SPONSOR-INVESTIGATOR ROLES & RESPONSIBILITIES IN DEVICE TRIALS

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
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Topics For Discussion

- What is good clinical practice?
- Role and responsibilities of a sponsor-investigator
- FDA inspections
- Suggestions for conducting a quality study
Good Clinical Practices (GCP)

- Principles/guidelines for conducting a study
- Ethical and scientific quality standard for designing, conducting, recording, and reporting trials
Sponsor-Investigator

Dual Role
An individual who both initiates and actually conducts the study

Dual Responsibilities
Sponsor and Investigator
Sponsor Responsibilities

- Select qualified investigators
- Provide them with information they need to conduct study
- Ensure IRB approval is obtained

CFR 812.40
Sponsor Responsibilities (cont)

- Ship investigational device only to qualified investigator
- Maintain device accountability records
- Submit reports to IRBs and FDA
Sponsor Responsibilities (cont)

- Select qualified monitors
- Ensure proper monitoring
- Ensure investigator compliance
Monitor

- An individual designated by a sponsor or contract research organization to oversee the progress of an investigation.
  - Must be qualified by training and experience to monitor the investigation

21 CFR 812.3(j) & 21 CFR 812.43(d)
Purpose of Monitoring

- Protect human subjects
- Ensure reliability of the data
- Compliance of investigator with:
  - Protection of human subjects
  - Protocol
  - Applicable regulations
Monitoring

Does the sponsor-investigator need to ensure adequate monitoring of the investigation at his/her own site?
YES
Investigator Agreement

- Contract between the sponsor and clinical investigator
- Establishes roles and responsibilities of the clinical investigator
Sponsor Records

- Correspondence with other investigators, IRBs, and FDA
- Signed investigator agreements
- Adverse device effects
- Device accountability
- Any other records
Sponsor Records (Device Accountability)

- Records:
  - Shipment and disposition of devices including:
    - Name and address received
    - Type and quantity
      - Batch number or code
    - Disposition of device
    - Any returns
      - Batch number or code
Documentation

If it is not documented it did not occur!
# Summary of Required Reports

<table>
<thead>
<tr>
<th>Type Report</th>
<th>To FDA</th>
<th>To all Reviewing IRBs</th>
<th>To Other Investigational Sites</th>
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<tbody>
<tr>
<td>Unanticipated Adverse Device Effects</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Withdrawal of IRB approval</td>
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<tr>
<td>Withdrawal of FDA approval</td>
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<td>Investigator List</td>
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<td>Annual Progress Report</td>
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<td>Recall and Device Disposition</td>
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<td>Final Report</td>
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<td>Use of Device Without Informed Consent</td>
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<td>Significant Risk Determination</td>
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<tr>
<td>Protocol Deviations</td>
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<tr>
<td>Other Reports requested by FDA or IRBs</td>
<td>X</td>
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Investigator
Investigator Responsibilities

- Obtain IRB approval prior to enrolling any subjects
- Obtain and document informed consent
- Follow the protocol
Investigator Responsibilities (cont)

- Implant/use device only in/on subjects enrolled on study
- Ensure adverse effects (AEs) are appropriately documented and reported
- Maintain adequate records
Investigator Records

- Records of receipt, use, and disposition of device
- Any relevant observations related to the study
Investigator Responsibilities
- Study Deviations

- Document dates and reasons for any deviations from the study protocol.
- Obtain prior approval from the sponsor, IRB, and FDA for changes or deviations from the investigational plan.
- Emergency deviations must be reported to the sponsor and IRB within 5 days.
Adverse Effect (AE)

- Any adverse medical occurrence that may or may not be related to the investigational device.

All adverse events should be documented
Unanticipated Adverse Device Effect (UADE)

- Any serious adverse effect that is possibly caused by or related to the investigational device:
  - Not previously identified in nature, severity, or degree, or
  - Any other unanticipated serious problem associated with a device.

21 CFR 812.3(s)
Investigator Responsibilities-AEs and UADEs

- Maintain records of all AEs (anticipated or unanticipated)
- Report Unanticipated AEs to sponsor and IRB within 10 working days
- Follow the sponsor’s requirements for reporting and recording of AEs and UADEs
FDA Is Coming!
OBJECTIVES BIMO PROGRAM

- Protect human research subjects from undue hazard or risk
- To ensure the quality and integrity of data submitted in support of device applications.
FDA INSPECTORS
Who Do We Inspect?

