Fundamentals of Good Clinical Practice

Wajeeh Bajwa, Ph. D.
Director, Regulatory Knowledge And Support Program
Clinical and Translational Science Institute
University of Florida

Disclaimer

- There are no financial relationships to disclose.
- This presentation is a basic overview of the guidance and the regulations that exist for conducting human subject research. This presentation was current at the time of writing.
- The listener/reader should seek advice regarding specific questions/concerns from the relevant department or the regulatory agency.
Notice

This ICH E6 GCP Investigator Site Training meets the Minimum Criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate BioPharma Inc. as necessary to enable mutual recognition of GCP training among trial sponsors.

Outline of the Presentation

- Learning Objectives
- Abbreviations
- Background of the GCP Regulations
- GCP Overview
- GCDMP (Good clinical data management practice)

- GCP:
  - Investigator Qualifications and Agreements
  - Resources
  - Medical Care of Research Subjects
  - Communication with the regulatory entities (IRB, FDA etc.)
  - Protocol Compliance
  - Randomization Procedures and Unblinding
  - Informed Consent
  - Records and Reports
  - Safety Reporting
  - Investigational Products
  - Progress Reporting/ Final Reports

- FDA Inspections
- Testing your knolwedge
- Points to Remember
Learning Objectives

• Review principles and regulatory requirements for Good Clinical Practice (GCP).
• Discuss roles and responsibilities of the Principal Investigator and study’s staff, protocol compliance, and other criteria for conducting clinical trials.
• Examine best practices, examples of GCP noncompliance, and corrective actions for protocol or procedural deviations.
• Discuss compliance scenarios related to regulatory and protocol compliance.

Abbreviations

• cGxP = Current Good x Practice
  ◦ Where x =
  ◦ C = Clinical
  ◦ L = Laboratory
  ◦ M = Manufacturing
  ◦ T = Tissue
• IND = Investigational New Drug
• IDE = Investigational Device Exemption
• IRB = Institutional Review Board
• FDA = Food and Drug Administration
• DHHS = United States Department of Health and Human Services
• AE = Adverse Event
• SAE = Serious Adverse Event
• ICH = International Conference on Harmonization
Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials which provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

(ICH E6 Guidelines)

Goals of the GCP

• To protect the rights, safety and welfare of humans participating in research
• To assure the quality, reliability and integrity of data collected.
• To provide standards and guidelines for the conduct of clinical research.
• Good Clinical Practice = Ethics + Quality Data
Foundations for the GCP

- The Nuremberg Code (1947)
- The Declaration of Helsinki (1964)
- The Belmont Report (1979)
- International Conference on Harmonization (ICH 6)
- International Standards Organization (ISO) 14155
- Code of Federal Regulations

Why GCP Guidelines

Experiments were performed on concentration camp internees during World War II to obtain information that would be useful to the German military. These experiments included exposure to chemical and biological agents resulting in many deaths. When this information became public knowledge, the men behind this, the Nuremberg Doctors, were charged with murder and torture. Fifteen individuals were found guilty and seven were sentenced to death. As a result of this, the Nuremberg Code was adopted.
The Nuremberg Code (1947)

- Voluntary Participation
- Informed Consent
- Minimization of risk

Why GCP Guidelines (cont.)

- In 1947 another example of the lack of good clinical practices was found in the “Tuskegee Study of Untreated Syphilis in Negro Males”. This study was sponsored by the US Public Health Service (predecessor of the CDC) and was designed to study the effects of untreated syphilis on black males. Although penicillin became the standard of care for syphilis in 1943, the subjects in this study continued untreated since the study represented a “never again opportunity”. This study actually began in 1932 and was supposed to end within one year, it went on for the next ten years without review and the public was unaware of it until 1972.

- The story finally broke in the Washington Star on July 25, 1972, in an article by Jean Heller of the Associated Press. Her source was Peter Buxton, a former PHS venereal disease interviewer and one of the few whistle blowers over the years. The PHS, however, remained unrepentant, claiming the men had been “volunteers” and “were always happy to see the doctors;” an Alabama state health officer who had been involved claimed “somebody is trying to make a mountain out of a molehill.”
After the end of the study, 28 men had died of syphilis, 100 were dead of related complications, 40 of their wives had been infected, and 19 of their children had been born with congenital syphilis.
Declaration of Helsinki (1964)

- Well-being of subject takes precedence
- Respect for persons
- Protection of subjects’ health and rights
- Special protection for vulnerable populations (children, prisoners, minorities, the elderly, students, employees, etc.)

