

Good Clinical Practice

GCP Essential Elements for Clinical Trials



What is Good Clinical Practice?

- Good Clinical Practice is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials to provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.



Regulatory Development

- The FDA was established in 1906 through the Pure Food and Drug Act to regulate products intended for human use
 - Correct labeling
 - No testing for safety or efficacy
- In 1938 Congress created the Food, Drug and Cosmetic Act
 - Required testing of every product for safety and efficacy before acceptance for human use.

Regulatory Development

- The Nuremberg Code (1947)
- Kefauver-Harris Amendments (1962) to Food, Drug and Cosmetic Act
 - Requires sponsors of clinical trials to submit detailed safety and efficacy data
 - Resulted because of deaths caused by the use of drugs that were insufficiently tested
- The Declaration of Helsinki (1964)
(International ethical guidelines for physicians involved in the conduct of research in human subjects.)

Regulatory Development

- FDA produced the Code of Federal Regulations (CFR) in 1977 (21 CFR)
 - Applies to all research conducted in the United States
 - Introduction of Good Clinical Practice
 - Combines
 - Ethics
 - Sound scientific practices
 - Quality data

Federal Regulations

Department of Health & Human Services (DHHS)

National Institutes of Health (NIH) Other Agencies under DHHS

- 45 CFR 46
Protection of Human Subjects
- 45 CFR 94
Conflict of Interests

Food & Drug Administration (FDA)

- 21 CFR 11
Electronic Records, Electronic Signatures
- 21 CFR 50
Protection of Human Subjects
- 21 CFR 54
Financial Disclosure by Investigators
- 21 CFR 56
Institutional Review Boards
- 21 CFR 312
Investigational New Drug Application
- 21 CFR 314
FDA Approval to for Marketing New Drug
- 21 CFR 600
Biological Products
- 21 CFR 803
Medical Device Reporting
- 21 CFR 812
Investigational Device Exemptions
- 21 CFR 814
Pre-Market Approval of Medical Devices

International Conference on Harmonization (ICH)

Established in 1996 the International Conference on Harmonization (ICH) provided guidelines for

- A common set of research standards for the international research community
- Standard Good Clinical Practices
 - Protection of trial subjects
 - Scientific support of clinical trials & good quality data
 - Integrity in the conduct of the trial
- ICH GCP Guidance for Industry clarified GCP requirements
 - E6 Good Clinical Practice: Consolidated Guidance www.fda.gov/cder/guidance/959fnl.pdf

13 Principles of GCP

- *Ethical principles*
- *Risks vs. Benefits*
- *Rights, safety and well-being of subjects come first*
- *Supporting information for all data*
- *Scientifically sound and clearly described*
- *IRB approval is required*
- *Qualified physician or dentist*
- *Qualified research team*
- *Informed Consent*
- *Accurate reporting, interpretation and verification of information*
- *Confidentiality of subjects*
- *Good Manufacturing Practice (GMP)*
- *Quality systems for reliability of data*

The 13 GCP Principles Govern

- *Institutional Review Boards (IRBs)* GCP 3.1-3.4
- *Investigators and Research Staff* GCP 4.1-4.13
- *Sponsors, Monitors and Contract Research Organizations (CROs)* GCP 5.1-5.23
- *Protocols and Protocol Amendments* GCP 6.1-6.16
- *Investigational Drug Brochures* GCP 7.1-7.5
- *Essential documents for the conduct of the clinical trial* GCP 8.1-8.4

Challenges in Conducting Good Clinical Practices

- Problems inherent in clinical trials
 - Inadequate and inaccurate records
 - Failure to conduct the study according to the protocol
 - Failure to maintain accountability for investigational product
 - Problems with informed consent
 - Timely and accurate reporting of adverse events



Challenges in Conducting Good Clinical Practices

**Failure to follow the approved
protocol**

Deficiency cited in 32% of FDA
inspections



Challenges in Conducting Good Clinical Practices

Drug Accountability

Deficiencies cited in 19% of FDA
inspections



Why is GCP Important for Record Keeping?

- It is the “Gold Standard” in record keeping requirements against which most studies will be compared
- Represents FDA’s current thinking on
 - Conduct of clinical trials
 - Recordkeeping for those trials
- The FDA will consider clinical studies conducted under ICH GCP as meeting GCP standards acceptable to the agency (www.fda.gov/cder/present/dia698/diafda2/sld024.htm)
- Incorporates standardized principles for ensuring quality control, audibility and subject protection



Investigator Responsibilities

Investigator's Responsibilities

For Investigator initiated research trials
where the investigator holds the IND

- The investigator has the normal responsibilities of an Investigator plus the responsibilities of a Sponsor

Investigator-Initiated Trials/Research, Strategies for Success

John F. Ennever, Md. Ph.D.

