Inspections and Study Monitoring

IRB Education Series
2006

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Audits and Inspections
Monitoring

Skeeter
(1992-2006)
In reality… it’s a little of all worlds, and they all mean the same thing.

Woody
Typical Inspectors

- Sponsor
- U.S. Food and Drug Administration (FDA)
- Office for Human Research Protections (OHRP)
- Institutional Review Board (IRB)
Types of Inspections

- Routine
- For-cause
Reasons for Inspections

• Routine
  • Top recruiter
    • Good or bad
  • Importance of the study
  • Impact of site’s data
  • Data are inconsistent with data from other sites
  • Principal Investigator’s reputation
    • Good or bad
  • “Luck of the draw”
  • May also inspect the IRB at the same time
Reasons for Inspections Continued

• **For-cause**
  • Suspicion of false or fraudulent data
  • PI appears to be “outside” of specialty
  • Evidence the sponsor has rejected data from the site
  • Evidence of delay in submitting safety data from the site (slow adverse event reporting)
  • Evidence of inadequate monitoring
  • Evidence of inadequate or inappropriate informed consent
  • Evidence of delayed or inappropriate IRB approval
  • Study is of “singular importance” in approval
Reasons for Inspections Continued

- For-cause
  - Complaint
    - Subject/Family member
    - Institution
    - Sponsor
  - Outlier data
- Suspicion of COI among research team at the site
Scope of an Inspection

- Site (source documents) records/data are compared with FDA data
  - Paper and electronic records
  - Integrity of records
    - Storage
    - Accuracy – completeness, condition, legibility
- Interviews
  - Principal Investigator
  - Research team members
  - IRB Chair, members, staff
What’s typically inspected?

- Protocol
- IRB approvals
- Informed Consent Forms (ICF)
- Reported changes/deviations to the sponsor and IRB
  - An exception to the protocol must first be approved by the sponsor and then the IRB must also approve or concur with the exception.
- Source documents
- Violations
  - FDA defines deviation and violation the SAME
- Drug/device accountability
- General study management
What’s typically inspected?

- Protocol
  - Version used
  - Approval of changes
  - Appropriateness
  - Advertisements
  - Questionnaires, etc.
What’s typically inspected?

- **Informed Consent Forms**
  - Appropriateness and accuracy of ICF
- **Consent process**
  - Who obtained consent
    - Qualifications
    - Experience with consent process
    - Experience and familiarity with study
  - When consent was obtained
  - Was consent process documented
What’s typically inspected?

- Drug/device accountability
  - Shipping
  - Storage
  - Dispensing/administration
  - Disposition
  - Integrity of randomization/blinding
- General study management
  - **Tasks** may be delegated by the Principal Investigator, **not responsibility**
Advance Preparation

• Remember: Inspectors have detailed information about the protocol, the site, etc., before they arrive for the inspection.
• Have records available, including drop-outs
• Verify IRB and sponsor are aware of inspection
• Ensure a functioning photocopier is available
  • Always make 2 copies
    • One for inspector
    • One for PI
Advance Preparation

- Reserve space for inspector, interviews, etc.
  - Quiet
  - Away from clinical areas
- Notify all research staff
  - Review study
  - Ensure availability during inspection
- Assign a point person/facilitator
- Review study files
  - All documents, versions present
  - Compare PI files with IRB files
FDA Advance Notice Inspection

- Notification
- Interview
- Process
- Closing meeting/exit interview
FDA Inspection

• Notification
  • Typically the sponsor, PI or IRB is notified
  • Time to gather records
  • Delays raise suspicion
  • Inspections are typically 3-5 days
  • Inspections typically concentrate on one study
FDA Inspection

• Interview
  • Credentials of inspector presented
  • Scope of inspection
  • May use Compliance Program Guidance Manual as interview guide:
    http://www.fda.gov/ora/cpgm/default.htm
FDA Inspection

- **Process**
  - Record review, interviews
    - Who did what?
  - Answer politely, completely, and accurately
  - Avoid unsolicited questions, hypothetical situations, delays
  - Do not sign affidavits
  - Review findings at end of each day
FDA Inspection

• Closing meeting/Exit interview
  • Responsible study personnel present
  • Review findings
  • Correct incorrect information
  • Clarify misunderstandings
  • Suggest voluntary corrective actions
  • Take notes!!
  • Report findings to IRB
FDA No Advance Notice Inspection

- There’s a reason!
- Stay calm!
- Find a quiet space for the inspector, away from clinical areas
- Don’t delay getting records, etc., – the inspector is the new top priority!
- Immediately notify the IRB
- Notify all research team members
- Same interview, process, exit interview issues
- Stay calm!
FDA Terminology

- FDA Form 482 – Notice of Inspection
- FDA Form 483 – Inspection observations – if deviations are cited
- FDA Form 1572 – Investigator statement
- EIR – Establishment inspection Report
- BiMo – Bioresearch monitoring
FDA Form 483 – Common Findings

- Protocol violations
- Inadequate, incomplete, inaccurate records
- Inappropriate delegation
- Consent issues
- Adverse event reporting issues
- IRB issues
Results/FDA Classifications

- NAI – no action indicated
- VAI – voluntary action indicated
- OAI – official action indicated
What **NOT** to do

- **DO NOT**...
  - Create or “fix” records
  - Use “white out” or correction tape/fluid
  - Destroy records
  - Withhold data from inspectors
  - Volunteer information not asked for
  - Provide financial information (salary, budgets)
  - Delay scheduling inspection
What NOT to do

• **DO NOT**
  • Volunteer tours
  • Leave the inspector unattended
  • Let the inspector make the photocopies
  • Back date documents
    • e.g., signatures on ICFs dates 2003, version date in the footer was 2006.
    • Study tests were conducted before the ICF signature date
Continuous/Ongoing Monitoring

Skeeter
Suggestions

• Continuous monitoring
• Create a start-up checklist
  • Depends on the type of study
• Have an on-going checklist
• Depending on rate of enrollment, review study documents at fixed intervals
Suggestions Continued

- Keep good records!
  - Contemporaneous
  - Accurate
  - Legible
  - Originals
- ALL subject documents are subject to inspection; keep all source documents (21 CFR 312.62(c))
  - ICFs
  - Photographs
  - Questionnaires, Rating scales
  - Diaries
Suggestions Continued

• If the PI is meant to have the original (e.g., IRB letters), ensure it is present. If not present document why absent.

• Document
  • Events
  • Telephone calls
Reminders

• If the study is industry sponsored, create an “appendix” to the protocol
  • Recruitment methodology
  • Number of subjects to be enrolled locally
  • Payment
  • Consent process
    • Who will conduct it?
    • When and where will consent be obtained?
Training

- Train all research team members
- Expect staff changes
- Consider creating SOPs
  - Pros
    - Good reference
    - Helpful for new research team members
  - Cons
    - Very bad if you have them and do not follow them
Problem Solving

- Identify the problem
- Conduct a root cause analysis
- Implement a corrective action plan
- Implement the corrective actions
- Re-evaluate
IRB Leadership

• IRB Chair: David P. Chelmow, MD
• IRB Vice-Chairs: Edward L. Decker, PharmD
  Judith A. Frazier, RN, Med
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IRB Members are from more than 17 divisions at Tufts-NEMC and Tufts University, including TUSM, TUSDM, the HNRCA, etc., and community representatives who are not affiliated with either institution.
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