Belmont Report Ethical Principles (1979)

- Respect for Persons
  - Informed consent
  - Protection of vulnerable populations
- Beneficence
  - Non-Maleficence (wrongdoing or misconduct)
- Justice
  - Fairness
The International Conference on Harmonization (ICH)

• **GCP** is an international quality standard that is provided by the International Conference on Harmonization (ICH).

• **Goals**: Harmonize technical procedures and standards; improve quality; speed time to market.

• In 1997, the FDA endorsed the GCP Guidelines developed by ICH.

• ICH guidelines have been adopted into law in several countries, but used as guidance for the FDA in the form of GCP.

Principles of the ICH-GCP

• **Ethics**:
  • Ethical conduct of clinical trials.
  • Benefits justify risks.
  • Rights, safety, and well-being of subjects prevail.

• **Protocol and science**:
  • Non-clinical and clinical information supports the trial.
  • Compliance with a scientifically sound, detailed protocol.
Principles of the ICH-GCP (cont.)

- **Responsibilities:**
  - IRB/IEC approval prior to initiation.
  - Medical care/decisions by qualified physician.
  - Each individual is qualified (education, training, experience) to perform his/her tasks.

- **Informed Consent:**
  - Freely given by every subject prior to participation.

---

Principles of the ICH-GCP (cont.)

- **Data quality and integrity:**
  - Accurate reporting, interpretation, and verification.
  - Protects confidentiality of records.

- **Investigational Products:**
  - Conform to GMPs and used per protocol.

- **Quality Control/Quality Assurance:**
  - Systems with procedures to ensure quality of every aspect of the trial.
International Standards Organization (ISO)

- ISO 14155: Clinical Investigation of Medical Devices for Human Subjects
  - Assists sponsors, monitors, and clinical investigators in the design and conduct of device clinical investigations.
  - Assists regulatory bodies and ethics committees in their roles of reviewing clinical investigational plans.

Sources of Regulatory Information for Conduct of Clinical Trials

- Code of Federal Regulations
  - 21 CFR 11 – Electronic Records & Signatures
  - 21 CFR 50 – Protection of Human Subjects
  - 21 CFR 54 – Financial Disclosure
  - 21 CFR 56 – Institutional Review Boards
  - 21 CFR 812 – Investigational Device Exemptions
  - 21 CFR 814 – Premarket Approval of Medical Devices
  - FDA Information Sheets and Guidance Documents
Sources of Regulatory Information for Conduct of Clinical Trials (cont.)

- **ICH 6 Guidelines:**
  - **In Europe:** Adopted by Committee for Medicinal Products for Human Use (CPMP, July 1996, issued as CPMP/ICH/135/95/Step5, Explanatory Note and Comments to the above, issued as CPMP/768/97) - *CPMP is now known as CHMP*
  - **In Japan:** Adopted by Ministry of Health, Labor and Welfare (MHLW) March 27, 1997; PAB Notification No.430, MHLW Ordinance No.28
  - **In USA:** Adopted by the FDA and Published in the Federal Register, Vol. 62, No. 90, May 9, 1997, pages 25691-25709

GCP in a Nutshell
Drug development timeline

Drug Development Process

© 2016 — Wajeeh Bajwa, Ph. D. — All rights reserved
Entities involved in human research protection

Federal:
HHS (OHRP, FDA, NIH)
Laws (CFR)

Clinical Trial:
Implementation of GCPs

Institutional:
IRB Policies/Procedures

International:
ICH (including FDA)

Who is responsible for GCP compliance?

• Sponsors
• Clinical Investigators
• Independent Ethics Committees – Institutional Review Boards (IRBs)
• Contract Research Organizations (CROs)
• Research Nurses
• Clinical Research Coordinators
• Clinical Research Associates
• Medical Monitors
• Data Entry Personnel
• Others (involved in the conduct/design/data collection etc.)
**Principals of GCP Apply to:**

- Many types of human research:
  - Clinical trials for medical products
  - Trials with non-medicinal products (nutritional supplements)
  - Laboratory studies on tissue samples
  - Epidemiological research studies
  - Behavioral research studies
  - Marketing research studies

---

**GCP in a Nutshell**

1. **Prepare regulatory documents/reports**
2. **Submit documents to IRB/Sponsor/ FDA**
3. **Obtain acknowledgement, file, track, and archive**
4. **Make changes/corrections**
5. **Resubmit**

Source: Conducting Clinical Research, Judy Stone, MD (Mountainside MD Press)
Life of a Clinical Study

Study Plan Development
- Protocol
- Schedule
- Resources
- Site visit

Preparation Activities
- Standard Operating Procedures (SOPs)
- Qualification/Training
- Equipment
- Drug Information

Active Study Period
- Enrollment Log
- Consent Form
- Case Report Forms
- Safety Reports

Life of a Clinical Study (cont.)

