How to Prepare for Federal Inspections and What to Expect

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“Audits and Inspections”

• Have a negative and aggressive connotation.
• Conjure images of “IRS audits.”
• Might incorrectly lead a PI to think s/he is suspected of wrong-doing if s/he is being “audited” or “inspected.”
• A systematic review of study files, including study documents (e.g., ICFs, protocols, participant files, source documents) and activities. Interviews are routinely performed as part of the process. Audits tend to be classified as either “routine” (or “not for cause”) or “directed” (or “for cause”).
“Monitoring”

- Has a “softer” connotation.
- Does not “sound” as threatening.
- Imparts a more collegial feeling to the activity.
- An internal review activity often performed periodically or episodically to ensure regulations, policies, and procedures are being followed.
Entities Typically Inspected

- Principal Investigators/study sites
- Institutional Review Boards (IRBs)
- Institutions
- Sponsors
Inspectors

• May be internal or external, Federal or institutional
  — Study sponsor – usually use the term “monitoring”
  — U.S. Food and Drug Administration (FDA)
  — Office for Human Research Protections (OHRP)
  — IRB
  — Institutional research compliance office
Types of Inspections

- Routine or “not for-cause”
- Directed or “for-cause”
Common Reasons for PI Federal Inspectors

• Routine (not for-cause)
  • Top recruiter
  • Principal Investigator’s reputation
    • Good or bad
  • Data are inconsistent with data from other sites, outliers
  • Importance of a particular study
  • Impact of site’s data
  • “Luck of the draw”
  • Scheduled pre-planned inspection
Common Reasons for PI Federal Inspections

Continued

- Directed (for-cause)
  - Suspicion of false or fraudulent data; outlier data
  - PI appears to be “outside” of specialty
  - Evidence that the sponsor has rejected data from the site
  - Evidence of delay in submitting safety data from the site (slow SAE or unanticipated problem (UP) reporting)
  - Evidence of inadequate sponsor or PI-sponsor monitoring
  - Evidence of inadequate or inappropriate informed consent
  - Evidence of delayed or inappropriate IRB approval
  - Study is of “singular importance” to test article approval
  - Concerns about the site’s IRB
Common Reasons for PI Federal Inspections

Continued

- Directed (for-cause)
  - Complaint
    - Subject/family member
    - Research team member
    - Institution
    - Sponsor
  - Suspicion of conflict of interest (COI) among research team at the site
Scope of a PI Federal Inspection

- Site records (source documents)/data are compared with FDA data
  - Paper and electronic records
  - Integrity of records
    - Storage
    - Accuracy – completeness, condition, legibility
- Interviews
  - Principal Investigator
  - Research team members
Documents Typically Inspected

- Protocol
- Source documents
- IRB-related documents
  - Submissions to IRB
  - IRB approvals
  - PI/study team communications to & from IRB
- Informed Consent Forms (ICF)
- Reported changes/deviations to the sponsor and IRB
  - Deviation: An exception to the protocol must first be approved by the sponsor and then approved or concurred with by the IRB.
- Violations
- Test article accountability
- General study management
Documents Typically Inspected

Continued

• Protocol
  • Version
  • Compliance
  • Approval of changes
  • Appropriateness
  • Safety monitoring
  • Advertisements
  • Questionnaires, etc.
Documents Typically Inspected

Informed Consent Forms
- Appropriateness and accuracy of ICF
- Maintenance of documents
- Consent process
  - Who obtained consent
    - Qualifications
    - Experience with research consent process
    - Experience and familiarity with study
  - When consent was obtained
  - How consent process was documented
- FDA regulation requires that the study participant sign and date an ICF (21 CFR 50.27)
• Drug/device accountability
  • Typically managed by the Investigational Drug Service (IDS)
    • Shipping
    • Storage
    • Dispensing/administration
    • Disposition
    • Integrity of randomization/blinding

• General study management
  • Tasks may be delegated by the Principal Investigator, not responsibility
  • 2009 DHHS/FDA guidance
How to Prepare for Any Type of Inspection
(e.g., sponsor, federal)

• It’s not reasonable to think you can prepare on short notice
given the typical scope and depth of an inspection.
• Maintain high quality records and procedures every day.
• Ensure research team is thoroughly trained and qualified to
perform tasks and job responsibilities; document trainings.
• Perform periodic in-services with research team if there have
been large or numerous study amendments – or problems or
staff turn over.
• Conduct periodic QA/QI initiatives.
How to Prepare for Any Type of Inspection
(e.g., sponsor, federal)
Continued

• Develop a plan to periodically perform internal routine monitoring:
  • Based on frequency of subject enrollment
  • Based complexity of the study
  • Based on available resources

• Establish procedures for the research team to follow in the event of an inspection (announced and unannounced) and make sure everyone is familiar with them – preparation helps ensure calm as people focus on their pre-determined task. Consider creating a reference guide.

• Maintain records that are always inspection-ready.
Advance PI Preparation for a Federal Inspection

- Federal inspectors have detailed information about the protocol, the site, the sponsor, etc., before they arrive.
- Have records available, including drop-out and screen failure records
- Verify IRB and sponsor are aware of inspection
  - Others, as needed – IDS
- Ask IRB or QA/QI office for help preparing for the inspection
- Ensure a functioning photocopier is available
  - Always make 2 copies
    - One for inspector
    - One for PI
Advance Preparation

- Reserve an office for inspector(s) to work, perform interviews, etc.
  - Quiet, comfortable; away from clinical areas
  - No files or research records should be stored in the room.
- Notify all research staff
  - Ensure PI and study team availability during inspection. PI should set aside time each day to talk with the inspector, as well as be available for questions that may arise.
- Assign a point person/facilitator who is readily available to the inspector
- Review study files
  - Ensure all documents are present and chronological.
  - Compare PI files with IRB files.
Advance Notice of a Routine Federal Inspection

- Notification
- Interview
- Process
- Closing meeting/exit interview
Typically the sponsor, PI, and/or IRB receive notification via telephone from the inspector who will perform inspection. ~1 or 2 week advance notice.

