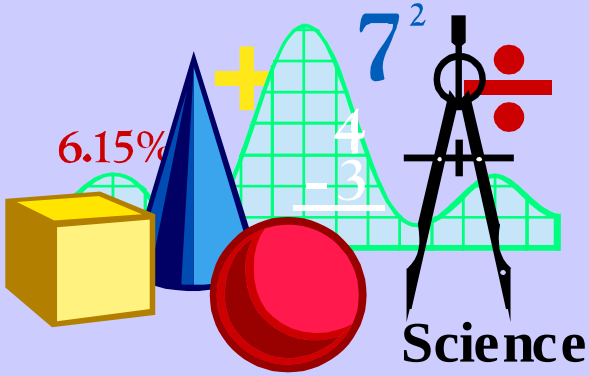
trials that involves participation of human subjects



Medicine



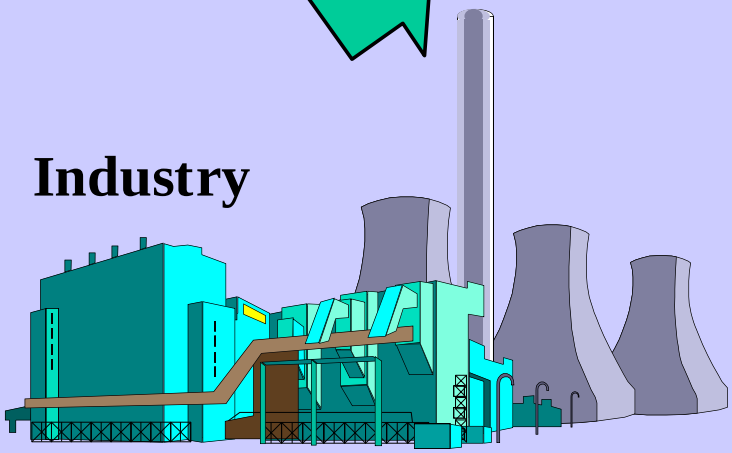
GCPs



Science

Human Rights

Industry



WHY GCPs ?

- Legal Requirement
- Protects the rights, integrity and confidentiality of research subjects
- Provides assurance that the data/results are credible and accurate
- Global Acceptance of the data

Applicable GCP Guidelines

- ICH GCP Guidelines, 1997
- Ethical Guidelines for Biomedical Research on Human Subjects, 2006 (ICMR Code)
- Good Clinical Practices, 2001 (Indian GCP)

Evolution of GCP Guidelines

Situation	Action	Result
Fraud, Misbranding, Impure Food and Drugs	→ 1906 Pure Food & Drug Act (USA)	→ "Truth in Labeling"
Sulfanilamide Disaster (107 deaths)	→ 1938 Food, Drug & Cosmetic (FD&C) Act (USA)	→ Demonstrated safety prior to approval
Wartime Medical Atrocities Revealed	→ Code of Nuremberg (Global) → Declaration of Helsinki (Global, 1964)	→ Patient protection → Guidelines for Ethical Conduct of Clinical Research (WHO)
Thalidomide Disaster (birth defects)	→ Major legislation: → **Kefauver Harris Amendment (USA, 1964)** → **Medicines Act (UK,1967)**	→ Demonstrated safety and efficacy prior to approval → Development of GCPs in US, elsewhere → Safer / more rigorous studies

Milestones in the Evolution of GCP

- 1906 US Federal Food and Drugs Act
- 1937 Sulfanilamide disaster
- 1938 US Food, Drug & Cosmetic Act
- 1947 Nuremberg Trial
- 1960 Thalidomide Disaster
- 1962 US Kefauver-Harris Drug Amendment
- 1964 Declaration of Helsinki
- 1978 Belmont Report
- 1993 International Ethical Guidelines for Biomedical Research (WHO Geneva)
- 1997 ICH GCP

Nuremberg Code 1948

- Established for preventing the atrocities of the Nazi experiments from happening again
- Participation in clinical trial must be **voluntary**
- Experiments must be supported by strong **scientific rationale**
- Physical/ mental suffering or damage is not acceptable (no harm)
- Right to **stop participation** in trial at any time

Thalidomide Tragedy

- In 1960s, >8000 children were born with congenital malformations in Europe, Canada and Latin America
- Mothers consumed thalidomide during pregnancy
- Thalidomide tragedy led to the Kefauver- Harris amendment in 1962, requiring strict safety and efficacy control for new drugs

