



FDA Inspections and Avoiding Common Mistakes in Clinical Research

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Objectives

- Describe how FDA inspects clinical trials
- Discuss the most common mistakes FDA finds during inspections
- Suggest actions to prevent study problems



FDA's Bioresearch Monitoring Program (BIMO) Inspects....

Clinical Investigators

Sponsors/Monitors/Contract Research

Organizations

Institutional Review Boards

Nonclinical Laboratories





When are BIMO Inspections Conducted ?

- Submission of marketing applications NDA / BLA / PMA
- Referrals from Center staff
- Referrals from other parts of FDA
- Complaints from sponsors, IRBs, and consumers
- Surveillance of ongoing studies under IND / IDE

■ ■ ■ FDA Inspection Assignment Package

- Background information
- Protocol
- Signed Form FDA1572 (drug/biologic)
or investigator agreement (medical device)
- Line listings of individual subjects' data
- Adverse events
- Informed Consent Form
- Number of subjects enrolled
- Site specific information (deviations, outcomes, etc.)

■■■ Inspection Logistics

The FDA investigator will call to announce the inspection and request that ALL documents should be available for the inspection.

You arrange for a place for the FDA investigator to work and a copier.

The FDA investigator will show credentials to the most responsible person, and present a Form FDA-482 “Notice of Inspection” for domestic inspections. There is an opening interview.

The FDA investigator will review documents. Please make time each day to meet with the FDA investigator to answer questions.



■ ■ ■ FDA Review of Records

- Protocol and amendments
- Informed consent forms
- Drug accountability records
- Correspondence with Sponsor and IRB
 - IRB Approvals -- Progress reports -- AE reports
- Case Report Forms
 - How data are recorded and corrected
 - Compared to source documents
- Supporting Files (Source Documentation)
 - Hospital/clinic chart, labs, diaries, etc.

Exit Interview

- Discuss inspection findings
- May issue a Form FDA-483 “Inspectional Observations”
 - Represents investigator’s opinion of deviations from federal regulations for clinical investigators
- Your verbal responses to FDA-483
- Your letter responding to the issues should be received within 15 days to be considered in deciding FDA’s actions.

After the Inspection...

- The inspection report is written by the FDA investigator and sent to the Center.
- The Center evaluates the report and determines the corrective action, and classifies the inspection:
 - NAI = No Action Indicated, or
 - VAI = Voluntary Action Indicated, or
 - OAI = Official Action Indicated
- We write a letter following most inspections
- OAI inspections have consequences (warning letter, etc.)

■ ■ ■ Most Common Investigator Violations

- Failure to follow the protocol
- Recordkeeping errors
- Informed consent problems
- Test article accountability



Most Significant Violations

- Enrollment of ineligible subjects
- Violation of protocol affecting safety
- Extensive data corrections and questionable changes
- Inadequate oversight of study personnel
 - Inappropriate delegation of authority*
 - Poor oversight of satellite sites*
- No informed consent
- Failure to communicate with IRB
- Falsification



Significance of Violations

Do the violations

...affect rights, safety, or welfare of subjects?

...directly impact integrity of data set?

...indicate systemic problems within the study?

sponsor problems?

Did the sponsor report the problems to FDA?

...indicate that other studies at that site might be impacted? *investigator problems*

■■■ The Protocol Violation Spectrum

Minor**

- a missed lab test, a missed visit

Major*

- ineligible subject enrolled
- safety or efficacy assessments not done
- did not report serious adverse events (SAEs) to IRB



Suggestions to Improve Protocol Compliance

- Review and understand protocol
- Identify any procedures in the protocol that differ from standard practice at your establishment
- Thoroughly train study staff
- Use well-designed study-specific forms for documentation



Protocol Compliance - 2

- Identify study-specific procedures and at what points of the study they are required; develop a plan/schedule
- Perform study-required procedures and visits within the required window
 - A large number of out-of-window procedures/visits may indicate too tight a window or poor planning/scheduling



Protocol Compliance - 3

- Carefully review amendments
- Inform all study personnel of any changes in the amendment
- Track versions of the protocol and use the correct version



Protocol Compliance - 4

- Document all protocol deviations
- Review the deviations for trends
- Trends may indicate re-training or a protocol amendment is necessary
- Use the deviations to develop corrective actions to prevent future occurrence



