Review of GCP: Goals /Principles/ Roles/Responsibilities

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APEC GCP Inspection Workshop
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What This Lecture will Address/Review

- Key Activities in a Clinical Trial
  - The Process Approach
- Brief History of GCP (U.S. and international)
- Goals and Principles of GCP
- Roles and Responsibilities Under GCP
  - Investigators
  - Sponsors/Contract Research Organizations
  - Ethics Committees
Inspector’s View of a Clinical Trial

- Premise: A clinical trial can be viewed as a series of key activities
  - WHO Handbook for GCP identifies 15 key activities in conducting a single clinical study
    - The order of these activities may vary
    - Activities may be completed simultaneously
  - Multiple parties (including the investigator --- but also the sponsor, ethics committee[s], and regulator[s]) are responsible for the success of each of these activities

Key Activities and The Process Approach

- Thesis: To achieve quality of the clinical trial as a whole, quality must be defined, controlled, and assured for each key activity
- An inspection should address each of the key activities that take place at the inspected site and for which the inspected party is responsible
Thinking Like an Inspector: Questions to Ask -1-

- What are these 15 key activities?
- Which of these 15 are the responsibility of the party I am inspecting?

The 15 Key Activities in a Regulated Clinical Trial -1-

1. Development of the Study Protocol
2. Development of Written Standard Operating Procedures (SOPs)
3. Development of Support Systems and Tools
4. Generation and Approval of Study-Related Documents
5. Selection of Study Sites and Qualified Investigators
### The 15 Key Activities in a Regulated Clinical Trial -2-

1. Ethics Committee Review and Approval of the Protocol
2. Review by Regulatory Authorities
3. Enrollment of Subjects: Recruitment, Eligibility, and Informed Consent
4. The Investigational Product(s): Quality, Handling, and Accounting
5. Conducting the Study: Study Data Acquisition

### The 15 Key Activities in a Regulated Clinical Trial -3-

6. Safety Management and Reporting
7. Monitoring the Study
8. Managing Study Data
9. Quality Assurance of Study Performance and Data
10. Reporting the Study
Thinking Like an Inspector: Questions to Ask -2-

- What information do I have about each key activity before I start the inspection?
- What do I ask/review on-site to assess each key activity?
- What are the inspected party’s responsibilities in each key area and what is the standard I use to evaluate these?

GCP: Origins in the Successes and Failures of Research

- Successes
  - Scientific Method and Evidence-Based Medicine
  - Principles of Conduct (Hippocratic Oath and beyond)
- Failures
  - Ethical Atrocities (War-time research; others)
  - Scientific Fraud
  - Preventable Research Deaths/Injury
GCP in the U.S.: A Brief History -1-

- In contrast to GMP (Good Manufacturing Practices) and GLP (Good Laboratory Practices: for animal toxicology studies), the term “Good Clinical Practice” (or GCP) does not appear in U.S. law or FDA regulations
- But FDA has a long history of regulating and inspecting clinical research

GCP in the U.S.: A Brief History -2-

- 1960’s
  - Requirement for “adequate and well-controlled clinical investigations” to support marketing applications
  - Requirement for research permits (IND) to conduct human subjects research with investigational products
  - First FDA inspections of clinical investigators
GCP in the U.S.: A Brief History -3-

- 1970’s
  - FDA regulations for each of the parties involved in clinical research
    - Clinical Investigators
    - Sponsors/Monitors/Contract Research Organizations
    - Ethics Committees (IRBs/IECs)
  - Comprehensive Bioresearch Monitoring (BIMO) Program of inspections: Inspecting each party
  - Extension of law/regulations to medical devices

GCP in the U.S.: A Brief History -4-

- 1980’s
  - Acceptance of non-U.S. studies in support of a U.S. marketing application
    - A marketing application (NDA; PMA) can be submitted to the U.S. with only foreign studies --- no requirement for a U.S. study
  - FDA began inspection of clinical investigators and sponsors outside of the U.S.
**FDA CI International Inspections***

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*Conducted for FDA/CDER from 1980 through 08/8/07; total: 810
**data reviewed in U.S.

