



Good Clinical Practice (GCP) Key Concepts

Bridget Foltz

Policy Analyst

Office of Good Clinical Practice

Office of Special Medical Programs

Office of Medical Products and Tobacco



Objectives

- Definition and goals of GCP
- Key GCP principles
 - ICH E6 GCP and R(2) Addendum
 - FDA's Regulations Relating to GCP
- Responsibilities of some key players
- Informed Consent
- Resources on Electronic Documents/Source Data
- FDA's Resources on GCP/HSP

What is Good Clinical Practice (GCP)?

- Good clinical practice (GCP) is an **international ethical and scientific quality standard** for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

What is Good Clinical Practice (GCP)?

- While FDA regulations do not have a stand alone definition of GCP, it is defined in 21 CFR 312.120 (*Foreign clinical studies not conducted under an IND*):
 - For the purposes of this section, GCP is defined as a standard for the **design, conduct, performance, monitoring, auditing, recording, analysis, and reporting** of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.

What is Good Clinical Practice (GCP)?

GCP stand alone definition in the 1996 ICH GCP E6 consolidated guidance:

- 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 is protected.

International Conference on Harmonisation (ICH)

- Efforts to bring together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.
- ICH has gradually evolved, to respond to the increasingly global face of drug development, so that the benefits of international harmonisation for better global health can be realised worldwide.
- ICH mission is to achieve greater harmonisation to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

ICH Guidance

- ICH work products include Quality Guidelines, Safety Guidelines, Efficacy Guidelines and Multidisciplinary Guidelines (see <http://www.ich.org/home.html>)
- ICH E6 Good Clinical Practice: Consolidated Guidance is recognized as official FDA guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf>

GCP: Overarching Themes

- Responsibility(-ies)
- Attention to Detail
- Documentation
- Quality
 - Data/Scientific Quality; Ethical Quality; Process Quality
- Risk and Risk Management
- Validation/Verification/Inspection

The Goals of GCP

To provide standards and guidelines for the conduct of clinical research that include provisions for:

- Protecting Research Subjects
 - Subject safety
 - Rights as subjects (research ethics)
 - Right to be informed
 - Right NOT to participate
 - Right to withdraw at any time
 - Right to protection of privacy
 - ... and other Rights

The Goals of GCP

- Ensuring the quality and integrity of research data for regulatory decision-making
 - Based on a scientifically sound protocol that is designed to meet its stated objectives
 - Based on the quality conduct and oversight of the clinical study

The Goals of GCP

- Assuring the existence and operation of “quality systems”
 - Including but not just for the current study
 - By each party (investigator, sponsor, IRB, and regulatory authority)
 - Based on written procedures
 - Assured through self- and cross-evaluation
 - Leveraged: Regulatory authority can’t do it all



Good Clinical Practice = Ethics + Quality Data

Why is GCP important?

- Adherence to the principles of GCPs, including adequate human subject protection (HSP) is universally recognized as a critical requirement to the conduct of research involving human subjects.

Why is GCP important?

- GCP compliance provides public assurance that the rights, safety and wellbeing of human subjects involved in research are protected.
- Promotes data integrity and reliability.

GCP/Laws and Regulations

- Many countries have adopted GCP principles as laws and/or regulations.
- The FDA's regulations for the conduct of clinical trials, which have been in effect since the 1970s, address both GCP and HSP.

Principles of ICH GCP

Ethics:

1. Ethical conduct of clinical trials
2. Benefits justify risks
3. Rights, safety, and well-being of subjects prevail

Protocol and Science:

4. Nonclinical and clinical information supports the trial
5. Compliance with a scientifically sound, detailed protocol

Principles of ICH GCP

Responsibilities:

6. IRB/IEC approval prior to initiation
7. Medical care/decisions by qualified physician
8. Each individual is qualified (education, training, experience) to perform his/her tasks

Informed Consent:

9. Freely given from every subject prior to participation

Principles of ICH GCP

Data Quality and Integrity:

10. Accurate reporting, interpretation, and verification
11. Protects confidentiality of records

Investigational Products:

12. Conform to GMP's and used per protocol

Quality Control/Quality Assurance:

13. Systems with procedures to ensure quality of every aspect of the trial

ICH E6(R2) Addendum

ICH E6(R1) has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and reliability of trial results

Integrated Format of the Addendum

- The addendum supplements ICH E6(R1) with additional text
- This guideline should be read in conjunction with other ICH guidelines relevant to clinical trial conduct (for example, ICH E2A, E3, E7, E8, E9, and E11)
- In the event of any conflict between E6(R1) text and the addendum text, the addendum text should take priority

What Constitutes GCP in Clinical Trials?

