Clinical Investigator Site Inspections – What to Expect

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Learning Objectives

- Review the Regulatory Responsibilities of Clinical Investigators (CIs)
- Discuss the Purpose and Focus of CI Inspections
- Describe the Inspection Timeline and Activities
- Discuss Potential Enforcement Actions

Regulatory Responsibilities of CIs

- Ensuring that an investigation is conducted according to the investigational plan (i.e., protocol) and applicable regulations
- Protecting the rights, safety, and welfare of subjects
- Obtaining informed consent
- Obtaining IRB review/approvals
- Control of drugs under investigation

Good Clinical Practice (GCP) Inspections

- Evaluate clinical trials for compliance with GCP and regulations
  - Ensure the rights, safety, and welfare of human subjects
  - Ensure reliability of the safety and efficacy data submitted to FDA in marketing applications
- Other inspected clinical trial entities:
  - Sponsors, Contract Research Organizations, and Institutional Review Boards (IRBs)

Focus of CI Inspections

Trial Conduct Question #1: Was the study conducted according to the protocol?

- Inclusion/exclusion criteria
- Randomization and blinding procedures
- Data flow
- Study visits, procedures, evaluations
- Administration of study drug

Focus of CI Inspections

Trial Conduct Question #2: Did the study conduct comply with regulations?

- AE reporting
- IRB approvals/communications
- Consent procedures
- Financial disclosures
- Electronic records management
- Study drug accountability

Overview of CI Inspections

Source Data Verification:

Comparison of the original data generated by the site to the data submitted to FDA

- Primary endpoint data
- Adverse events
- Protocol deviations
- Laboratory data

Overview of CI Inspections

Types of Inspections:

- Routine/Surveillance
  - Pre-marketing application review
  - Generally pre-announced
- For-cause/Directed
  - Investigate potential regulatory violations
  - Related to a complaint from sponsor, IRB, study staff, study participant, etc.
  - Generally unannounced*

- Foreign inspections generally announced

Challenge Question #1

Which is not a regulatory responsibility of CIs?

A. Obtaining informed consent

B. Obtaining IRB review/approval

C. Paying subjects for trial participation

D. Ensuring the investigation is conducted according to the investigational protocol

CI Inspection Timeline and Activities

Pre-Inspection Activities

Preannouncement (if applicable):

- Up to 5 days before start of inspection
- Inspection scope and logistics:
  - Protocols
  - Location of records
    - Storage/retrieval
    - Computer system access
  - Anticipated length of inspection
  - Access to internet and workspace

Inspection Activities

Opening Meeting

- FDA team:
  - Investigator from the Office of Regulatory Affairs – Consumer Safety Officer
  - Subject Matter Expert from the Center having jurisdiction over the product being researched
- Presentation of Credentials
- Form 482: Notice of Inspection

Inspection Activities

Opening Meeting

Basis and Scope of the Inspection

- Number of studies, subjects, data to be verified
- CI and research staff availability for meetings or questions
- Process to provide/obtain requested copies of documents electronically (usually scanning)

Inspection Activities

Interview

- How the CI was selected by the sponsor
- Overview of the study at the site
- How subjects were recruited
- Any significant issues experienced
  - Protocol deviations
  - Serious adverse events
- List of studies conducted by the CI

Inspection Activities

Facility Tour

- Storage of the investigational medical product
- Exam rooms
- Laboratory space

Inspection Activities

Review of Study Records

- Protocol(s)
- IRB correspondence
- Sponsor correspondence
- Monitoring reports
- Signed investigator statements (Form 1572)
- Financial Disclosure Forms
- Training Logs
- Delegation of Authority Log
- Laboratory certifications
- Medical product accountability records (shipping/receipt)

Inspection Activities

Review of Subject Records

- Informed Consent Forms
- Visit worksheets
- Laboratory reports
- Progress notes
- Adverse event reports
- Efficacy endpoint assessments
- Medical product accountability records – dosing and administration

Inspection Activities

Inspection Close-Out Meeting

- Summary of Inspection Findings
- Form 483: Observations of possible deviations from federal regulations

NOTE: FDA Center determines whether each observation constitutes a regulatory violation and if so, determines the impact on data integrity and subject safety

Inspection Activities

- CI Response
  - Verbal Response from CI
    - Inspection Close-Out Meeting
  - Written Response from CI
    - Optional, but should be received by FDA field investigator within 15 business days of inspection close

Post-Inspection Activities

Written Response to a Form 483: Why Submit?

- Demonstrates your acknowledgement and understanding of the observations to FDA
- Demonstrates your commitment to correct the observation to FDA
- May be considered in the final FDA compliance decision

Post-Inspection Activities

Contents of a Written Response to a Form 483:

- Submit a corrective and preventive action plan for each observation
- Provide timeline for completion of actions
- Provide a method of verification or monitoring the effectiveness of the actions
- Submit documentation (training records, standard operating procedures, etc.)

Post-Inspection Activities

Final FDA Classification

- After review of inspection report, 483, and written response
- Objectionable conditions
  - Subjects exposed to unreasonable and significant risk of injury
  - Subjects' rights, welfare and safety compromised
  - Data integrity or reliability compromised

Post-Inspection Activities

Final FDA Classification

No Action Indicated (NAI): No objectionable conditions or practices OR the significance of the documented objectionable conditions found does not justify further FDA action.

- Letter from FDA

Post-Inspection Activities

Final FDA Classification

Voluntary Action Indicated (VAI): Objectionable conditions were found and documented but the Center is not prepared to take or recommend regulatory action since the objectionable conditions do not meet the threshold for regulatory action.

- Letter from FDA describing those objectionable conditions

Post-Inspection Activities

Final FDA Classification

Official Action Indicated (OAI): Objectionable conditions were found, and regulatory action recommended

Common Inspection Findings

Finding	Regulation
Investigation not conducted in accordance with the investigational plan	312.60
Investigation not conducted in accordance with the signed statement of investigator	312.60
Failure to prepare or maintain accurate case histories	312.62(b)
Failure to obtain informed consent in accordance with 21 CFR Part 50	312.60

Common Inspection Findings

Finding	Regulation
Investigational drug disposition records not adequate	312.62(a)
Failure to report promptly to the IRB all unanticipated problems involving risk to subjects	312.66
Failure to report AEs promptly to the sponsor	312.64(b)

Enforcement Actions

OAI Outcomes

- Untitled Letter
- Warning Letter
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) Letter
  - Investigator not able to conduct clinical investigations involving products regulated by FDA

Enforcement Actions

Other Actions

- Debarment (usually result of a federal felony conviction related to drug trial conduct)
  - Individual may not provide services in any capacity to a drug company
- Civil Money Penalties

Challenge Question #2

Which of the following statements is NOT true?

A. A written response to a 483 is required.

B. A written response to a 483 is due within 15 business days of inspection close.

C. Outcomes of an OAI classification could include disqualification or letter.

D. A written response may be considered in the final FDA compliance decision

Resources

- Compliance Manual for Clinical Investigators and Sponsor-Investigators https://www.fda.gov/media/75927/download

Summary

- Regulatory Responsibilities of CI
  - Purpose and Focus of CI Inspections
  - Inspection Activities
- Now that you know what to expect, you can be prepared if an inspection occurs.

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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