COMPLIANCE PROGRAMS:

CP 7348.811 - Clinical Investigator (CI)
CP 7348.810 - Sponsor/Monitor/CRO
CP 7348.809 - Institutional Review Board (IRB)
CP 7348.808 - Good Laboratory Practices (Nonclinical Laboratories)

Located at: [http://www.fda.gov/ora/cpgm/default.htm#bimo](http://www.fda.gov/ora/cpgm/default.htm#bimo)
Types of Inspections (Devices)

- **Routine:**
  - Pre-Market Applications (PMAs) (devices)
  - Surveillance

- **Directed:**
  - Investigate problems that have been identified at the Investigational Device Exemption (IDE) stage
  - Investigate complaints that have been reported to the FDA
  - Compliance follow-up for previous deficiencies

- **For Cause:**
  - Investigate complaints that have been reported to the FDA
  - Usually unannounced
Inspection Classification

- **NAI**
  - No action indicated
- **VAI**
  - Voluntary action indicated
- **OAI**
  - Official action indicated
Preparing for Sponsor Inspection

- Mock inspection (practice)
- Inspector may call 2-5 days ahead to announce routine inspection
  - Inspection typically last 2-3 days (longer if necessary)

Have available
- A person knowledgeable about the study
- A place to review records with access to a photocopier

Have available and organized
- All study documents
- Standard Operating Procedures (SOPs)
What Do We inspect?

Sponsor

- Protocol (original & revisions)
- Investigator Agreements
- Sponsor/IRB/FDA/CI Correspondence
- Device distribution records
- Monitoring plan
What Do We inspect?

Sponsor (cont)

- Training records
- Case report forms (CRFs)
- Adverse event records
- Data line listings
Common Sponsor Deficiencies

- Inadequate monitoring
- Failure to secure investigator compliance
- Inadequate device accountability
- Failure to obtain FDA/IRB approval
Preparing for CI Inspection

- Mock inspection (practice)
- Inspector may call 2-5 days ahead to announce routine inspection
  - Inspection typically last 2-3 days (longer if necessary)
- Have available
  - A person knowledgeable about the study
  - A place to review records with access to a photocopier
- Have available and organized
  - All study documents
  - Standard Operating Procedures (SOPs)
What Do We Inspect?

Clinical Investigator

- Protocol
- Informed Consent Forms
- Case Report Forms
- Hospital records
- CI Progress Reports
- Sponsor/IRB/FDA correspondence
- Radiological Files

- Laboratory Reports
- Device Accountability Records
- Monitoring Logs
- SOPs
- Adverse Events
- Protocol Deviations
Common CI Deficiencies

- Failure to follow investigational plan/regulations
- Protocol deviations
- Inadequate subject protection/IC
- Inadequate device accountability
- Lack of FDA &/or IRB approval prior to the conduct of the investigation
Inspection Conclusion

- Inspector will conduct an exit interview with management
- A Form FDA 483-Inspectional Observations may be issued if significant deviations from the regulations were noted
- Opportunity to respond to observations
How Not to Respond to a 483

Failure to maintain complete, current and accurate case histories.

**Response:** "It's all about dotting all the i's and crossing all t's. How many nit-picky inconsequential things could they find? It's very unfair, unfounded and unjust." "They came in here looking for something negative, and the only things they could find were clerical things and that is sad."
How *Not* to respond to a 483

**Failure to adequately supervise the conduct of the study.**

- **Response:** “I am not, nor ever have been involved with any data collection or entry in any study. If my life depended on it, I could not access data. I do not know how. I do not know which patients are enrolled in the current FDA study.”
How *Not* to Respond to a 483

**Failure to ensure that the current, IRB-approved version of the informed consent was executed by each of the subjects in the study.**

- **Response:** “Virtually all of the serious documentation problems appear to have been the work of a single research coordinator who was delinquent in fulfilling her assigned study duties. She has been fired.”
How *Not* to Respond to a 483

*During the time the IRB approval had lapsed, you enrolled and performed study surgery on at least three subjects.*

- **Response:** “I obtained verbal IRB approval for the three patients cited on a case by case basis.”
How *Not* to Respond to a 483

**Device Accountability:**

- **Response:** “Regarding device control and accountability, you clearly then see, I can’t participate in, and have no responsibility over it. The FDA investigator insisted that any device tracking is my responsibility—which is ludicrous and lacking in common sense.”
How *Not* to Respond to a 483

Failure to adequately supervise the conduct of the study.