Final Report
- Interpretation
- Analysis
- Reporting Results

Post Report
- Archiving (storage – for how long?)
Definitions used in GCP Guidelines

- **Sponsor** is an individual, company, academic institution, or other organization that takes responsibility for and initiates a clinical investigation.

- **Investigator** is an individual under whose immediate direction a drug is administered or dispensed.

- **Sub-Investigator** Any member of a clinical trial team—e.g., associate, resident, research fellow—who is supervised by the investigator at a trial site and allowed to perform critical trial-related procedures and/or to make key trial-related decisions.

Definitions (cont.)

- **Sub-Investigator:**
  - "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 to make important trial-related decisions (e.g., associates, residents, research fellows)."
  - It is important to note that any study staff who "make direct and significant contribution to the data" are considered "sub-investigators" which means they would also be listed in the FDA Form 1572.
Preparation Activities

- Each and every process/system should have a **Standard Operating Procedure** (SOP).
  - Sample list of SOPs:
    - Format and Organization of SOPs
    - Authorizing/Establishment of an SOP
    - Developing and Writing an SOP
    - SOP Review and Approval Procedure
    - Maintenance and Revision of SOPs
    - Establishing a Study File
    - Obtaining and Maintaining IRB Approval

Preparation Activities (cont.)

- **Standard Operating Procedure (SOP) (cont.):**
  - Handling Protocol Amendments
  - Internal/External Audit Procedure
  - Training Procedure
  - Informed Consent Document Development and Review
  - Obtaining Informed Consent for Clinical Trials
  - Advertisement of Clinical Trial
  - Telephone Screening of Potential Volunteers
  - Establishing Study Specific Screening Log
Preparation Activities (cont.)

• Standard Operating Procedure (SOP) (cont.):
  • Completing and Maintaining Case Report Forms
  • Documentation and Reporting Adverse Events
  • Handling of Deviations
  • Incoming Material Receipt, Storage, and Handling
  • Labeling Study Drug Specimens
  • Test Article (Study Drug) Accountability

Preparation Activities (cont.)

• Training File:
  • Curriculum Vitae (CV) - dated (and signed)
  • Position Description/Job Description
  • SOP Review/Training Log
  • General Training Information (meetings, seminars, courses):
    ◦ Title of Training
    ◦ Date of Training
    ◦ Handouts/Summary
    ◦ Host, Facilitator and/or Instructor
  • Meetings and Seminars
    ◦ Presenter, Title of the presentation, and Date
Regulatory Binder

• Study Protocol (signed)
  • Amendments (signed)
• Investigator’s Brochure (must for multi-center trials)
• FDA Form 1572
• Curriculum Vitae (CV) for all individuals listed on 1572
• Approval letter from the IRB
• All IRB correspondence

Regulatory Binder (cont.)

• IND/IDE Safety reports
  • Acknowledgement from the IRB
• Safety reports (AE or DSMB Reports)
  • Acknowledgement from the IRB/DSMB
• Approved consent form
• Advertisements (approval from the IRB)
• IRB Membership list
• Drug inventory/shipping log
Regulatory Binder (cont.)

• Telephone logs
• Laboratory normal and reference ranges (lab certification)
• Study initiation/Close-out letter
• Visit logs for monitors

Tracking

• Screening and enrollment log:
  • Any exceptions should be noted (in case of a borderline inclusion criteria) – must be approved by the sponsor (in writing).
  • Any protocol deviation - must be approved by the sponsor (in writing).
Tracking (cont.)

- Subject Outcome Log:
  - Paper or electronic
  - Items to track:
    - Date
    - Subject number
    - Age, Sex
    - Disease
    - Diagnosis
    - Clinical outcome
    - Lab outcome
    - Adverse Event
    - Comments
- Consent form must mention that this information will be collected
- IRB Approval Required

Tracking (cont.)