Declaration of Helsinki,1964

- Developed by World Medical Association (WMA)
- Establishes the principles and rationale for research in human subjects
- Introduced the concept of :
  - Protocol approval by an independent ethics committee
  - Investigator as responsible for care of participating subjects
  - Written informed consent

Belmont Report 1978

- Reviews the ethical principals in clinical research :
  - Autonomy
  - Beneficence
  - Justice

International Ethical Guidelines for Biomedical Research (WHO Geneva 1993)

- Guidelines consisting of a comprehensive review of :
  - Informed consent
  - Selection of research subjects
  - Confidentiality of data
  - Compensation for injury
  - Procedures for ERC
  - Obligations of Sponsor
- Reviewed by more than 150 representatives from different countries
- Recommendations for developing countries

Who Should Comply To GCPs ?

- Sponsor
- CRO
- Investigator Site
- ERB/IRB/EC

Definitions

- **Sponsor** – An individual or a company or an institution that takes responsibility for the overall trial conduct.
- **Contract Research Organization (CRO)** – An organization which sponsor hires for the conduct of trial on its behalf.
- **Investigator** – A person responsible for the conduct of clinical trial at a site/hospital.
- **Ethics Committee** - An independent body constituted of medical/ scientific professionals and non medical/ non scientific members to ensure a competent review of scientific and ethical aspects of a clinical trial.

Responsibilities of Sponsor

- Trial Design
- Preparation of Protocol/ICD/IB/CRF etc.
- Project/ Logistics Planning
- Manufacturing, Packaging, Labeling, Coding and Accountability of Investigational Product
- Investigator Selection
- Regulatory Approvals
- Investigator Training

Responsibilities of Sponsor…

- Monitoring
- GCP/Regulatory Compliance
- Safety Reporting
- Amendment(s)
- Auditing/QA/QC
- Trial Closure/Termination/Suspension
- Clinical Study Report/Publication
- Trial Closure/Archival

Responsibilities of Investigator

- Communication with ERB/Sponsor
- Constitution of Study Team
- Training
- Essential Documents
- ICD Administration
- Medical Care of Trial Subject
- Drug Accountability
- Protocol Compliance
- Source Document
- Safety Reporting
- GCP/Regulatory Compliance
- Site Closure/Archival

Ethics Committee (EC)

- An independent body constituted of medical/ scientific professionals and non medical/ non scientific members.
- Responsibility is to ensure the protection of rights, safety and well being of human subject involved in a study.
- Ensures a competent review of scientific and ethical aspects of a research study and executes the same free from any bias and influence that could affect their objectivity.
- Reviews, approves/ provides favorable opinion on trial protocol and suitability of Investigator (s) facilities and methods and materials to be used in obtaining and documenting “Informed Consent” of trial subjects.

Ethics Committee (EC)…

- The EC should exercise particular care to protect the rights, safety and well being of all vulnerable subjects participating in the study, such as:
  - Members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, staff and students of medical, nursing and pharmacy/academic institutions)
  - Patients with incurable diseases
  - Unemployed or impoverished persons
  - Patients in emergency situations
  - Ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally giving consent

Composition of Ethics Committee

ICH-GCP Guidelines

- At least 5 members (quorum)
- At least one member whose primary area of interest is in non scientific area
- At least one member who is independent of the institution / trial site
- Only those EC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial related matter.
- A list of EC members and their qualifications should be maintained

Composition of Ethics Committee…

Schedule-Y of Drugs and Cosmetics Act

- At least 7 members with following representation:
  - Basic medical scientists (preferably one pharmacologist)
  - Clinicians
  - Legal expert
  - Social scientist/representative of NGO/philosopher/ethicist/theologian or similar person
  - Lay person from the community
- EC should appoint from among its members, a Chairperson (who is from outside the institution) and a Member Secretary.
- Presence of at least one member each of the above representation (*quorum*) is must at every EC meeting in order to qualify it as a valid meeting. Besides there should be appropriate gender representation.
- Only those EC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial related matter.

