What FDA Looks for When Inspecting IRBs and Sponsors

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Objectives/Agenda

- Institutional Review Board Inspection
  - Background
  - Techniques used in FDA's Inspections
  - Frequently found IRB Deficiencies
- Sponsor Inspection
  - Background
  - Techniques used in FDA's Inspections
  - FDA Administrative Actions
  - Frequently found Sponsor Deficiencies

FDA's Compliance Program-IRB

- Background
  - Title 21 Code of Federal Regulations Parts 50, 56, 312, 812
  - Goal is to achieve IRB compliance with regulations
  - FDA's Center personnel issue requests
  - Field Investigators/District Office conducts inspections

What FDA Looks For IRB Inspection

- FDA Compliance Program Manual
- http://www.fda/gov/ora/cpgm/default.htm
- Four components
  - Interviews
  - Review of written procedures
  - Review of records and reports
  - Exit meeting

  Followed by: Center's review and assessment

Techniques of IRB Inspection

- Interviews
- Questions about
  - IRB membership,
  - responsibilities,
  - functions and operations and records

Techniques used in IRB Inspection

- Review IRB Written Procedures
  - Sufficient detail
  - Compare with information gathered at interview
  - Compare with regulations

Techniques used in IRB Inspection

- Review records and reports (copies made)
  - Research studies
  - Protocol versions
  - Informed consent versions
  - Continuing review reports
  - Adverse events reports
  - New findings given to subjects
  - IRB minutes
  - Correspondence
  - IRB roster

Techniques used in IRB Inspection

- Exit meeting with management
  - Form FDA 483
  - Other observations
- Center's assessment of inspection-report
- Untitled Letters/Warning Letters and other FDA administrative actions
- Centers follow up to ensure IRB comply

Common IRB Deficiencies

- Written procedures
  - Incomplete – inadequate – not followed
- Expedited review
- Device SR/NSR
- Inadequate continuing reviews
- Minutes insufficient
- Vote not recorded by number of votes
- Adverse events not adequately reviewed

Common IRB Deficiencies

- Majority of members not at meeting
- Majority of members not present for vote
- Non-scientific member not present
- Fail to report to FDA when study is suspended or terminated

FDA Compliance - Sponsors

- Background
- Techniques
  - Interviews
  - Review of procedures and records
  - Exit interview
- FDA's administrative actions
- Frequently found deficiencies

FDA's Compliance Program Sponsors

- Background
  - Objective: determine how Sponsors assure validity of data and comply with regulations
  - Title 21 Code of Federal Regulations Parts 312, 314, 812, 814, 58, 21, 50, and 56
  - Differences between drug and device inspect.
  - Criteria to choose Sponsor for inspection

What FDA Looks For Sponsor Inspection

- FDA Compliance Program Manual
  - http://www.fda/gov/ora/cpgm/default.htm
- Interviews
  - Organization – responsibilities – authority – contractor oversight- adverse event review
  - Selection of clinical investigators

What FDA Looks For Sponsor Inspection

- Selection of Clinical Investigator (CI)
  - Signed FDA 1572 or Investigator agreements
  - Criteria for selection of CIs
  - Necessary information given to CI
  - How sponsor obtained compliance from non-compliant CI

What FDA Looks For Sponsor Inspection

- Selection of Monitors
  - Responsibilities
  - Written monitoring procedures
    - Frequency of site visits
    - Scope and processes
    - Review monitoring records to verify procedures

What FDA Looks For Sponsor Inspection

- Review of Records
  - CI selection criteria
  - Monitoring procedures and activities
  - Subjects records and clinical data
  - IRB approval
  - Informed consents
  - Automated data entry
  - Test article accountability

What FDA Looks For Sponsor Inspection

- Review of records
  - Adverse event (AE) reporting

  Difference between drug/biologics and devices
    - Drug/biologics telephone report within 7 calendar days for fatal or life-threatening situation and a written report within 15 days for both serious and unexpected AE
    - Device studies – written report within 10 working days for unanticipated AE

What FDA Looks For Sponsor Inspection

- Copies made of documents, example
  - Written procedures
  - Organizational charts
  - Written agreements transferring responsibility
  - List of monitors/job descriptions/qualifications
  - List of clinical investigators
  - Protocol amendments, changes
  - Research article accountability
  - Notices to Clinical Investigators/subjects

Exit meeting with management

(Sponsors may clarify any misunderstandings during the inspection)

At exit meeting Field Investigator meets with most responsible person and others.

- Discuss Form FDA 483 observations
- Other observations
- Sponsor participates

FDA Administrative Actions

- Center personnel review and analyze inspectional report from Field Investigators to assess Sponsor's compliance
  - **Untitled Letters**
  - **Warning Letters**
  - Rejection of clinical data in marketing application
  - Application Integrity Policy
  - Civil Penalties
  - Seizure of product or Injunction
  - Prosecution

Frequently Found Sponsor Deficiencies

- Inadequate monitoring
- Lack of CI training
- Lack of product accountability
- Insufficient recordkeeping
- Failure to report all unanticipated AEs
- Inadequate sample Informed Consent
- Application has false or fabricated data
- Failure to secure CI compliance

Summary

- Institutional Review Board Inspection
  - Background
  - Techniques used in FDA's Inspections
  - Frequently found IRB Deficiencies
- Sponsor Inspection
  - Background
  - Techniques used in FDA's Inspections
  - FDA Administrative Actions
  - Frequently found Sponsor Deficiencies