- Drug Accountability:
  - All movement of study drug should be tracked.
    - Company (sponsor) → study site → subject → unused drug to sponsor.
  - Investigational drug must be kept in a designated area (separate from regular drug supply).
  - Checking for drug accountability is FDA's favorite (one of the Top 5 areas of non-compliance)
Source Document

• What is a source document?
  • Medical record and any additional documents related to the protocol (case report forms).
    ◦ Any original data or record (Memorandums, Diaries, EKGs, etc.)

Source Document (cont.)

• Disaster recovery plan?
  • Fire, flood, theft, etc.
Data Entry

- Blank pages/sections should be crossed out with initials and date.
- Source document relating to multiple studies:
  - Photocopies are acceptable as long as:
    - Copy is stamped/marked with “Exact copy of the Original,” signed and dated
    - Location of the original is recorded
  - Photocopies of all printouts on thermal paper (a must!)

Data Entry (cont.)

- Notes to file:
  - Explain an error, omission or potentially ambiguous data.
  - Document decisions (logistical problem), instructions from the sponsor, or problem encountered.
  - Excessive notes to file show that Protocol/Consent form may need amendment!
Electronic Data Entry

• Individual entering data into system should be identified (requires system/software validation)
• Changes are permitted as long as:
  • Audit trail exists and the original data is not deleted
  • Individual making change is identified
  • Changes are dated
  • Reason(s) for change(s) is recorded

Audit

• The following documents, activities or systems may be subject to audit:
  • **SOPs**: To ensure that the SOPs comply with all the appropriate standards of GCP.
  • **Protocol, Amendments and CRFs**: To ensure that all essential items required for the proper conduct of the study are included and that data required by the protocol is reflected in the design of the CRFs.
  • **Investigator Brochures**: To ensure that it contains appropriate information, that it is up to date, and has been approved by the appropriate authorities.
Audit (cont.)

- **Qualifications of investigators and key personnel**: To determine whether the investigator and key personnel are qualified and have experience in the therapeutic area.

- **Investigator agreements**: To verify that the requirements of GCP are appropriately stated. The protocol and agreements covering the conduct of the study, confidentiality, indemnity, insurance and finances can be audited.

- **Personnel availability**: Investigators, key personnel, and monitors will be required to be available at each site audit.

Audit (cont.)

- The auditor sends a follow-up letter to the site personnel explaining major findings*1. Investigator is responsible for following up on all outstanding issues at the study site and should respond to auditor’s findings/concerns within given time frame.

*1: Auditor/Sponsor can choose to share only summary of the audit findings and not full copy of the audit report.
Investigator Responsibilities

(21 CFR 312.60-68)

• The Investigator should:
  • Be qualified (documented) by education, training and experience to assume responsibility for proper trial conduct.
  • Be familiar with the appropriate use of the investigational product, investigator’s brochure (IB), and other information provided by sponsor.
  • Be aware of, and should comply with GCP and the applicable regulatory requirements.
  • Permit monitoring, auditing and inspection.
  • Delegate duties to appropriately qualified persons only.
**Adequate Resources**

- The Investigator should:
  - Demonstrate adequate potential for recruitment.
  - Have sufficient time for trial conduct and completion.
  - Have adequate staff and facilities to conduct the trial.
  - Ensure training for staff.

---

**Medical Care of Research Subjects**

- The Investigator should:
  - Ensure that qualified physician investigators/sub-investigators for the trial are responsible for all trial-related medical decisions.
  - Adequate medical care during and after trial participation.
  - Make reasonable efforts in case of premature withdrawal from trial is necessary.
  - Inform subject’s primary physician about the subject’s participation in the trial, if the subject has a primary physician and if the subject agrees to the primary physician being informed.
Communication with IRB

- The Investigator should:
  - Seek written and dated approval for trial protocol, informed consent document, recruitment procedures prior to trial initiation.
  - Provide latest copies of Investigator Brochure (IB) to IRB (if applicable).
  - Provide all relevant documents available for review (audit) during trial.

Compliance with Protocol

- The Investigator should:
  - Conduct trial in accordance with the protocol version agreed and documented by the sponsor, IRB and regulatory authority.
  - Ensure that no changes are allowed in the protocol except in case of immediate hazard to the patient.
Investigational Product

- **The Investigator:**
  - Is responsible for investigational product accountability at the site.
  - Responsibility may be assigned to pharmacist or another individual.
  - Ensure that investigational product is stored as specified by sponsor or regulatory authority.
  - Ensure that the investigational product is used only in accordance with the protocol.