- Record inspector’s name and contact information.
- Ask inspector for start date and expected duration of inspection.
- Typically last 3-5 days.
- Inspections typically concentrate on one study; be certain to specifically ask which study or PI will be inspected.
- Ask inspector what specific documents and study personnel should be available for his/her arrival.
- Advise inspector you will confirm PI’s availability that day – delays raise suspicion.
Federal Inspection Interview

• Interview
  • Credentials of inspector presented, if not – ask to see them.
    • Verify; record name and title. Again, don’t be nervous or intimidated.
  • Scope of inspection
  • FDA: Compliance Program Guidance Manual as an interview guide may be helpful:
    http://www.fda.gov/ora/cpgm/default.htm
Process of a Federal Inspection

- Only documents specifically requested by the inspector should be provided for review.
- Record review, interviews
  - Who did what?
  - Was protocol followed?
  - Were federal requirements followed?
- Answer politely, completely, accurately, and confidently. Don’t guess.
- Avoid unsolicited questions, hypothetical situations, delays.
- Do not volunteer information, tours, etc.
  - Don’t be intimidated by silence.
- Do not sign affidavits – contact institutional legal counsel.
- Keep notes about each day – inspector’s questions, responses
- Request an end of day meeting with the inspector(s) each day to get a summary update. This should include the PI. Take notes!
- Review findings with study team at the end of each day.
Close-out Meeting/Exit Interview of a Federal Inspection

- Responsible study personnel present
- Review findings
- Correct inaccurate information
- Clarify misunderstandings; ask questions if clarification is needed.
- Suggest voluntary corrective actions
- Take detailed notes!!
- Report findings to the IRB or other institutional office with oversight – they can help!
No Advance Notice of a PI Federal Inspection

- There’s a reason
- Stay calm
- Find a quiet and comfortable space for the inspector, away from clinical areas
- Don’t delay getting records, *etc.*, – the inspector is the new top priority!
- Consider rescheduling study visits, if needed
- 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
- SAE or UP reporting issues
- Lack of IRB review/approval issues
- Test article accountability issues
- Not following SOPs
Results/FDA Classifications

- NAI – no action indicated
- VAI – voluntary action indicated
- OAI – official action indicated
Responding to a FDA Form 483

- Reply to each point addressed in the report.
- Be factual, specific, and detailed.
- Describe corrective actions – and be certain they are implemented!
- The response should be sent to the FDA within 30 days.
- Consult with the IRB, QA/QI, or other institutional office that oversees and assists with this aspect of human research.
What NOT to do

• **DO NOT**…
  • Panic
  • Create or “fix” records
  • Use “white out” or correction tape/fluid
  • Destroy records
  • Back date documents
  • Delay scheduling inspection
  • Withhold data from inspector
  • Argue or complain
What NOT to do

Continued

- **DO NOT**…
  - Make excuses or “blame” previous employees or other staff members or departments
  - Guess or speculate. It is OK to defer to the PI or other study staff if you don’t know the answer.
  - Volunteer information
  - Provide financial information (e.g., salary, budgets)
  - Volunteer tours
  - Leave the inspector to wander area unattended
  - Let the inspector make the photocopies - make them for him/her (and a copy for the PI)
Suggestions for What TO DO day-to-day

- Keep good records!
  - Available, accessible, accurate, and attributable
  - Legible
  - Complete
  - Contemporaneous
  - Original

- ALL participant documents are subject to inspection; keep all source documents (21 CFR 312.62(c))
  - ICFs
  - Photographs
  - Questionnaires, rating scales
  - Diaries

- Be prepared; keep up day-to-day
Suggestions for What TO DO day-to-day

Continued

• If the PI is meant to have the original (i.e., IRB letters), ensure it is present. If not present, document why absent or obtain a copy.
• Explain a gap, error, etc., with a memorandum to file.
• Document
  • Events
  • Telephone calls
• Evaluate study/program status
Training

• Train all research team members, including PI
• Expect staff changes
• Consider creating or updating guidance/procedure reference documents

• Pros
  — Good reference
  — Helpful for new research team members

• Cons
  — Very bad if you have them and do not follow them – especially if they’re “SOP”
  — If not updated regularly can be much worse than not having them.
Problem Solving

- Identify the problem
- Conduct a root cause analysis
- Implement a corrective action plan
- Implement the corrective actions
- Re-evaluate
References and Guides

- FDA Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators, June 2010  
  [link](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf)

- FDA Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: FDA Institutional Review Board Inspections, January 2006  
  [link](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126555.pdf)

- FDA Guidance: Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009  

- OHRP’s Compliance Oversight Procedures for Evaluating Institutions, October 2009  
  [link](http://www.hhs.gov/ohrp/compliance/evaluation/ohrpcomp.pdf)

- OHRP Investigator Responsibilities – FAQs  
  [link](http://answers.hhs.gov/ohrp/categories/1567)
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