Inspections

Clinical Research Coordinator Training Program

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June 24, 2011
Goals of this Course

• **Become familiar with:**
  – Standard GCP compliance activities
  – FDA organization structure as it relates to inspections
  – CFR for Investigator Responsibility and Disqualification

• **Learn:**
  – How to prepare for and facilitate an inspection
  – What to do after an inspection

• **Identify:**
  – Potential outcomes of an inspection
  – Actions FDA can take following an inspection
GCP – It’s What We Do

- A way of thinking and doing that is consistent with the laws that govern regulated trials
- Applies to all human clinical trials, even if the FDA does not regulate the investigation or the product is not investigational

Following GCP will help you with an inspection
# Compliance Activities

<table>
<thead>
<tr>
<th>Method</th>
<th>Conducted by</th>
<th>Purpose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Sponsor</td>
<td>Critical ongoing component of conducting a clinical trial.</td>
<td>Assess and assure compliance with the study protocol on an ongoing basis.</td>
</tr>
<tr>
<td>Audit</td>
<td>Sponsor or CRO</td>
<td>Quality assurance measure to verify data integrity and clinical trial processes.</td>
<td>May result in SOP changes and/or recommendations for the monitoring process.</td>
</tr>
<tr>
<td>Inspection</td>
<td>Regulatory Agency</td>
<td>Verify data, assure compliance with regulations, and assure protection of research subjects.</td>
<td>Affects the agency's decision to accept data supporting a marketing application. May have implications for the investigator if misconduct (e.g., fraud, falsification, or fabrication) is found.</td>
</tr>
</tbody>
</table>
• Administration for Children and Families (ACF)
• Administration on Aging (AoA)
• Agency for Healthcare Research and Quality (AHRQ)
• Agency for Toxic Substances and Disease Registry (ATSDR)
• Centers for Disease Control and Prevention (CDC)
• Centers for Medicare and Medicaid Services
• Food and Drug Administration (FDA)
• Health Resources and Services Administration (HRSA)
• Indian Health Service (IHS)
• National Institutes of Health (NIH)
• Office of the Inspector General (OIG)
• Substance Abuse and Mental Health Services Administration (SAMHSA)
• Food
• Drugs
• Medical Devices
• Vaccines, Blood, & Biologics
• Cosmetics
• Radiation-Emitting Products
• Tobacco Products

Desired Public Health Outcomes
• Increase years of healthy life by increasing access to life-saving and life-enhancing medical products
• Reduce the number of deaths and injuries associated with the quality and unsafe use of FDA- regulated medical products
Office of Regulatory Affairs

Inspections, Compliance, Enforcement, and Criminal Investigations

http://www.fda.gov/ICECI/default.htm
The Scariest Words

“Doctor, the FDA is on the phone...”
“BiMo”

Bioresearch Monitoring Program

• FDA Office of Regulatory Affairs
• Evaluates investigators, sites, sponsors/monitors, laboratories, and IRBs
• Adherence to regulations and protection of human subjects
• Usually occur upon submission of an application for approval (NDA/PMA)
• May occur if evidence of research misconduct (“for cause”)

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CLINICAL & TRANSLATIONAL SCIENCE CENTER
BiMo Compliance Programs

- In Vivo Bioequivalence
- Good Laboratory Practices
- Institutional Review Boards
- Radioactive Drug Research
- Sponsors, CROs, and Monitors
- Clinical Investigators
# Investigator Responsibilities

## 21 CFR 312

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 – General</td>
<td>Conduct study appropriately, protect the rights, safety, and welfare of subjects, control devices, ensure informed consent is obtained</td>
</tr>
<tr>
<td>61 – Control of Drug</td>
<td>Supervise drug administration</td>
</tr>
<tr>
<td>62 – Records and Retention</td>
<td>Maintain records (study participation, case histories, device exposure), retain records</td>
</tr>
<tr>
<td>64 – Reports</td>
<td>Progress, safety, final, financial disclosure</td>
</tr>
<tr>
<td>66 – Assure IRB Review</td>
<td></td>
</tr>
<tr>
<td>68 – Inspection</td>
<td>Allow entry and inspection</td>
</tr>
</tbody>
</table>