Randomization Procedures and Un-blinding

- **The Investigator:**
  - Should follow the trial's randomization procedure.
  - Any premature un-blinding to be explained to the sponsor.
Informed Consent

• The Investigator should:
  - Comply with regulatory requirement, GCP and ethical principles.
  - Document communication of revised consent document to the IRB and research subject(s).
  - Not influence or coerce subject(s) to participate.
  - Ensure that the subject(s) or their legal representative are fully informed in their own language.
  - Review research subjects’ responsibilities as part of the informed consent process.

Informed Consent (cont.)

• The Investigator should:
  - Ensure that the informed consent document does not contain technical language.
  - Allow ample time for the consent process and opportunity for exchange of information or subject questions.
  - Provide an impartial witness for illiterate subjects.
  - Provide research subjects with a copy of the signed and dated informed consent document.
Informed Consent (cont.)

• Ensures the initial and ongoing consent process is performed and documented (in compliance with FDA, ICH-GCP, institutional, sponsor, IRB, and other applicable regulations, guidance, and policies).
• Participates in the education of research subjects about the clinical trial and significant new information that becomes available during or after the conduct of the trial.
• Assesses for barriers to effective informed consent discussions and implements plans to overcome them.

Safety Reporting

• The Investigator should:
  • Ensure accuracy, completeness, legibility, and timeliness of data to sponsor in CRF.
  • Ensure corrections on a CRF are signed and dated.
  • Maintain trial-related documents (duration of storage!).
  • Ensure all financial agreements are in place prior to research subject enrollment.
  • Provide access to records by monitor, regulatory agency, or auditors.
  • Submit progress reports to IRB (on time!).
Safety Reporting

- The Investigator should:
  - Report all serious adverse events (SAE), including deaths, to sponsor and IRB/regulatory agency, as stipulated in the protocol or SOP.

Premature Termination of Trial

- The Investigator should:
  - Inform subjects about the early termination, with the reason.
  - Assure therapy and follow-up.
  - Inform sponsor, IRB, and other regulatory authorities.
Final Report

- Investigator should:
  - Provide the IRB and other regulatory authorities with a summary of the trial’s outcome upon completion of the study.
  - Update information at clinicaltrials.gov (if a registered trial).

Subject Recruitment

- The Investigator should ensure that study staff:
  - Assists in implementation of recruitment plans to identify and assess individuals who might be eligible for clinical trials, taking into consideration the study entry criteria, required procedures, and other potential factors.
  - Identifies and develops processes to overcome barriers to recruitment related to patient demographic factors, underserved populations, and healthcare system influences.
  - Identifies institutional (e.g., “Healthstreet”) or other community-based resources or groups that can assist in achieving recruitment goals.
Data Management

- The Investigator should not:
  - Encourage intentional deception
  - Intentional wrongdoing
  - Falsification of data, either through omission (failing to reveal data) or commission (altering or fabricating data)

  ◦ Above points amount to “Research Misconduct”

Sponsoring Multi-site Trials

SPONSOR RESPONSIBILITIES
Sponsor’s Role in Clinical Trial
Consequences of not fulfilling Investigator Responsibilities

Investigator Responsibilities
(21 CFR 312.60-68)

Informed Consent and Record Keeping:

3. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60 and 21 CFR 50].

   Subject 8210 was randomized to protocol (b)(4) on June 12, 2006. You did not obtain informed consent from this subject until June 26, 2006.

4. You failed to maintain adequate records of the disposition of the drug including dates, quantity, and use by subjects [21 CFR 312.62(a)].

   Protocol (b)(4)

   a. You did not maintain adequate records of the disposition of the drug. For example, the Master Drug Dispensation Log (MDDL) contained no drug accountability documentation for any subject in the study at Visit 5 or later.
Investigator Responsibilities
(21 CFR 312.60-68)

Lack of supervision:

1. You failed to personally conduct or supervise the clinical investigations as you committed to do when you signed the Form FDA 1572, in violation of 21 CFR 312.60.

   a. Your lack of supervision caused the submission of false information to the sponsor in required reports for the study of investigational new drugs that are subject to Section 505 of the Federal Food, Drug, and Cosmetic Act, as demonstrated by the violations described below.

   b. Your lack of supervision allowed the study coordinator, who was not a licensed physician in California, to write medical orders that were not always co-signed by a licensed physician.