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**GCP in the U.S.: A Brief History**

- **1990’s:**
  - International GCP harmonization through ICH (International Conference on Harmonization)
    - Harmonization between industry and regulators in U.S., European Union, and Japan
    - First “formal” use of the term GCP at FDA
    - Resulted in ICH GCP (E6) Consolidated Guideline
  - Published in the U.S. in May 1997 as official FDA “guidance”
GCP in the 21st Century

- Beyond Drugs/Biologics
  - Global Harmonization Task Force (GHTF)

- Globalization

- Global Acceptance and Expectation
  - FDA proposed “new” rule for acceptance of non-U.S. studies: expects compliance with international GCP

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 Hierarchy of GCP

The Goals of GCP –1-

- 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 –2-

- 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 –3-

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

- The identification of Principles of GCP was/is a major achievement of ICH GCP carried through to all other international GCP guidelines (ISO, PAHO, WHO...)
- Each of the 13 Principles can be linked to one or more of the goals of GCP
- The GCP Principles reflect internationally accepted ethical and quality principles found in other internationally accepted documents
- Achieving a Principle requires that each party and all parties together meet their corresponding responsibilities

A Listing of the Principles

- #1: Trials should be conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki.
- #2: Before a trial is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified.
A Listing of the Principles

- #3: A trial should be initiated and continued only if the anticipated benefit(s) for the individual trial subject and society clearly outweigh the risks.
  - Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well-being of the trial subjects.

A Listing of the Principles

- #4: The trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
- #5: Approval of trials of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.
# A Listing of the Principles

- #6: A trial should be scientifically sound, and described in a clear, detailed protocol.

- #7: Freely given informed consent should be obtained from every subject prior to trial participation in accordance with national culture(s) and requirements. When the subject is mentally or legally incapable, consent should be obtained from a legally acceptable representative.

# A Listing of the Principles

- #8: Qualified medical personnel (i.e., physician or, when appropriate dentist) should be responsible for the medical care of trial subjects, and for any medical decision made on their behalf.

- #9: Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) and currently licensed to do so, where required.
A Listing of the Principles

- #10: All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
- #11: The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

A Listing of the Principles

- #12: Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and should be used in accordance with the approved protocol.
- #13: Systems with procedures that assure the quality of every aspect of the trial should be implemented.
Goals and Principles of GCP: Thinking Like an Inspector

- Violations so serious as to compromise the goals and principles of GCP:
  - Are the most important to detect in inspection
  - Are most likely to result in official (enforcement) action
  - Must be most thoroughly documented

Roles and Responsibilities: The Framework of the Inspection
Responsible Parties

- Study sponsor/contract research organization (CRO)
- Clinical investigators (CIs)
- Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

Shared Responsibilities

- Responsibilities overlap - system of checks and balances
- Non-compliance by any party does not eliminate need for other parties to be compliant
- FDA regulations and ICH GCP definitions - similar and include/imply responsibilities
Sponsor -1-

- **Definition**: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial
- **Includes**: commercial (pharmaceutical and device) companies, government funding agencies, private foundations, and individuals
- **Sponsor-investigators** - must comply with both sponsor and investigator responsibilities
Sponsor -2-

- GCP requires certain direct communications and interactions between the sponsor and the regulatory authority

Contract Research Organization (CRO)

- A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor’s trial-related duties and functions
- FDA’s pharmaceutical regulation covers transfer of regulatory responsibility; not addressed in device regulation
- Sponsor ultimately responsible for the conduct of the study
Monitor

- Employee of the sponsor (or CRO) who works to oversee the progress of a clinical study through on-site visits and other means
  - To ensure that the study is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirement(s). (Quality control)

Medical Expert ("Medical Monitor")

- Employee of the sponsor (or CRO) who is readily available to advise on trial-related medical questions or problems
  - If necessary, outside consultant(s) may be appointed for this person
Independent Data Monitoring Committee (DMC; DSMB)

- A committee established by, but acting independent of, the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial
  - Every study needs safety monitoring; but not every study requires a DMC/DSMB

Sponsor Responsibilities -1-

- Obtain regulatory approval, where 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 -2-

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

Sponsor Responsibilities -3-

- Disseminate appropriate information to investigators
  - Commonly = Investigator’s Brochure for pharmaceutical studies
  - Update as necessary
- Select qualified persons to monitor the conduct of the studies
Sponsor Responsibilities -4-

- Adequately monitor 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 -5-

- 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
Financing/Compensation

- FDA regulations
  - Do not address the financing of clinical studies or compensation to research subjects
  - Are silent on liability for injury to subjects in a clinical study
  - Address financial disclosure by investigators and other study staff
- ICH GCP recommends
  - The financial aspects of the study be documented in an agreement between the sponsor and investigator
  - Compensation, insurance, and any costs of treatment in the event of study-related injury be addressed in the sponsor’s policies

CLINICAL INVESTIGATOR
Clinical Investigator

- ICH GCP definition: A person responsible for the conduct of the clinical trial at a trial site
- Suggests an investigator at each site; multisite study may have a coordinating investigator, but there should be a responsible party at each site
- The investigator is
  - THE contact with study subjects
  - Responsible for study site compliance with GCP

Subinvestigator(s)

- FDA does not specifically define
- ICH GCP: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or make important trial-related decisions
Investigator Responsibilities -1-