FDA Form 1571

Investigational New Drug (IND)

- Contract between the FDA and the Investigator (If investigator holds IND)
- No drug may be shipped or clinical investigation begun until an IND form for that investigation is in effect (21 CFR 312.40)
- Investigator agrees to:
 - Not to begin investigational activities until 30 days after FDA receipt of IND
 - Not to begin or continue investigational studies placed on hold
 - Requires the investigator assures the IRB complies with 21 CFR 56 for initial and continuing reviews
 - Requires conduct of study in accordance with all applicable regulations
 - Complete, sign FDA Form 1571 and send before beginning research

FDA Form 1572

Statement of the Investigator

- Contract between the FDA and the Investigator
- No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator Form FDA 1572 (21 CFR 312.53)
- Complete, sign and submit FDA Form 1572 or an Investigator Agreement (device trials) **before** beginning research

Investigator's Responsibilities Identified on FDA Form 1572

Section 9 of Form 1572:

- Conduct the study according to the approved protocol*
- Personally supervise or conduct the study*
- Inform subjects of investigational status of the study and comply with 21 CFR 50 and 21 CFR 56*
- Report adverse experiences to the sponsor and the IRB*
- Read and understand the Investigator's brochure*
- Inform all study personnel of study requirements, commitments and their obligations under the study*
- Ensure subject safety and protect subject rights (CFR 21 CFR 312.60)*
- Maintain adequate records, make them available for inspection and retain them according to regulations (21 CFR 312.62 & 21 CFR 312.68)*
- Ensure IRB complies with 21 CFR 56*
- Comply with Investigator responsibilities as detailed in 21 CFR 312 or 21 CFR 812*

Investigator Responsibilities

– *Reporting Responsibilities:*

- *Report changes to the study to the IRB and the sponsor*
- *Report unanticipated and serious risks to the IRB*
- *Retain records and issue specific reports to sponsors and the IRB*
- *Provide the IRB with appropriate information for initial and continuing reviews*

Investigator Responsibilities

Study Drug Accountability :

- *Maintain strict control of investigational drugs in secure (locked) enclosures under conditions recommended by manufacturer (21 CFR 312.10)*
- *Administer the test article only to subjects under the Investigator's supervision and do not supply the test article to any unauthorized person (21 CFR 812.110.c)*
- *Keep records of disposition, dates of administration, quantity and use by subjects (21 CFR 312.6)*
- *Return unused supplies to the sponsor (21 CFR 312.62 & 21 CFR 812.64)*
- *DEA registration is needed for use of controlled substances*

Investigator Responsibilities

Study Drug Accountability:

- Properly train all associates involved in the study of their responsibilities and the associated risks and benefits of the test article
- *Maintain records of receipt, shipment and disposition of IND drugs, batch number, date, quantity and batch code for each shipment (21 CFR 312.57 & 312.59)*
- Properly label each unit of test article supply (21 CFR 312.65)
- Ship the test article only to qualified Investigators (21 CFR 812.43b)
- Provide written instructions for storage conditions and subject administration to Investigators to whom test article is shipped (21 CFR 312.23)



Record Keeping

*“If it’s not documented,
it didn’t happen!”*

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- GCP Essential Documents for Clinical Trials

Essential Documents

- Investigator's Brochure
- Signed protocol and amendments and sample CRF
- Information given to trial subjects
 - Informed Consent including translations
 - All written information
 - Advertisement for recruitment
- Financial documents / agreements
- Insurance statement (if required)

**Keep all versions of these documents during the trial
Refer to regulations & institutional policies for maintaining records**

Essential Documents

- Signed agreements between all involved parties:
 - Investigator
 - Institution
 - Sponsor
 - CRO
 - Regulatory authorities (where required)
- Dated & approved IRB documents
 - Dated & approved Protocol and amendments
 - Dated & approved Case Report Forms (when applicable)

**Keep all versions of these documents during the trial
Refer to regulations & institutional policies for maintaining records**

Essential Documents

- Dated & approved IRB documents (continued)
 - Informed consent forms
 - All other written information provided to subjects
 - Advertisements for subject recruitment
 - Subject Compensation (if any)
 - Other documents approved by IRB

Keep all versions of these documents during the trial
Refer to regulations & institutional policies for maintaining records

Essential Documents

- IRB review board and ethics committee composition or FWA in lieu of an IRB Roster
- Regulatory authorization (where required)
- Curriculum Vitae of investigators and sub-investigators
 - Updated, signed and dated every 2 years
- Normal value ranges for laboratory tests