Ethics Committee Charter

- Must have written Standard Operating Procedures (SOPs).
- Maintain records of its activities and minutes of its meetings.
- Comply with ICH GCP and with applicable regulatory requirement (s).
- Make its decision at announced meetings (at which at least a *quorum*), as stipulated in its operating procedures, is present.
- Only members who participate in the review and discussion should vote/provide their opinion and/or advise.
- Only those members who are independent of the investigator and of the trial should vote/ provide opinion on trial related matter.
- Investigator may provide information on any aspect of trial but shouldn't participate in the voting process.
- Ethics Committee may invite nonmembers with expertise in special areas for assistance.
- Based on the requirement of research area, e.g. HIV/AIDS, genetic disorders etc. specific patient groups may also be represented in the EC as far as possible.

ERB-SOP

- Objective
- Composition
- Responsibility
- Operating Procedure
- Documentation
- Membership

Ethics Committee

The Chief Responsibilities are:

- Approval/Permission for the Conduct of Clinical Trial
- Review of Progress
- Compliance with the Regulatory Requirements

Approval/Permission for the Conduct of Clinical Trials

- No clinical trial should be initiated at any investigator site without obtaining the written approval/permission of essential trial document from the respective EC.
- Following documents requires EC review and approval before initiating a clinical trial at a site:
  - Protocol and study rationale
  - Patient Information Sheet and Informed Consent Form (PIS-ICF)
  - Translations of PIS-ICF in regional languages
  - Investigator's Brochure (IB)
  - Subject's questionnaire/diaries (if any)
  - Principal Investigator's current CV and Undertaking (Appendix-VIII)
  - Investigator's Agreement with the Sponsor

Approval/Permission for the Conduct of Clinical Trials

- Insurance Policy/compensation for participation and for SAE occurring during study participation
- Regulatory approval (DCGI clearance to the study)
- The review should be done through formal meetings and should not resort to decisions through circulation of proposals.

Review of Progress

- After granting the approval for the conduct of a clinical trial it is the responsibility of EC to have an ongoing review of the trial progress.
- This includes:
  - Review of safety reports (reports of SAEs)
  - Review and approval of the amendment(s) if any
  - Review of protocol/process deviations or violations
  - Periodic report about the progress of the trial/termination/closure
- The frequency of periodic review may vary across institutions but it should occur at least once a year.

Compliance with Regulatory Requirements

- In order to ensure regulatory compliance each EC is required to maintain following records:
  - Written standard operating procedures or charter
  - Membership list with CVs of all members
  - List of occupations/ affiliations of members
  - Copies of all the trial (s) documents received for review
  - Minutes of meetings
  - Correspondence between EC and Investigator (progress report, amendments, SAEs/SUSARs etc.)
  - Agenda and minutes of all EC meetings
  - Final report of the study

* All records should be retained for at least 3 years after completion of trials

Inspection Targets

Which investigators get inspected?

- High enrollers
- Sites that do a lot of studies
- Research outside area of expertise,
- Statistical outliers
  - safety, efficacy data inconsistent with other sites in study
- For Cause: Complaints, media spotlight

Regulatory Inspection Process

1. Agency contacts Investigator in advance to schedule a visit
2. Inspector arrives at site with credentials and "Notice of Inspection"
3. Interviews with site personnel to determine who did what and how it was done
4. Documentation review
5. Wrap up meeting
6. Legal or regulatory consequences

Documentation Review

To establish that:

- Research was conducted under proper authority
- Patients' rights and safety were protected
- Study can be reconstructed
- Data supports conclusions

Research Conducted Under Proper Authority

- Regulatory authorization is available
- Sponsor's authority (e.g. Clinical Trial Agreement, signed protocol) is available
- Institutional Review Board approval is available
- Documentation of duty delegation at the sites

Patient's Rights and Safety Protected

- Informed Consent Process is adequate
- Consent is obtained before any study procedures
- No coercion is made to participate or continue participation
- Inclusion / Exclusion Criteria are observed strictly
- ERB is promptly notified of all Serious Adverse Events

Study Can be Reconstructed...

- Protocol was followed
- Patients are real
- Patients took study drug
- No "interfering" medications were given
- All adverse events are collected and reported

Data Supports Conclusions...