## 21 CFR 812

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 – General</td>
<td>Conduct study appropriately, protect the rights, safety, and welfare of subjects, control devices, ensure informed consent is obtained</td>
</tr>
<tr>
<td>110 – Specific</td>
<td>Await approval, compliance, supervise device use, financial disclosure, device disposition</td>
</tr>
<tr>
<td>140 – Records and reports</td>
<td>Maintain records (study participation, case histories, device use, adverse events), retain records</td>
</tr>
<tr>
<td>145 – Inspection</td>
<td>Allow entry and inspection</td>
</tr>
</tbody>
</table>
Criteria for Site Inspection

- Number of patients enrolled (high/low)
- High/low numbers of subjects responding to the study treatment
- High number of:
  - Outliers
  - Dropouts
  - Adverse Events
  - Protocol Violations
- Conducting research outside of the investigator's specialty
- Past inspection history
The Goal of an Inspection

• Assure compliance with regulatory requirements
• Protect human research subjects
• Assure data integrity and study validity
The Antidote

Prepare!!!
A Typical Inspection

- Evaluate the facility
- Review regulatory files and informed consent
- Compare subject data submitted (CRFs) to the FDA with the source records (Medical Record)
- Have discussions with key ancillary personnel (laboratory technicians, pharmacists, coordinators, sub-investigators), as needed
- Evaluate investigational product accountability and control
## Documents Reviewed

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB Roster / Correspondence</td>
<td>Site Signature List</td>
</tr>
<tr>
<td>Investigator's Brochure</td>
<td>Monitoring Log</td>
</tr>
<tr>
<td>Investigator Curriculum Vitae</td>
<td>CRFs (blank and completed)</td>
</tr>
<tr>
<td>Protocol / Amendments</td>
<td>Source Documents</td>
</tr>
<tr>
<td>Form FDA 1572 or Inv Agreement</td>
<td>Laboratory Certification</td>
</tr>
<tr>
<td>Informed Consent Form (approved versions)</td>
<td>Laboratory Normal Value Ranges</td>
</tr>
<tr>
<td>Signed Consent Forms</td>
<td>Investigational Product Records</td>
</tr>
<tr>
<td>Correspondence (to/from sponsor, laboratories, etc.)</td>
<td>Standard Operating Procedures</td>
</tr>
</tbody>
</table>
Documents NOT Reviewed

- Financial data not required by 21 CFR 54
- Personnel data excluding qualifications of technical and professional persons
- Data or files from studies not covered by the FDA 482 (Notice of Inspection)
- Non-study data or records
Violations Could Result In...

- **Form FDA 483**
  - Observations noted during inspection
- **Warning Letter**
  - Formal (public) notice of deficiencies
- **Disqualification of Investigator**
  - Subject rights, safety, welfare
  - Repeated, deliberate submission of false information
FDA 483

- Minor observations
- Usually procedural deficiencies where subject rights, safety, and welfare are not in jeopardy

Notify and work with the Sponsor to develop a response within 2 weeks
Warning Letter

• Issues often include failure to...
  – Conduct continuing review
  – Follow protocol
  – Document and track complications
  – Report/investigate AEs
  – Maintain records
  – Produce required reports
  – Maintain investigational product accountability

Notify Sponsor Immediately
  – Work with the Sponsor to develop a response
  – Submit response within 2 weeks
Investigator Disqualification

21 CFR 312.70
Repeated or deliberate failure to
• Comply with 312, 50, or 56
• Submitted false information to sponsor or in any required report
Notify Investigator/Sponsor
• Ineligible to receive product
Other IND/NDAs examined
Unreliable data are removed
• Regulatory hearing
• Trials may be terminated
• Approvals may be rescinded
Reinstatement
• Investigator provides adequate assurance of compliance