      For example, the study coordinator signed orders on physician order sheets for subjects 115-125, 105-107, 111-125, and 100-006.

Investigator Responsibilities
(21 CFR 312.70)

Falsification of data:

2. You submitted false information to the sponsor, in violation of 21 CFR 312.70(a).

   a. Subject 100-732: The medical history sheet documented chest pain lasting 10-20 seconds since catheterization and PTCA in 12/97. Further down the same page of the medical history sheet was information that this pain lasted "21-25 minutes". While "**" was alleged to represent "min" for minutes, it appears to be written over something else which is not clearly visible. The chest pain duration of 10-20 seconds written on the upper portion of the same page indicated that "**" was falsified.

   b. Subject 105-445: The patient medical history sheet, dated 3/31/98, documented chest pain lasting approximately 1 minute when walking for less than 1 block. There is a systems notation of chest pain in which the last episode lasted approximately "100 minutes" after walking more than 1 block, without the date of the last chest pain being recorded. It appears that two zeros have been added to "1" to make it "100 minutes". The subject's clinical history sheet dated 7/3/98, notes that chest pain occurs after walking less than 1 block which lasted approximately "91 minutes". Here, the number "9" appeared to have been added before the number "1" to make it "91".
# Consequences

## Clinical Investigators - Disqualification Proceedings

<table>
<thead>
<tr>
<th>Name</th>
<th>Center</th>
<th>Status</th>
<th>Date of status</th>
<th>Data NDIPOC Issued</th>
<th>Date BOOH Issued</th>
<th>Link to NDIPOC Letter</th>
<th>Link to BOOH Letter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabral, Ronival G</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>12/15/2015</td>
<td>02/02/2015</td>
<td>04/10/2015</td>
<td>PDF</td>
<td>PDF</td>
</tr>
<tr>
<td>Haddock, John D, MD</td>
<td>CDEP</td>
<td>Post Disqualified</td>
<td>11/27/2015</td>
<td>01/29/2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marquez, Neida, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>08/40/2015</td>
<td>02/19/2015</td>
<td></td>
<td>PDF</td>
<td></td>
</tr>
<tr>
<td>Kaplan, John G, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>11/32/2014</td>
<td>24/01/2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger, Dan L, MD</td>
<td>CDEP</td>
<td>Post Disqualified</td>
<td>08/30/2014</td>
<td>11/20/2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corbett, Al Brown, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>08/30/2014</td>
<td>01/10/2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxwell, Dan, MD</td>
<td>CDEP</td>
<td>Post Disqualified</td>
<td>07/28/2014</td>
<td>01/10/2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger, Mark, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>09/50/2014</td>
<td>06/09/2014</td>
<td>12/10/2012</td>
<td>PDF Text</td>
<td>PDF</td>
</tr>
<tr>
<td>Perez, Michael, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>03/50/2014</td>
<td>04/12/2014</td>
<td>03/16/2013</td>
<td>PDF Text</td>
<td>PDF</td>
</tr>
<tr>
<td>Mericola, Thomas</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>01/42/2014</td>
<td>11/20/2011</td>
<td>03/16/2013</td>
<td>PDF Text</td>
<td>PDF</td>
</tr>
<tr>
<td>Johnson, Dhruve, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>09/10/2013</td>
<td>03/17/2012</td>
<td>09/16/2012</td>
<td>Test</td>
<td></td>
</tr>
<tr>
<td>Lozada, Germain Perez, MD</td>
<td>CDEP</td>
<td>Restricted</td>
<td>07/10/2013</td>
<td>02/10/2012</td>
<td>PDF Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodriquez, Joaquin, MD</td>
<td>CDEP</td>
<td>Restricted</td>
<td>08/40/2013</td>
<td>06/20/2012</td>
<td>PDF Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canfield, Frank R, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>05/10/2012</td>
<td>05/01/2012</td>
<td>09/10/2011</td>
<td>PDF Test</td>
<td></td>
</tr>
<tr>
<td>Sadeh, Grant M, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>07/27/2011</td>
<td>02/04/2010</td>
<td>11/17/2010</td>
<td>PDF Test</td>
<td></td>
</tr>
<tr>
<td>Spearer, Wayne E, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>05/16/2011</td>
<td>04/20/2011</td>
<td>05/10/2011</td>
<td>PDF Test</td>
<td>PDF Test</td>
</tr>
<tr>
<td>Falcone, Henry, MD</td>
<td>CDEP</td>
<td>Disqualified</td>
<td>03/10/2011</td>
<td>12/01/2000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


© 2016 — Wajeeh Bajwa, Ph. D. — All rights reserved

---

# Site Monitor Visit/ FDA Inspection

© 2016 — Wajeeh Bajwa, Ph. D. — All rights reserved
Site Inspection (cont.)