Source documents

- exist
- are readily available
- accurately support data reported
- tell the whole story

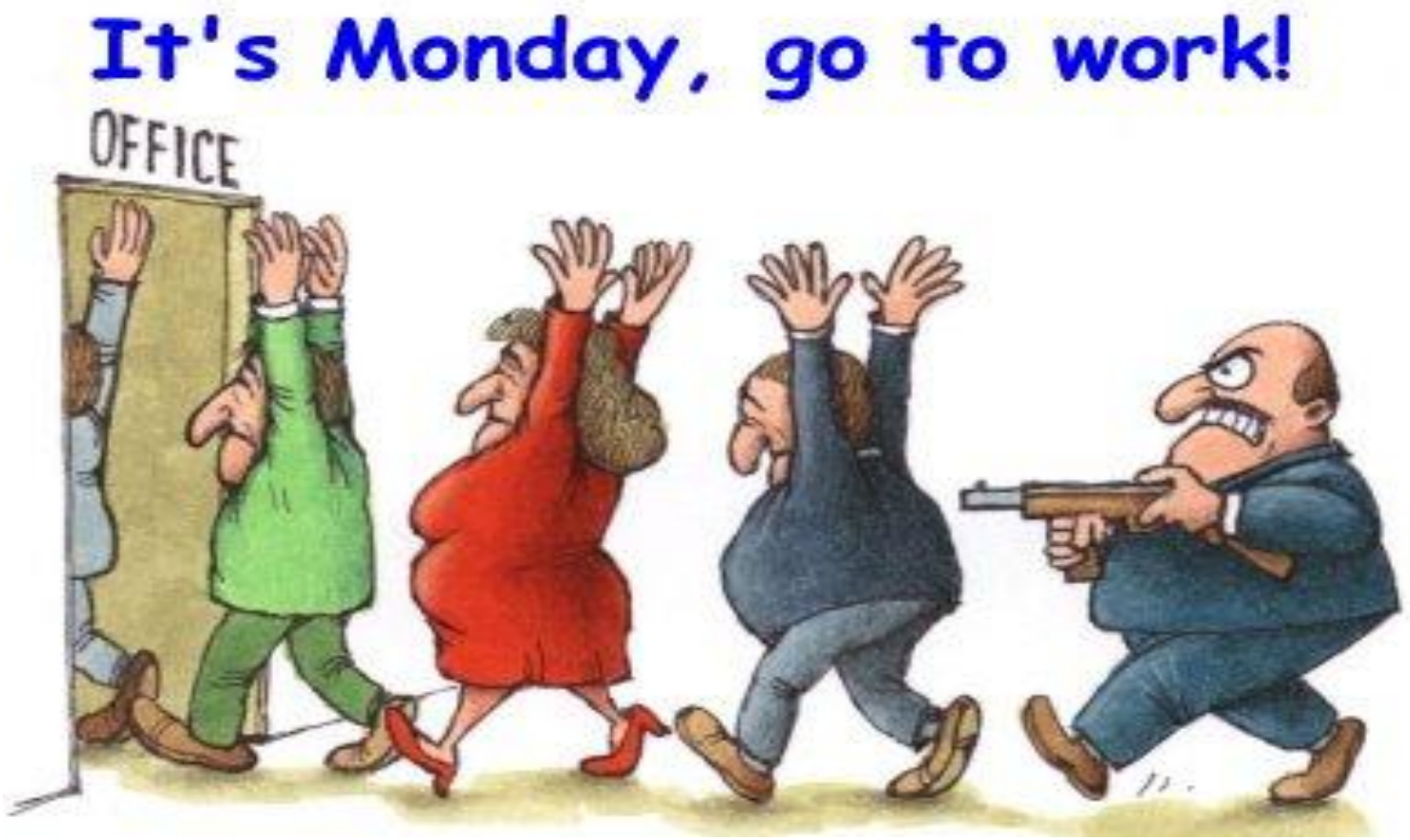
Danger Signals

- Records not readily retrievable
- Source for CRF data can not be identified or found
- Process not consistently followed
- Disorganization
- No "audit trail" for data corrections
- Lack of accountability for study drug

Proven methods to improve GCP compliance

- Comply to the protocol, GCP, SOP and applicable regulatory guidelines
- Be aware of interfering medications
- Clearly define who will do what, when and how
- Obtain informed consent before any study procedure
- Have source documentation of all reported data
- Keep neat and well organized records
- Keep 100% accountability of investigational product
- Keep audit trail for all data corrections
- Demonstrate involvement in the study
- Be able to describe unusual events e.g. early discontinuations serious adverse events, protocol /process violations
- Retain the study records for the stipulated time-frame

GCP Compliance Not by Force But in True Spirits



THANK YOU


SPECT
Society for
the Promotion
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