21 CFR 812.119
Repeated or deliberate failure to
• Comply with 812, 50, or 56
• Submitted false information to sponsor or in any required report
Notify Investigator/Sponsor/IRB
• Ineligible to receive product
Unreliable data are removed
• Regulatory hearing
• Trial may be terminated
• Clearance or Approval may be rescinded
Reinstatement
• Investigator provides adequate assurance of compliance
Additional Actions

- **Termination of Trials**
- **Withdrawal of Applications**
- **Application Integrity Policy**
  - Defer substantive scientific review of one or more applications and/or proceeding withdrawal of approvals
    http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/u cm134453.htm
- **Civil Money Penalties (CMP)**
- **Seizure**
- **Injunction**
- **Prosecution**
The Inspection
Before the Inspection

NOTIFY the study Sponsor IMMEDIATELY

• Work with Sponsor to prepare files
• Identify and prepare a room
• Train staff
  – Avoid small talk in open areas
  – Do not address the inspector first
  – If asked a question, be polite and succinct
  – Do not guess or volunteer information
During the Inspection

DO:

• Read the Form FDA 482 (Notice of Inspection)
• Examine inspector’s credentials
• Designate a key person to address questions
• Remain calm and composed
• Isolate the inspector in a room – remove all records, charts, letter, etc.
• Be available
• Provide an escort at all times
• Have files ready and separated

Provide ONLY what is requested specifically
During the Inspection

DO:
- Be polite
- Avoid small talk, keep conversation concise and honest
- Answer only the question asked – do not embellish
- Be honest – do not give false, inaccurate, or misleading information
- If you don’t know the answer, clarify before responding
- Document everything discussed or asked
- Make two copies – mark CONFIDENTIAL
  - Mark all copies provided to FDA as “confidential”
  - Make a second copy for the sponsor

Keep sponsor apprised
During the Inspection

DO NOT:

• Permit access to records unrelated to the study under review
• Give the inspector open access to all the study records – bring them what they request and ONLY what they request (specific files, charts, etc.)
• Sign any documents presented by FDA inspector – if an affidavit is presented, do not read, review, or sign it, provide to counsel for review
After the Inspection

- Review findings and ask questions
- Provide clarification if needed

Notify Sponsor immediately

- Form FDA 483 (if issued and is a preliminary report)
- Establishment Inspection Report (EIR)
- Letter of findings

- No Action Indicated (NAI): No violations observed
- Voluntary Action Indicated (VAI): Minor violations noted, corrective action should be taken, investigator advised to respond
- Official Action Indicated (OAI) or “Warning Letter”: Significant violations found, investigator must respond
Deficiency Responses

- FDA 483 or Warning Letter
- Work with the study Sponsor
- Acknowledge the issue
- Develop a corrective action plan
  - Implement
  - Monitor
  - Verify
  - Update
- Be specific, business-like, and polite
- Reply within 2 weeks
Overview

- Inspector calls the investigator to establish a date for the inspection
  - The investigator should ask:
    - Which study (or studies) will be involved
    - Scope of the visit
  - **NOTIFY THE SPONSOR IMMEDIATELY**
- The auditor will present credentials and Form FDA 482 (Notice of Inspection)
  - At the outset, the inspector will meet with the investigator and study coordinator to discuss the process
  - An exit interview with the investigator by reviewing Form FDA 483 (Inspectional Observations), if applicable, and provide feedback
  - It’s OK to clarify and try to satisfy any concerns in advance of the final EIR
- Prepare a response to **every** deficiency noted
Some Final Thoughts

• Document, document, document
• If it wasn’t written down, it wasn’t done
• Make corrections correctly properly
• Follow the protocol
• Consent Forms
• IRB reviews and approvals
• Abide by GCP
• Stay calm and composed
• Maintain files as you go
• **Don’t leave an inadvertent trail** (e.g., memos with other IDs)
If You are Prepared

Inspections will be challenging, but not scary.

“Doctor, the FDA is on the phone…”