- **Response:** …thought things were going fine but things were not getting done…
  - “matters diverted my attention… a partner embezzled a quarter of a million dollars
  - An employee embezzled money, then her husband crashed the entire clinical practice computer losing months of data
  - Excessive strife between employees and my family members
  - Two year separation from my wife then a divorce”
**Clinical investigator responses:**

- “I don’t intend to continue with this research project or do I ever intend to participate in another FDA research project….if this is the same as disqualification, then consider myself disqualified.”… “My eyes have been opened to the fact that life is too short and this is something I need to eliminate from my life.”

- “From now on, I will follow the *book* to a tee.”
How *Not* to Respond to a 483

**Clinical investigator responses:**

- I can’t get off the boat. I don’t know how you want me to respond when you ask for documentation of corrective action plans. It’s like being on a boat, sailing in the ocean, it is drifting, and I can’t get off. I have already spent 2,000 dollars to a person that has not given me a single document.

- “I am currently being treated for depression and for me to worry about this issue would be counter productive for my health.”
How *Not* to Respond to a 483

**Clinical investigator responses:**

- “We are unavailable to review with a member of your staff regarding the impossibility of perfection with every detail of a complicated documentation system for which many of the deficiencies are truly trivial and inconsequential when placed in context.”
BEIJING -- China's former top drug regulator was sentenced to death Tuesday in an unusually harsh punishment for taking bribes to approve substandard medicines, including an antibiotic blamed for at least 10 deaths.
A Written Response Should Include:

- An evaluation of the extent of the problem
- Assessment of the root cause of the problem
- Any corrective actions
- Not just a statement that you will correct them, but plan to correct, implementation, training and assessment of correction
- Supporting documentation
- Any preventive actions to prevent recurrence of the problem in future studies
Case Report Forms (CRFs) were incomplete in that the information needed to determine study eligibility was missing.

- A SOP has been developed and implemented to assist with documentation practices for determining study eligibility. A copy of the procedure is attached. This SOP contains a form that will be completed by a member of the study team and confirmed and signed by an investigator prior to any subject being enrolled in the study. All study personnel have been trained on this new procedure and it was implemented on ------. After 3 months eligibility documentation practices will be evaluated to determine if this corrective action assists with ensuring all information is documented to determine eligibility.
Helpful Hints:

- Keep files organized at all times
- Keep ALL correspondence – sponsor, IRB, monitors, study subjects
  - letters, faxes, e-mails, memos, phone contacts
- Know your IRB’s requirements
Helpful Hints:

- Know the sponsor’s adverse event reporting requirements
- Know the protocol:
  - Inclusion/exclusion criteria, study windows, study procedures
- Know each study staff member’s roles and responsibilities – the PI is ultimately responsible
Helpful Hints:

- Keep all test article accountability records:
  - Shipping receipts, enrollment logs, dispensing logs
Helpful Hints:

- Have written procedures:
  - SOPs, Quality Policy, training procedures, job descriptions
- Have a Corrective and Preventive Action Plan
Documentation

If it is not documented it did not occur!
BIMO REGULATIONS (All Products)

- **21 CFR 50**: Protection of Human Subjects
- **21 CFR 54**: Financial Disclosure
- **21 CFR 56**: Institutional Review Boards
- **21 CFR 58**: Good Laboratory Practice for Non-Clinical Laboratory Studies
BIMO REGULATIONS (Devices)

- **21 CFR 807**: Premarket Notification
- **21 CFR 809**: In Vitro Diagnostic Products
- **21 CFR 812**: Investigational Device Exemption (IDE)
- **21 CFR 814**: Pre-Market Approval Applications (PMA)
- **21 CFR 820**: Quality Systems Regulations
For More Information:

- FDA Home Page
  www.fda.gov
- Center for Devices and Radiological Health
  www.fda.gov/cdrh/
- Device Advice
  www.fda.gov/cdrh/devadvice
- CDRH BIMO site
  www.fda.gov/cdrh/comp/bimo.html
- FDA Good Clinical Practices
  www.fda.gov/oc/gcp/default.htm
- Code of Federal Regulations (CFR): Main Page
- FDA Consumer Magazine
  www.fda.gov/fdac/
THANK YOU!

QUESTIONS?

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