Ways to Prevent Enrollment of Ineligible Subjects

- Protocol criteria should be clear, not subject to differing interpretations
- Train all study personnel involved in determining eligibility to understand the inclusion and exclusion criteria
- Use a form that lists each criterion to assist during subject assessment



Ways to Prevent Enrollment of Ineligible Subjects - 2

- Do not rely on exemptions from the sponsor
 - If there are numerous exemptions, perhaps the protocol inclusion or exclusion criteria should be revised
 - Sponsor's waiver of entry criterion should be in writing and prospective
 - Consult with IRB for its instructions about waivers

■ ■ ■ Adequate and Accurate Case Histories

Record keeping errors may be minor, or they might impact the safety or welfare of the subject, impact the study data, or undermine the clinical trial process

Examples:

- extensive or uncorroborated data corrections
- adverse event severity is under-reported to sponsor or IRB
- AEs are reported *LATE* to sponsor or IRB



Suggestions to Improve Recordkeeping

- Make sure the staff know how to use the sponsor's computer system and understand the expectations
- Use a consistent format to document all aspects of the subject's evaluation and treatment
- Keep records organized and complete
- Develop a system to track and maintain files



FDA has observed that sponsors and monitors may have conflicting instructions for how they want investigators to prepare and maintain case histories, and perform corrections.



Where is the Term “Source Data” Defined?

NOT defined in 21 CFR 312 (investigational drugs)
or 812 (investigational devices)

See Nonclinical Laboratory regulations

21 CFR 58.3(k) – “raw data”

21 CFR 58.130(e) – describes how data are to be recorded, corrected, and describes automated systems.



Elements of Documentation Integrity

Attributable

Legible/readable

Contemporaneous

Original

Accurate

Common Informed Consent Problems

Study-specific procedures are performed before informed consent is obtained.

The informed consent discussion is conducted by someone who is not authorized.

What is the IRB's intent for the investigator's signature on the form if another person discusses the study?
What if the investigator signs later?

What is the sponsor's/IRB's expectation for "re-consent" when the consent form is revised?



Clinical Investigator Supervision and Authority

- Verify credentials – is your study coordinator a “nurse” with only a high school education?
- How will you (CI) supervise the conduct of sub-investigators, particularly if they are located at a distance?



Clinical Investigator Supervision and Authority - 2

- What authority do you have over the personnel assisting in the trial?
- Can you fire a study coordinator or other personnel employed by the sponsor?
- How do you report inadequate performance of a monitor hired by the sponsor?



Inappropriate Delegation to Sub-investigators

Investigator – individual who actually conducts an investigation (i.e., under whose immediate direction the drug is administered or dispensed to subjects.

**** How many miles (or states!) away ????

Sponsor must ensure that the clinical investigator controls the study

***** BIG challenge for study coordinators and support staff



Test Article Accountability

- Records should be sufficient to show:
 - Subjects received proper dose/device
 - Which dose/vial/device was provided to which subject and when
 - Accountability for all investigational product
 - Product was shipped, received, and stored at the proper temperature and conditions



Suggestions for Investigators to Prevent Noncompliance

- *BEFORE* -

- Understand what you are responsible for...
.....And get training
- Document the delegation of duties
- Develop forms or checklists to make sure all screening tests and study visit activities are performed...*if not provided by the sponsor*
- Don't overextend to many concurrent projects



Suggestions to Prevent Noncompliance - *BEFORE* -

- Develop a plan for organizing records
 - Clearly understand what records are to be maintained and how they should be completed
 - Original source data for critical study endpoints
 - Use your site's existing record-keeping system as much as possible, discuss this with the sponsor up front
 - All records should meet the ALCOA test
- Train study staff before the study starts....and train replacements when staff leave



Suggestions to Prevent Noncompliance - *During* -

- Track dates when reports are due to the IRB and the sponsor
- Promptly report protocol violations to IRB and sponsor.
- Obtain written approval from the sponsor before you do something that is outside of the protocol
- Verify that delegated duties are performed
- Work with monitors
- Correct small problems before they grow
- Question unusual results



Suggestions to Prevent Noncompliance - *After* -

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 - depending on the sponsor and phase of the research)



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