How to Survive an FDA Inspection

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Overview of Topics

- What is an FDA BIMO Inspection?
- Preparing for the Inspection
- What happens during an Inspection?
- Tips for a Successful Inspection
- Outcomes of the Inspection
- Advice from coordinators who have been through an Inspection

Biomedical Monitoring Program (BIMO)

- **FDA program for conducting on-site inspections to monitor study conduct, data and reporting of FDA-regulated research studies**
- **BIMO Program types:**
  - Clinical Investigators
  - Sponsors, Contract Research Organizations, and Monitors
  - Institutional Review Boards
  - Good Laboratory Practices

Purpose of BIMO Inspections

- **Protect the rights, safety and welfare of subjects;**
- **Verify accuracy and reliability of data submitted to FDA in support of research or marketing applications; and**
- **Assess compliance with FDA regulations**

BIMO Metrics

Center	Clinical Investigator Inspection	IRB	Sponsor/CRO/ Monitor Inspection	Good Laboratory Practice	Total
CDER	344	90	62	28	524
CDRH	193	76	53	10	332
CBER	91	8	4	1	104

- **Penn Medicine BIMO Metrics**
  - *3 Principle Investigators audited by FDA in 2013*
  - *IRB last audited by FDA in 2008*

Source: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/UCM381797.pdf

FDA Inspection Notification

- **FDA field investigator contacts PI to inform him/her of selection for BIMO inspection**
- **May arrive unannounced**
- **Usually call ahead and schedule day(s) at site**
- **Notifying Others**
  - Inform PI (if someone else fielded the call)
  - Inform entire study team (including Sponsor)
  - Notify IRB and OCR
    - Cancer studies notify Vicki Sallee
  - Inform Department/Section Chair
  - Sponsor (as applicable)
  - Investigational Drug Service (IDS) Pharmacy (as applicable)

Location for Inspection

- **Identify a private conference room or office for FDA field investigator to work**
  - Internet access
  - Photocopier/fax access
  - Proximity to rest room
- **Identify a nearby room or office for main research personnel to work from**

FDA Inspection Logistics

- **Do not offer food or drink to FDA field investigator**
- **Notify those working near the room that the FDA field investigator is on site**
- **Request that people be quiet and respectful in the hallways and working space**
- **Plan for FDA field investigator to be on site anywhere from 2 -10 days**

Preparing for the Inspection

- **Organize Regulatory files**
- **Ensure all IRB correspondence and Sponsor correspondence is printed and filed (or saved to an accessible electronic file)**
- **Review Subject Research Files for completeness**
- **Notify EPIC/ Medical Records that FDA Investigator (name) will be on site and that a request for access to records may need to be expedited**
- **Do not change or alter data!**
- **Address issues with Note**
- **Ensure list of Adverse Events and Protocol Deviations are complete**

Meeting the FDA Field Investigator

- Arrange to meet at the main entrance
- Check into Vendormate (if in hospital)
- FDA field investigator shows identification
- FDA Presents Form 482- Notice of Inspection
- FDA will present an additional Form 482 to the PI if not available for the opening meeting

Inspection Begins

- **Field investigator will tell PI/research personnel what he/she wants to review**
  - Will specify order or review
  - May wish to provide all files at once
- **Requests list of all studies performed by investigator**
  - Protocol number
  - Title
  - Regulatory Sponsor name
  - Study dates

Inspection Process

- **Review of records**
  - Compare source documents to case report forms
  - Compare files on site to sponsor-provided data
  - Reviews product management if investigational product still on site
- **Requests additional documents, information, source, etc.**
- **May request to meet with certain study personnel or ask study team clarifying questions**

Inspection Process (continued)

- **May request copies of records that demonstrate discrepancies between source data, CRFs, or data from sponsor**
  - Research team member should make 2 copies
  - 1 copy for FDA field investigator
  - 2nd copy for our internal file
- **Request a daily debriefing meeting with FDA Field Investigator**

Frequently Asked Questions by FDA Investigator

- **Do you have experience as a Principal Investigator?**
- **Can you summarize the protocol?**
- **Who were the research team members involved in seeing subjects and collecting data?**
- **Who completed case report forms (CRF)?**
- **How is/was the test article controlled?**