Keep all copies of these documents during the trial
Refer to regulations & institutional policies for maintaining records

Essential Documents

- Lab certifications and accreditations - if required
 - CAP/CLIA certifications
 - QA/QC assessment
 - Other validation as required
- Shipping and receiving records for investigational products
- Decoding procedures for blinded trials
- Master randomization list
- Trial initiation monitoring report (if applicable)

**Keep all copies of these documents during the trial
Refer to regulations & institutional policies for maintaining records**

Essential Documents – During the Trial

- Investigator's brochure updates
- Revisions to original:
 - Protocol & amendments
 - Informed consent form
 - Case Report Forms (CRFs)
 - Materials provided to subjects
 - Advertisements for subject recruitment

Keep all copies of these documents during the trial according to records retention policies noted at the end of this presentation



Essential Documents – During the Trial

- Regulatory authorizations and approvals
- Curriculum Vitae for new investigators or sub-investigators
 - Signed, dated and updated every 2 years
- Updates to lab values/certifications
- Investigational product and trial related materials shipment and receipt

**Keep all copies of these documents during the trial
Refer to regulations & institutional policies for maintaining records**

Essential Documents – During the Trial

- **Correspondence / Communications**
 - Letters, meeting notes, notes of telephone calls and emails
- **Signed Informed Consent Forms**
- **Source Documents**
 - Documents in which data collected for a clinical trial is first recorded, these data are usually later entered in the case report form
 - Examples of source documents include: medical records, lab reports, subject diaries, x-rays, ECG printouts
- **Signed, dated and completed case report forms (CRFs)**
 - The Case Report Form is the tool used to collect data from the study.
 - Copies of CRF corrections

**Keep all copies of these documents during the trial
Refer to regulations & institutional policies for maintaining records**

Essential Documents – During the Trial

- Adverse Event reports
- Unexpected and Serious Adverse Event Reports
- Safety information notifications
- Interim or Annual reports to IRB and authorities
- Subject Screening Log
- Subject Identification code list
- Subject enrollment log

Keep all copies of these documents during the trial
Refer to regulations & institutional policies for maintaining records



Essential Documents – During the Trial

- Drug / device accountability log
- Site signature / delegation of duties log
- Record of retained body fluids and tissues

**Keep all copies of these documents during the trial
Refer to regulations & institutional policies for maintaining records**



Essential Documents – After Trial is Completed

- Completed drug / device accountability log
- Documentation of return or destruction of investigational product
- Completed subject identification code list
- Final report by investigator
- Clinical study report

**Keep all copies of these documents during the trial
Refer to regulations & institutional policies for maintaining records**

How Long To Keep Research Records?

Regulatory minimum:

- Drugs
 - 2 years from the date of application to market (whether approved or not)
- Devices
 - 2 years from study completion, termination or when records to support approval are no longer needed

State of Texas requirements

- 13 years after regulatory minimums

Summary

- The Investigator is always responsible for the conduct of the study and must understand
 - Obligations
 - Exposure
 - Liabilities
- Good Clinical Practices can help the Investigator mitigate exposure and liability by providing data that is
 - Reliable
 - Accurate
 - Supports conclusion of the research



Questions?

Resources

- Belmont Report
 - <http://oshr.od.nih.gov/mpa/belmont.php3>
- Center for Biologic Research & Evaluation (CBER)
 - <http://www.fda.gov/cber>
- Center for Devices & Radiological Health (CDRH)
 - <http://www.fda.gov/cdrh>
- Center for Drug Evaluation & Research (CDER)
 - <http://www.fda.gov/cder>
- Code of Federal Regulations
 - <http://www.access.gpo.gov/nara/cfr/index.html>
- Declaration of Helsinki (1987, recognized by the FDA)
 - <http://www.fda.gov/cder/guidance/fstud.htm>
- Declaration of Helsinki (2000)
 - <http://www.wma.net/e/policy/b3.html>
- Department of Health and Human Services (DHHS)
 - <http://www.os.dhhs.gov>

Resources (continued)

- Food & Drug Administration (FDA): Homepage
 - <http://www.fda.gov>
- FDA Information Sheets
 - <http://www.fda.gov/oc/ohrt/irbs/default.htm>
- Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance
 - <http://www.fda.gov/cder/guidance/959fnl.pdf>
- Federal Register Online
 - <http://www.gpoaccess.gov/fr/index.html>
- International Conference on Harmonization (ICH)
 - <http://www.ich.org>
- ICH Guidelines
 - <http://www.ifpma.org/ich5.html>
- NIH Online
 - <http://www.nih.gov>
- Office for Human Research Protection (OHRP)
 - <http://ohrp.osophs.dhhs.gov>