Fundamentals of ICH and GCP

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So you are going to run a clinical trial...
What is 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 patients.

- Compliance with this standard provides public assurance that the rights, safety and well-being of trial patients are protected and clinical trial data are credible.
What governs GCP?

- Code of Federal Regulations (www.fda.gov)
- Local laws
- Institutional operating procedures
- Ethical Principles (Belmont Report, Declaration of Helsinki, Nuremburg Code, etc.)
- SOPs: sponsor, CRO, IRB
- Standards of care
- International Conference on Harmonization (ICH Guidelines)
- FDA guidance documents
Good Clinical Practice

Regulatory agencies give sponsors and investigators a set of regulations and guidelines . . .

No two companies are the same with regard to how these requirements are interpreted.
ICH GCP versus Federal Regulations

• If you follow ICH Guidelines, you will be practicing a more stringent form of GCP

• If you are audited by FDA, however, they will reference the Federal Regulations in any citation (FDA Form 483)

• Read and understand both

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Investigator Contracts

- **Clinical Trial Agreement**
  - May reference Federal Regulations and GCP
- **Form FDA 1572**
  - Is a signed contract between the FDA and the principal investigator
- **Protocol Signature Page**
  - Certifies agreement to comply with the information within the protocol
  - *These documents are legally binding!!!*
Learning from other people's mistakes . . .

Top 10 Warning Letters of 2007
Top 10 Warning Letters of 2007

1. Failure to conduct the investigation according to the investigational plan (protocol)
2. Failure to ensure that investigations were conducted according the signed investigator statement (1572)
3. Failure to add key individuals with significant contribution to the study to the 1572
4. Failure to adequately oversee staff and the course of the investigation
Top 10 Warning Letters of 2007

5. Failure to report SAEs to the sponsor within 24 hours

6. Failure to promptly report to the IRB issues occurring during the study (SAEs, protocol deviations, etc.) and to comply with the IRBs schedule of update reports

7. Failure to obtain adequate informed consent; failure to have subjects sign updated ICFs
Top 10 Warning Letters of 2007

6. Failure to maintain adequate and accurate case histories including failure to maintain records on drug disposition and accountability
7. Failure to allow an FDA officer to have access to study records
8. Failure to assure adequate monitoring (sponsor finding)
1. Failure to follow the protocol

Protocols may be well written or not...
- But sites are expected to perform per the protocol
  - Get clarification from the sponsor or medical monitor on areas of “interpretation”
  - DOCUMENT all sponsor/monitor provided clarifications
  - Notify the sponsor of all protocol deviations
2. Failure to comply with the requirements of the 1572

What does the 1572 reference?
- Commitments: “I agree”; “I have read”; “I will ensure”
  - Conduct the study *in accordance with the protocol*...except when necessary to protect the safety, rights or welfare of subjects
  - To *personally* conduct or supervise the described study
  - To inform any patients that drugs are used for investigational purposes... *obtain informed consent* and *ensure IRB approval* is met
2. Failure to comply with the requirements of the 1572

The 1572 commitments continue...

- To report all AEs to the sponsor
- Understand the information in the Investigator Brochure
- Ensure all associates...assisting in the conduct of the study are informed about their obligations in meeting the above commitments
- Maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68
2. Failure to comply with the requirements of the 1572

The 1572 commitments still continue...

- Ensure that an IRB which complies with 21 CFR part 56 will be responsible for the initial and continuing review and approval of the clinical investigation and report to the IRB any changes in the research without IRB approval and all unanticipated problems involving risks to human subjects or others...

- will not make any changes in the research without IRB approval, except when necessary to eliminate immediate hazards to study subjects

Understand what you are signing!!

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3. Failure to add individuals to the 1572

- Investigators have been cited for not listing individuals who contributed to the study at their site on the 1572
  - Study coordinators
  - Personnel responsible for drug dispensing
  - Technologists responsible for collection of medical images

- Ensure the 1572 is complete and represents staff who are making an **active contribution** to the study

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4. Failure to adequately supervise staff

- ICH 1.34: Investigator
  - 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.

- 21 CFR 312.3 (b): Investigator
  - An individual who actually conducts a clinical investigation (under whose immediate direction the drug is administered or dispensed to a subject). In the event that an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.
Investigator Responsibilities (312.60)

- To respect the protocol as approved by the sponsor, FDA and IRB
- To protect the rights of subjects who participate in the clinical trial
- To be medically responsible for their subject’s care
- To manage the medication, its dispensing and accountability
- To obtain informed consent
- To provide financial disclosure
Subinvestigator

- **ICH 1.56**
  - Any individual member of the clinical trial team designated and supervised by the investigator at the trial site to perform critical trial-related procedures and/or to make important trial-related decisions

- **21 CFR 312.3 (b)**
  - Any other individual member of that team.
Documentation of Delegation

Delegation Log

- Ensure personnel are appropriately trained to conduct the following tasks:
  - Administer informed consent
  - Conduct patient physical exams
  - Collect blood or other biological samples
  - Prescribe medication
  - Review safety information and make assessments
  - Sign off on CRFs
  - Perform other critical study functions (imaging)
5. Failure to report SAEs within 24 hours

- Know the regulatory definition of a SAE
- The sponsor needs to know ASAP whether or not the event is considered related to the investigational agent
- Follow study specific instructions to report the information
But the Patient was Treated in the ER?