- IRB-approved protocol
- Valid Informed Consent
- Monitoring Plan
- Adverse Event (AE) Reporting
- Proper documentation
- Valid data collection/reporting procedures

How does FDA implement GCP?

- 21 CFR 11 – Electronic Records & Signatures
- 21 CFR 50 – Informed Consent
- 21 CFR 54 – Financial Disclosure
- 21 CFR 56 – Institutional Review Boards
- 21 CFR 312 – Investigational New Drug Applications

How does FDA implement GCP?

- 21 CFR 314 – New Drug Applications
- 21 CFR 320 – Bioavailability & Bioequivalence Requirements
- 21 CFR 601 – Biologic License Applications
- 21 CFR 812 – Investigational Device Exemptions
- 21 CFR 814 – Premarket Approval of Medical Devices

Shared Responsibilities

- Responsibility for GCP is shared by all parties involved in a clinical trial including:
 - Sponsors
 - Contract Research Organizations (CROs)
 - Investigators
 - Study site staff
 - IRBs
 - Research Subjects
 - FDA/other regulators

Sponsor Responsibilities

21 CFR Parts 312 and 812

- Obtain regulatory approval, as necessary, before initiating a study
- Manufacture and label investigational products appropriately
- Initiate, withhold, or discontinue studies as required
 - Includes protocol development, often in consultation with one or more clinical investigators

Sponsor Responsibilities

21 CFR Parts 312 and 812

- Refrain from commercialization of investigational products
- Control the distribution and return of investigational products
 - Detailed records
 - Proof of IRB approval before initial shipment
- Select qualified clinical investigators
 - Credentials can vary by study
 - “1572” commitments for pharmaceutical studies
 - Investigator agreements for medical device studies

Sponsor Responsibilities

21 CFR Parts 312 and 812

- Disseminate appropriate information to investigators
 - Commonly = Investigator's Brochure for pharmaceutical studies
 - Update as necessary
- Obtain investigator financial disclosure information
- Select qualified persons to monitor the conduct of the studies

Sponsor Responsibilities

21 CFR Parts 312 and 812

- Ensure adequate monitoring of clinical studies
 - Written SOPs desirable (required by FDA device regulation)
 - Requires access to site and subject records (privacy laws applicable)
 - Provides quality control – for assurance of subject protections and data integrity
 - Enables assurance of clinical investigator compliance

Sponsor Responsibilities

21 CFR Parts 312 and 812

- Evaluate and report adverse experiences
- Maintain adequate records
 - Retention according to regulatory requirements
- Submit all reports, including safety reports, annual/progress and final reports, as required

Investigator Responsibilities

21 CFR Parts 312 and 812

- Personally conduct and/or supervise the study
 - Cannot contract out any responsibilities; is entirely responsible for study conduct at site
 - Needs to ensure qualifications and training of anyone delegated study duties and meet with study staff on a regular basis
 - SOPs for site's conduct of studies and handling of problems

Investigator Responsibilities

21 CFR Parts 312 and 812

- Communicate with the IRB
 - Initial approval before initiation of study
 - Amendments/progress reports/continuing review
 - “Safety” reports
- Ensure proper informed consent process
 - IRB approved form
 - Documented prior to any study-related activities
 - If delegated, only to appropriate study staff

Investigator Responsibilities

21 CFR Parts 312 and 812

- Protocol compliance
 - No deviation without prior sponsor and IRB approval – unless to eliminate an **immediate** hazard to subjects
 - Protocol should be designed to facilitate compliance
- Control of investigational products
 - Detailed records – receipt, use, & disposition
 - Proper storage and handling – as defined in the protocol

Investigator Responsibilities

21 CFR Parts 312 and 812

- Maintenance of randomization and blinding; unblinding only for medical emergencies and then fully documented
- Safety reporting
 - Recognizing and reporting all adverse events
 - Special attention to serious and unexpected events – reporting to sponsor and IRB and regulatory bodies as required

Investigator Responsibilities

21 CFR Parts 312 and 812

- Recordkeeping
 - Accurate and complete case histories for each study subject – both those to whom investigational product was administered and controls that includes:
 - Source documents (Hospital charts, clinical laboratory reports, x-rays, ECGs, subject diaries, pharmacy records)
 - Case report forms
 - Correspondence
 - Other study-related documents – e.g., protocol, with all amendments; Investigator’s Brochure, screening logs
 - Quality and integrity of data essential
 - Maintained as required by applicable regulations