The Inspector Ascertains:

- Who performed various aspects of the protocol for the study (e.g., who verified inclusion and exclusion criteria, who obtained informed consent, who collected adverse event data).
- Whether the IRB approved the protocol, informed consent form, and any amendments to the protocol prior to implementation.

Site Inspection (cont.)

- Whether the clinical investigator and study staff adhered to the sponsor’s protocol and investigational plan.
- Whether protocol deviations were documented and reported appropriately.
- Whether informed consent documents were signed by the subject, or the subject’s legally-authorized representative, prior to entry in to the study (i.e., performance of any study-related procedures).
Site Inspection (cont.)

- Whether authority to conduct aspects of the study was delegated, and if so, how the conduct of the study was supervised by the clinical investigator.
- Where specific aspects of the investigation were performed.
- How the study data was obtained and where the study data was recorded.

Site Inspection (cont.)

- Accountability for the investigational product, including shipping records, and disposition of unused investigational product.
- Whether the clinical investigator disclosed information regarding his financial interests to the sponsor and/or the interests of any sub-investigator(s), spouse, and dependent children.
- The monitor's communications with the clinical investigator.
Site Inspection (cont.)

- The monitor’s evaluations of the progress of the investigation is valid.
- Corrective actions have been taken in response to previous FDA inspections, if any, and regulatory correspondence or sponsor and/or monitor correspondence.

Site Inspection (cont.)

The FDA investigator may also audit the study data by comparing:

- The data filed with the agency or the sponsor.
- Such records may include:
  - The case report forms
  - Supporting source documentation
  - Signed and dated consent forms
  - Medical records (including progress notes of the physician, the subject’s hospital chart(s), and the nurses’ notes)
- These records may be in hard copy and/or an electronic format.
- For electronic records and/or electronic signatures, the FDA investigator may gather information to determine whether 21 CFR Part 11 requirements have been met.
Common Findings at Clinical Sites

1. Failure to follow the protocol
   - Violations of inclusion/exclusion criteria
   - Failure to perform required tests
   - Changes not authorized by the sponsor

2. Inadequate Informed Consent
   - Elements of informed consent are missing
   - Obtained after admission to trial (*most common!*)
   - Obtained verbally
Common Findings at Clinical Sites (cont.)

3. Inadequate source documentation
   • Absence of supporting source documents
   • Inaccurate or incomplete source documents

4. Under-reporting of adverse events

5. Drug accountability

6. Inappropriate delegation of authority

Commonly Found Errors

- Misspelled words
- Mathematical errors (rounding error)
- Wrong entry (Date, Subject ID)
- Transposition
- Procedural change (not documented)
- Wrong conclusion
- Illegible entry
- White outs
Commonly Found Errors (cont.)

- Write over
- Incomplete entry
- No identification of individual making entry
- No date of entry
- No explanation/reason for change

Risk-Based Monitoring
Risk-Based Monitoring

FDA Issued Guidance for Industry in August 2013:

• Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

Risk-Based Monitoring (cont.)

• No single approach to monitoring is appropriate or necessary for every clinical trial.
• FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial.
Risk-Based Monitoring (cont.)

- Include a mix of centralized and on-site monitoring practices.
- The monitoring plan should identify the various methods intended to be used and the rationale for their use.
- Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes.

Risk-Based Monitoring (cont.)

- Sponsors should prospectively identify critical data and processes.
- Perform a risk assessment to identify and understand the risks.
- Develop a monitoring plan that focuses on the important and likely risks to critical data and processes.
Testing your knowledge!

Enrollment

A 46-year-old man is currently enrolled in a Phase 3 study of a drug for severe diabetic neuropathy. While the study is ongoing, a new drug becomes commercially available that may have equal or greater benefit to the subject. The investigator should do which of the following?