- 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 -2-

- Communicate with the IEC/IRB
  - Initial approval before initiation of study
  - Amendments/progress reports/continuing review
  - “Safety” reports
- Ensure proper informed consent process
  - IEC/IRB approved form
  - Documented prior to any study-related activities
  - If delegated, only to appropriate study staff
Investigator Responsibilities -3-

- Protocol compliance
  - No deviation without prior sponsor and IEC/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 -4-

- 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 IEC/IRB and regulatory bodies as required
Investigator Responsibilities -5-

- Recordkeeping
  - Accurate and complete case histories for each study subject – both those to whom investigational product was administered and controls
  - 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

Investigator Responsibilities -6-

- Recordkeeping (cont.)
  - Quality and integrity of data essential
  - Maintained as required by applicable regulations
Investigator Responsibilities -7-

- Reporting
  - Safety reports
  - Progress reports
    - To sponsor
    - To IEC/IRB for continuing review
  - Final report

Investigator Responsibilities -8-

- Medical care of study subjects (ICH/WHO)
  - Ensure access to reasonable standard of care
  - Investigator or other medically qualified member of study team
  - Recommends informing subject’s primary physician of participation in the study
IEC (U.S. = IRB)

References

- ICH Good Clinical Practice Consolidated Guideline (E6), 1996, Section 3
- Operational Guidelines for Ethics Committees that Review Biomedical Research, World Health Organization, 2000 (TDRPRDEthics2000.pdf)
Role of an Independent Ethics Committee (IEC) -1-

- Safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants
- Providing independent, competent, and timely ethical review of the proposed study
- Considering both the scientific and ethical aspects of the study – since scientifically unsound research is not ethical

Role of the IEC -2-

- To ensure
  - Risks to subjects are minimized
  - Risks are reasonable in relation to anticipated benefits
  - Selection of subjects is equitable
  - Informed consent is appropriately conducted and documented
  - Subject safety is adequately monitored
  - Subject privacy is adequately addressed
Rights of Research Subjects

- Subjects have the right to
  - Be informed
  - NOT participate
  - Withdraw at any time
  - Protection of their privacy

- Declaration of Helsinki – “In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.”

IEC Responsibilities -1-

- Membership – must be diverse and independent
  - At least 5 members
  - At least one from nonscientific area
  - At least one independent of institution/study site
  - Non-voting experts invited as necessary
IEC Responsibilities -2-

- Obtain and review pertinent documents
  - Protocols and amendments
  - Proposed informed consent document
  - Subject recruiting materials
  - Investigator’s Brochure
  - Available safety information
  - Investigator’s curriculum vitae, including all active studies
  - Other - as pertinent to specific study and IEC requirements

IEC Responsibilities -3-

- Schedule and document meetings
  - Time for adequate review by all members
  - Maintenance of detailed minutes
- Written procedures
  - Establishment of IEC authority
  - Definition of membership requirements and terms
  - Meeting schedule and quorum requirements
  - Details of initial and continuing review processes
  - Recordkeeping requirements
  - Procedures to minimize conflict of interest
IEC Responsibilities -4-

- 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
  - Review proposed compensations to investigator and subjects
  - Consider subject privacy and data confidentiality
  - Review issues that may raise community concerns
  - Ensure proposed informed consent process and form are appropriate

IEC Responsibilities -5-

- Decision-making
  - Normally at a convened meeting where a quorum is present
  - Method for reaching decision should be predetermined in written procedures (approval, disapproval, modifications requested, suspension/termination of previously approved study)
  - No one with a conflict of interest should participate
  - Non-members excluded from deliberations and vote
IEC Responsibilities -6-

- Communicating decisions
  - In writing to investigator, including responsibilities an approval entails
  - Suggestions for revision when modifications are required
  - Reasons for disapproval or termination/suspension of prior approval

IEC Responsibilities -7-

- Continuing review
  - As appropriate to risk of study, but at least annually
  - Substantive and at a convened meeting
- Documentation and archiving
  - Retention of all pertinent study documents and related correspondence
  - Maintained at least 3 years after completion of study
The IEC: Closing Perspectives

- The credibility of the IEC will affect the credibility (and acceptability) of clinical studies and study sites
- Developing “high quality” clinical trials depends on developing “high quality” IECs
- Developing methods to assess their adequacy is an important consideration for regulatory bodies
Disclaimer:

The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.

What This Lecture will Address/Review

- Key Activities in a Clinical Trial
  - The Process Approach
- Brief History of GCP (U.S. and international)
- Goals and Principles of GCP
- Roles and Responsibilities Under GCP
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  - Sponsors/Contract Research Organizations
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