Investigator Responsibilities

21 CFR Parts 312 and 812

- Reporting
 - Safety reports
 - Progress reports
 - To sponsor
 - To IRB for continuing review
 - Final report
 - Financial disclosure information to the sponsor

IRB Responsibilities

21 CFR Part 56

- Membership – must be diverse and independent
 - At least 5 members
 - At least one member from scientific area
 - At least one member from nonscientific area
 - At least one member not otherwise affiliated with the institution
 - Non-voting consultants/experts invited as necessary

IRB Responsibilities

21 CFR Part 56

- Written procedures
 - Initial and continuing review
 - Frequency of review and verification of changes
 - Prompt reporting of changes
 - No changes without IRB review and approval unless to eliminate apparent immediate hazard
 - Prompt reporting of unanticipated problems
 - Prompt reporting of serious or continuing noncompliance
 - Prompt reporting of suspension or termination of IRB approval

IRB Responsibilities

21 CFR Part 56

- Reviewing research
 - Full board, expedited review
 - Criteria for approval are met
 - Perform ethical reviews
 - Ensure proper expertise for scientific review
 - Review target subject population to ensure adequate inclusion/exclusion criteria and proper recruiting
 - Review investigator's qualifications and ability to supervise and conduct the study at the site
 - Consider subject privacy and data confidentiality
 - Ensure proposed informed consent process and form are appropriate

IRB Responsibilities

21 CFR Part 56

- Decision-making
 - Normally at a convened meeting where a quorum is present, unless qualifies for expedited review
 - Methods for reaching decisions should be outlined in written procedures (approval, modifications requested to secure approval, disapproval)
 - No IRB member with a conflict of interest should participate
 - Non-members excluded from deliberations and vote

IRB Responsibilities

21 CFR Part 56

- Communicating decisions
 - In writing to investigator and institution
 - Suggestions for revision when modifications are required
 - Reasons for disapproval or termination/suspension of prior approval

IRB Responsibilities

21 CFR Part 56

- Continuing review
 - As appropriate to risk of study, but at least annually
 - Substantive and at a convened meeting unless qualifies for expedited review
- Maintaining adequate records (e.g., correspondence, copies of all research proposals, approved sample ICDs, minutes of meetings) and record retention as required by applicable regulations

Informed Consent

21 CFR Part 50

- General requirements for informed consent
 - Consent prior to involvement in study
 - Consent process minimize possibility of coercion or undue influence
 - Consent in language understandable to subject
 - Consent form may not include exculpatory language

Informed Consent

21 CFR Part 50

- Exception of informed consent requirements for emergency research
- Elements of informed consent
 - Basic elements
 - Additional elements
- Documentation of informed consent
- Additional safeguards for children in clinical investigations

Electronic Records/Source Data

- Part 11 -Electronic Records -
www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf
- Computerized Systems Used in Clinical Investigations -
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf
- Electronic Source Data in Clinical Investigations -
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf
- Use of Electronic Informed Consent -
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf>

GCP Training Opportunities

- FDA
<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112925.htm>
- NIH
<https://gcp.nihtraining.com/>
- Collaborative Institutional Training Initiative (CITI) at the University of Miami
<https://www.citiprogram.org/index.cfm?pageID=22>
- ICH
<http://www.ich.org/trainings/ich-trainings/gcp-and-clinical-research-inspection.html>
- Other external professional organizations such as DIA, RAPS, SoCRA, ACRP, PRIM&R



Questions?

Thank You!

Bridget Foltz

Bridget.Foltz@fda.hhs.gov

or

gcp.questions@fda.hhs.gov

Resources

- ICH
 - <http://www.ich.org/home.html>

- ICH GCP E6 Consolidated Guidance
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>

- ICH E6(R2) Addendum
 - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4.pdf

- FDA's OGCP website
 - <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018191.htm>

- FDA's GCP Questions public mailbox
 - gcp.questions@fda.hhs.gov

Resources

- Previously answered queries from OGCP mailbox
 - <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriesToFDAonGoodClinicalPractice/default.htm>
- FDA GCP/HSP e-mail updates – sign up to receive
 - <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>
- Check out “In the News” for the latest updates
 - <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>
- OGCP staff contacts
 - <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134476.htm>