Options:
• Discuss the pros and cons of both the investigational drug and the commercially available drug, and then allow the subject to decide whether to withdraw from the research to take the new drug
• Do not tell the subject about the new drug since physicians have the right to try out new treatments with their patients
• Tell the subject about the new drug but discourage him from switching treatments until the study is completed
• Withhold this new information to avoid confusing the subject with other treatment options or alternatives
Study Audit

According to ICH E6 GCP, an "Audit" is defined as:

Options:

• The act of overseeing the progress of a clinical trial.
• An institutional self-assessment.
• An official review of documents, facilities, records, and any other resources related to a clinical trial.
• A systematic and independent examination of trial-related activities and documents.

AE Reporting

A subject is a passenger in a car involved in a motor vehicle crash. The subject sustained a broken wrist and mild concussion. The subject was treated and released from the Emergency department. What should the investigator do when learning of the crash?

Options:

• Report adverse events of both a broken wrist and a mild concussion.
• No report is needed because these are not serious adverse events.
• No report is needed because the subject was a passenger in the vehicle and not driving.
• Report only the concussion because it might become serious.
Name that Deviation!

Regulatory Non-Compliance, Protocol Non-Compliance, or No Issues?

Scenarios Provided by: Kimberly Foli, QA/QI Coordinator, UF IRB

Scenario 1:

“Informed Consent in a greater than minimal risk study was administered and signed by undergraduate research assistant volunteer on the research staff signature line. The volunteer was not listed as study staff in myIRB.”
Name that Deviation (cont.):

Scenario 2:
“I just completed my research study, analyzed the data, and submitted for publication but the journal says I have to get IRB approval. So here is my submission including the informed consents that I just wrote and had participants sign it.”

Name that Deviation (cont.):

Scenario 3:
“My research protocol says I can draw blood to analyze glucose, and now the PI has decided to investigate liver enzyme biomarkers in the DNA. It is still just one blood draw and we will continue to analyze glucose. There is no obvious increased risk to the participant. After all, it is leftover blood.”
Name that Deviation (cont.!)  

Scenario 4:  
“What if the sponsor initiated change in the protocol (scenario 3), and it was not submitted to IRB at the local level?”

Name that Deviation (cont.!)  

Scenario 5:  
“A research subject was allowed to participate in research, even though the subject did not meet inclusion/exclusion criteria exactly, but the subject was very close to the suggested guidelines.”
Name that Deviation (cont.)!

Scenario 5 (cont.):
“What if the sponsor agreed to accept the participant outside the inclusion/exclusion criteria?”

Name that Deviation (cont.)!

Scenario 6:
“There was extra blood leftover at the end of the study, so it was de-identified and stored in a deep freezer. Can I use this leftover blood to look for DNA markers to study another disease?”
Summary of GCP

HERE IS WHAT WE NEED TO REMEMBER

Implementation of GCP

• Studies must be conducted for valid (ethical and scientific) reasons.
• Research procedures must be declared in writing.
• All personnel must be experienced and qualified to undertake assigned tasks.
• All personnel understand their responsibilities.
• Documentation of qualifications and training must be evident.
Implementation of GCP (cont.)

• All studies must be independently reviewed and approved by ethics committees/IRBs. Review must continue throughout the study.
• All study subjects must be given the opportunity to assess the risk of study participation.
• All studies must have a valid study design documented in a protocol.
• The data collection and protection plans should be part of the protocol.

Implementation of GCP (cont.)

• Established procedure for frequent and thorough monitoring should exist.
• Investigational products should be prepared in accordance with GMP.
• The product being studied (test article/study drug/investigational product) must be properly managed with full accountability.
• Data must be honest.
Implementation of GCP (cont.)

- Systems for assuring quality and for checking quality must be established and followed at all stages.
- Documentation of research activities must be retained to provide evidence of activities.

Reminder for UF Personnel

- UF’s myTraining will not allow you to take the “IRB01 Local Training Refresher (IRB802)”, if your IRB01 Local Training (IRB800) certificate, or latest Refresher (IRB802), has expired. Pay attention to the expiration date of your training if you would like to take advantage of the Refresher Course. Otherwise, you will need to repeat the main IRB Local Training Course (IRB800) in its entirety.
Contact Information:
Wajeeh Bajwa, Ph. D.
E-mail: bajwa@ufl.edu
Phone: (352) 273-8702

Complete the online survey and get a copy of this presentation at:
http://tiny.cc/bajwagcp

Advertisement
• Are you interested in participating in a research study where two online, commercially available GCP training modules are being compared?
• If yes, please contact us:
  • Dr. Wajeeh Bajwa (bajwa@ufl.edu)
  • H. Robert Kolb (kolbhr@ufl.edu)
Questions