Glisland® Training Series:

Good Clinical Practices

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Clinical Trials

1. What are clinical trials?

   Biomedical or health-related research studies in human beings that follow a pre-defined protocol (ClinicalTrials.gov).

2. What is a clinical trial protocol?

   A carefully designed study plan on which all clinical trials are based to safeguard the health of the participants as well as answer specific research questions.

Type of Clinical Trials

1. Treatment trials
2. Prevention trials
3. Diagnostic trials
4. Screening trials
5. Quality of Life trials

Phases of Clinical Trials

1. Phase I Trials

   Studies on a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

2. Phase II Trials

   Studies on a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

3. Phase III Trials

   Studies on a large groups of people (1,000-3,000) to confirm the effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

4. Phase IV Trials

   Post marketing studies delineate additional information including the drug's risks, benefits, and optimal use

Good Clinical Practice Regulations

1. What are Good Clinical Practices (GCPs)?
   - They are collection of regulations, requirements and policies that govern clinical research involving human subjects.
   - They are rules applying to the design, conduct, recording and reporting of clinical trails.
   - They define the responsibilities of the sponsor, the investigator, the study monitor and the IRB (Institutional Review Board).
   - They are applicable to all clinical studies of FDA-regulated products.

Key GCPs Requirements and Guidances

1. Regulations:
   - Protection of Human Subjects (45 CFR Part 46 and 21 *CFR* Part 50)
   - Financial Disclosure by Clinical Investigators (21 *CFR* Part 54)
   - Institutional Review Boards (21 *CFR* Part 56)
2. Guidances:
   - ICH E6 *GCP Consolidated Guidance* (FR, 9 May 1997)
   - ICH M4 *Common Technical Document (CTD)*
   - ICH E3 *Guideline on the Structure and Content of Clinical Study Reports*
   - GHTF STEP program

GCP Regulation History

1. Nuremberg Code of Ethics of 1947
2. Declaration of Helsinki of 1964
3. Kefauver-Harris *Drug Amendments* of 1962
4. FDA adopted Declaration of Helsinki informed consent in 1966 and made subsequent regulatory changes in 1967
5. *Medical Device Amendments* of 1976
6. FDA published regulations concerning Institutional Review Board (IRB) and informed consent in 1981
7. FDA published the Financial Disclosure by Clinical Investigators regulation in 1999

The Principles of ICH GCP

1. Be consistent with Declaration of Helsinki principals and regulatory requirements
2. Weigh risks against benefit for the trial subject and society
3. The rights, safety, and well-being of trial subject vs. interests of science and society
4. Adequate available nonclinical and clinical information to support proposed trial
5. Scientifically sound, clear, detailed protocol.
6. IRB/IEC approval of protocol

The Principles of ICH GCP

7. Medical care and medical decisions
8. Qualification of investigator
9. Informed consent
10. Handling clinical trial information
11. Privacy and confidentiality rules
12. GMP requirement for investigational products
13. Quality assurance

Sponsor

- Definition:

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

- Responsibilities:
  1. Quality Assurance and Quality Control
  2. Medical Expertise
  3. Trial Design
  4. Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring
  5. Investigator Selection
  6. Notification/Submission to Regulatory Authority(ies)
  7. Others

Investigator

- Definition:

  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.

- Requirements and Compliance:
  1. Qualification and Agreements
  2. Adequate Resources
  3. Medical Care of Trial Subjects
  4. Communication with IRB/IEC
  5. Compliance with Protocol
  6. Records and Reports
  7. Others

Human Subject

- Definition:

  Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

- Special group protection (45 CFR Part 46):
  1. Pregnant Women, Human Fetuses and Neonates
  2. Prisoners
  3. Children

Protocol

- A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

IRB

- *Institutional Review Board (IRB):* 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. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act.

Informed Consent

- Definition:

  A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

- Regulation:
  - 21 CFR Part 50.
- Exceptions:
  - Armed forces and emergency research.

Responsibilities of IRB

1. Safeguard the rights, safety, and well-being of all trial subjects.
2. Obtain required documents including trial protocol(s)/amendment(s), written informed consent form(s), investigator's brochure, the investigator's current curriculum vitae.
3. Approve/disapprove protocols.
4. Terminate/suspend trial.
5. Review the trial for the risk to human subjects.
6. Review both the amount and method of payment to subjects.

How is IRB regulated?

1. IRB is regulated per 45 *CFR* 46, 21 *CFR* 50, 21 *CFR* 56.
2. IRB is required to register through Office for Human Research Protections (OHRP) under HHS.
3. Sponsors are required to submit IRB information in IND or IDE applications.
4. Actions FDA may take regarding IRB deficiencies:
   - Withhold approval of studies
   - Direct that no new subjects be added to ongoing studies
   - Terminate ongoing studies
   - Disqualify the IRB or its parent institution following a regulatory hearing

Record Keeping and Change Control

- Sponsors, investigators, and IRBs are required to comply with record keeping and change control regulations.
- Changes to the original protocol and consent form must be approved by the IRB.
- Investigators are required to submit annual and final report to IRB.

FDA Bioresearch Monitoring Program

- Established in 1977.
- Agency-wide program.
- Responsible for ensuring the integrity of clinical data submitted to the agency and for protecting the rights of human subjects.
- Inspects clinical investigators, sponsors, Contract Research Organizations (CROs), IRBs and nonclinical laboratories.
- Each center's bioresearch monitoring program directs inspection assignments, follow-up and close-out for clinical studies under its jurisdiction.

References

1. ICH GCP Consolidated Guidance:
   http://www.fda.gov/cder/guidance/959fnl.pdf
2. FDA GCP website:
   http://www.fda.gov/oc/gcp/default.htm
3. IRB FAQs:
   http://www.hhs.gov/ohrp/FWAfaq.html
4. NIH Clinical Trial Database
   http://www.clinicaltrials.gov