- Admission or greater than 24 hours in the ER = hospitalization

- Unexpected prolongation of a hospital stay can also be a SAE
6. Failure to report to the IRB

The FDA uses the IRB to:

- Provide local oversight and continuous monitoring
- The IRB must be made aware of all:
  - IND Safety Reports
  - SAEs
  - Protocol deviations
- Each IRB will also have a schedule of required reports
7. Failure to obtain adequate informed consent

- Consent form must be approved by your IRB
  - Confirm that you are administering the most current version of the IC
  - Always check the IRB expiration date
- Each time a new subject is consented check to see that all pages are appropriately completed and dates are supplied where indicated
- Give the subject a copy of the signed IC
7. Failure to obtain adequate informed consent

**REMEMBER:** Medicine has its own language and many of the terms used to describe medical information and procedures are unfamiliar to participants

- Be a good “translator”; EXPLAIN, don’t speak down to the prospective participant

- Present the information in a non-biased manner and avoid “pressure”
7. Failure to obtain adequate informed consent

When presenting an IC to a potential subject:

- Instill trust, know what is in the IC, answer questions honestly
- If you don’t know the answer to a question, say you don’t know but you will find someone who will be able to answer the question
- Confirm their understanding of the information presented in the IC
- Don’t rush the process
8. Failure to Maintain Adequate Records

Why is Documentation so Important?
- Do you remember what was for dinner last night?
- How about last Tuesday?
- What about August 5, 2001?

“If it isn’t written down, then it didn’t happen”
Subject Files

Source Documentation:

- **The first place** data/information on a study subject is written down
  - Medical charts
  - Laboratory and procedure results
  - Clinical Notes
  - Radiopharmacy Dispensing Records
  - X-rays and reports
  - Reports on Protocol Specific Procedures
  - Sponsor provided worksheets

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Subject Files

• **Case Report Form**
  - CRF pages (pink maintained at site post harvest)
  - Monitoring Notes
  - Data Clarification Forms (Queries)
  - Lab reports and ECGs (note clinical significance; sign and date)

• **Informed Consent Form**
  - All versions signed by the subject should be available

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Regulatory Document Files

- Protocol
- Protocol Amendments
- Investigators Brochure
- IND Safety Reports
- Study & Pharmacy Manuals
- Study Memoranda
- Randomization
- Lab certification
- Lab reference ranges
- Training materials
- Study communication
- Monitoring log
- Delegation log
- Financial disclosure
- Contract & CDA

- Form FDA 1572
- Signed protocol signature page & amendments
- IRB submissions
- IRB approved consent
- IRB Roster/Assurance
- Drug disposition doc’s
- Cv’s for PI and subPI’s
- Licenses for study personnel
- Lab cert. & ref. ranges
- Screening/Enrollment log

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Communication

• Document telephone conversations
• Memorandum regarding decision-making, protocol deviations, or protocol interpretations
• Keep: emails, letters, faxes
  - Study/protocol number, site #
  - Signature
  - Date
  - CC list
You’ll be grateful for a written note, when 2 years after your study is over, you need to explain a decision to an FDA auditor!!
When in doubt . . .

DOCUMENT!!!

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9. Failure to allow FDA access to study records

- Document Retention
  - Records shall be retained for 2 years after a marketing application has been approved, or until 2 years after shipment and delivery of the drug for investigational use has been discontinued and the FDA has been notified.

- Regulations stipulate that FDA must have access to study related records
10. Failure to provide adequate monitoring (sponsor finding)

The monitor is on the same team!
- Should not be considered a “police-person”
- The monitors goal is to ensure that the rights and welfare of trial subjects are protected and to assure the integrity of the data
Monitoring Visits

When a visit is scheduled...

- Provide the monitor with adequate space and a quiet place to work
- Orient them to the status of the documentation
- Let them know your availability
- Set up a time to meet later in the day
  • On some visits, a meeting with the PI will be necessary
Monitoring Visits

- Monitors will:
  - Document issues they find
  - Request that you clarify issues
  - Document all findings in a report to the sponsor and a follow-up letter to the PI
  - Meet with you to talk about issues

- Monitors should not:
  - Write in the CRF
  - Re-organize your files (without permission!)
  - Are not responsible for YOUR FILING!
A little advice from the FDA...

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Branch Chief, CBER
Division of Inspection and Surveillance
November 2007
FDA Advice to Investigators

Before the Study:
- Understand what you are responsible for...and get training
- Document the delegation of duties
- Develop forms or checklists to make sure all appropriate activities are performed
- Develop a plan for organizing records
- Train study staff before the study starts, and train replacements before they conduct work on the study
- Do not overextend to many concurrent projects
- Do not take on satellite sites you cannot directly supervise

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FDA Advice to Investigators

During the Study:
- Track the dates when reports are due to the IRB and the sponsor
- Promptly report protocol violations to the IRB and sponsor
- Obtain WRITTEN APPROVAL from the sponsor BEFORE you do something prohibited by the protocol
- Verify delegated duties are performed by appropriate study staff
- Work with the monitors
- Correct small problems before they grow

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FDA Advice to Investigators

After the Study

- Organize the study records
  - So non-study staff can find them
  - To show what a good job you did
  - To fulfill record retention requirements
  - For possible FDA inspection (years later...)

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