What is Reviewed: Regulatory Essential Documents

- 1572 / Investigator Agreement
- Appropriate delegation of study tasks by the PI
- IRB submission and correspondence history
- Protocol versions approved by IRB
- Sponsor correspondence and reporting history
- Consent Form versions approved by IRB
- Information about locations where subjects were seen
- Subject recruitment materials and process
- Enrollment log (will want a copy)
- Monitoring activities and reports

What is Reviewed: Subject Case Histories

- **Source records (hospital records, lab reports, subject diaries, etc.)**
- **Case Report Forms**
- **Eligibility criteria data**
- **Protocol compliance and documentation of deviations**
- **Signed, original informed consent forms**
- **Events and the appropriate recording and reporting of events**
- **Key Dates**
  - IRB approvals
  - 1572 / Investigator Agreement signature date
  - First subject screened;
  - First signed consent;
  - First administration of test article
  - Last follow-up for study subjects

What is Reviewed: Other Study Records

- **Confirmation that the investigator disclosed information about his/her financial interests to the sponsor**
- **Compliance with 21 CFR Part 11 electronic records and signatures for systems deemed applicable**
- **Applicable procedures and SOPs at the site**
- **Data collection practices**
- **Security of data**
- **Investigational product control**
  - Shipping, storage, destruction, etc.

Communicating with FDA Field Investigator

- **Do not answer any questions that you do not know the answer to**
  - Tell the inspector you will get the information requested and get back to him/her with the answer
- **Do not disparage the sponsor/funder/institution**
  - Any concerns you have with one of these entities should be communicated to the appropriate internal office for handling
- **The investigator must take responsibility for all aspects of the study management and file status as they ultimately signed the agreement indicating that they understood their responsibilities**
  - Denying responsibility to the FDA field investigator can be detrimental

Tips for a Successful BIMO Inspection

- **Be polite and respectful**
- **Provide anything that the field investigator requests**
- **Utilize your internal support team (IRB, OCR, Cancer Center)**
- **Remain available throughout the inspection**
- **Check in frequently and be clear when you will check in**
- **Identify a team member who can make copies as requested by the field investigator**

OCR Support with the Inspection

- **OCR can assist with FDA Inspection preparations**
  - Pre-inspection review of records
  - Meeting with team to review FDA Inspection process
  - Review of Regulatory and Subject files for completeness and organization
- **An OCR representative is available to participate in the initial meeting & the closing meeting**

IRB Support During the Inspection

- **Defer all IRB related questions to the IRB**
- **IRB representative will be available to the FDA field investigator throughout the audit**
- **During inspection, the FDA field investigator can request that the site's IRB be audited by the FDA if the IRB has**
  - Never been audited by the FDA; or
  - Has not been audited by the FDA within past 5 years

Inspection Closing

- **The FDA field investigator will request a meeting with the PI**
  - Recommend having a representative from the OCR or Cancer Center present
  - May wish to invite an IRB representative if findings may be related to IRB submissions or review
- **Opportunity for PI or Penn representative to ask questions and/or provide initial verbal response**

Common Inspection Findings- Clinical Investigator

- **Failure to follow investigational plan / Protocol deviations**
- **Failure to follow regulations**
- **Inadequate recordkeeping**
- **Inadequate investigational product accountability**
- **Inadequate IRB communication**
- **Inadequate subject protection**
  - Includes informed consent deficiencies

FDA Inspection Outcomes

- **No Written Observations**
- **Form 483- Inspectional Observations**
  - Observations that appear to constitute violation of the FD&C Act
  - Other observations may be discussed verbally
  - PI signs copy of 483
  - Copy left with site, FDA field investigator takes original
- **Warning Letter**

Responding to Form 483 Observations

- **Always respond formally in writing to inspectional observations written on the Form 483**
- **Work with IRB and OCR/Cancer Center to finalize response language**
- **Consult with legal, as appropriate**
- **Send in response within 15 days of inspection**
- **Provide the OCR with a copy of any additional correspondence from or to the FDA**

Advice from Experienced Research Personnel

- **Amanda Baer (Translational Medicine)**
- **Aaron Blouin (Gastroenterology)**
- **Mary Kelty (HemOnc)**
- **Elizabeth Mahoney (Psychology Addictions)**
- **Elizabeth Steider (Epidemiology)**