FDA Inspections

How to Survive an FDA Inspection

Cynthia Monahan, MBA, CIP
Quality Improvement Specialist
Partners Human Research Quality Improvement Program

June 11, 2015
Table of Contents

1. Overview of Bioresearch Monitoring (BIMO) Program
2. Preparing for the Inspection
3. The FDA Inspection
4. Post-Inspection
5. Most Common Findings
6. TIPS
7. Resources
FDA developed BIMO to ensure:
- The protection of the rights, safety, and welfare of human research subjects
- The quality and integrity of data submitted to the Agency

BIMO Program involves site visits to clinical investigators, IRBs, nonclinical (animal) laboratories, and bioequivalence analytical laboratories
Types of BIMO Inspections

- FDA conducts inspections of clinical investigators:
  - Routinely to verify data that has been submitted to the Agency
  - As a result of a complaint to the Agency about the conduct of the study at the site
  - In response to sponsor concerns or termination of the clinical site
  - At the request of an FDA review division
  - Related to certain classes of investigational products that FDA has identified as products of special interest in its current work plan
Types of BIMO Inspections

Routine Inspection

VS

For-Cause Inspection
Types of BIMO Inspections

- Routine inspection:
  - Triggered by a New Drug Application (NDA) or Pre-Market Application (PMA) submission
  - Routine inspections account for over 80% of the inspections performed each year
  - Clinical Investigators who enroll the most subjects in the NDA’s pivotal trial are the most likely to be inspected.
Types of BIMO Inspections

- For Cause Inspection:
  - Conducting a large volume of clinical trials
  - Conducting clinical studies outside of one’s field of specialization
  - Reporting significantly better efficacy, fewer adverse effects, or different laboratory results than other investigators studying the same drug
Types of BIMO Inspections

For-Cause Inspections (cont’d)

- Having apparent access to too many patients with a specific disease state for the locale or practice setting
- Complaints from a patient or sponsor of an alleged violation of the regulations, protocol, or human rights
- Evidence that an investigator has a significant financial interest in the product
1136 inspections conducted in 2014

Inspections by Center:

- Center for Biologics Evaluation and Research (CBER)—121
- Center for Drug Evaluation and Research (CDER)—675
- Center for Devices and Radiological Health (CDRH) – 313
- Center for Food Safety and Applied Nutrition (CFSAN) – 2
- Center for Veterinary Medicine (CVM) – 25
Inspections by entity:
- Clinical Investigators – 803
- IRBs – 152
- Sponsors/Monitors/CRO – 138
- Good Laboratory Practice – 4
BIMO Inspections

The FDA Has Called!!!

What is your next step???
BIMO Inspection
Preparing for the Inspection

- When FDA calls to schedule an inspection, obtain the following information:
  - FDA inspector name and contact information
  - Additional inspectors information, if applicable
  - The name of the PI being inspected
  - What studies are being inspected
  - The reason for the inspection
  - Does the FDA want specific personnel available
  - Does the FDA want specific documents available
Preparing for the Inspection

- Document any telephone conversation(s) that occurs between the FDA inspector and the study staff
- Notify study staff, Sponsor, QI Program, and Partners Human Research Committee
- The FDA inspector will usually request the inspection take place within 10 days
- Request the medical records for all subjects enrolled in the study
Preparing for the Inspection

- Reserve a room in a private area for the inspection
  - The room should contain no other files or records
  - A copy machine should be located next to the room
- Identify a person who will serve as an escort
- Prepare a general overview of the study for the PI and study staff
Preparing for the Inspection

- Update the Principal Investigator’s CV. This should include a list of all current studies.
- Ensure that all study documentation is available for review with the inspector.
- Review study documentation for:
  - Comprehensiveness, accuracy, and compliance
  - Weakness/gaps; correct those that can be corrected (i.e. file violations, notes-to-file, locate missing documents, etc.)
  - Unresolved or outstanding issues
During the Inspection

- The PI or his/her representatives should meet the inspector and receive and sign the FDA form 482 “Notice of Inspection.”
- Request to see the inspector’s identification if he/she does not present it to you.
- Write down the inspector’s identification information—you cannot make a copy of the inspector’s badge!!
During the Inspection

- FDA inspector may request a tour of the facility where research took place.
- Escort should accompany the inspector at all times.
- Upon request, provide the inspector only with files that have been requested.
If the inspector requests copies of documents:
- Remove subject identifiers from the copies given to the inspector
- Make a copy for yourself
- The inspector’s copies should be stamped ‘Confidential’ and your copies should be stamped ‘Copy.’

The PI should set aside time each day to talk with the inspector
During the Inspection

- How to answer questions from the inspector:
  - Be concise; answer only the question that is asked
  - Always be clear with answers to questions
  - Answer honestly and openly
  - DO NOT volunteer information
  - DO NOT guess or speculate
  - DO NOT argue
  - If you don’t know the answer, write down the question and refer it to the appropriate person
  - Keep a log of questions asked by the inspector
During the Inspection

- FDA Inspector will verify:
  - Who performed various aspects of the protocol (eligibility, consenting, etc.)
  - The degree of delegation of authority
  - Where specific aspects of the investigation were performed
  - How and where data were recorded
  - How were study staff oriented/trained on the protocol and investigational product
  - That the PI followed the study protocol approved by the IRB
During the Inspection

In addition, the inspector will record the following information:

- Dates of IRB approvals (original, continuing review, etc.)
- When the first subject was screened
- When the first subject was consented
- First administration of the investigational product
- Last follow-up for any study subject
Inspected Documents

- The following items are routinely examined:
  - Adequacy of communication with the IRB, including the initial submission, continuing reviews, adverse event reporting, progress reports, etc.
  - Completeness of accountability documentation for the receipt, storage, administration and return of the investigational product
  - Compliance with the study protocol and documentation that each deviation/amendment received IRB and sponsor approval
Inspected Documents

- Inspected documents (cont)
  - Appropriateness of the informed consent process
  - Prompt and complete reporting of adverse events to the IRB and sponsor
  - Compliance with record retention requirements
  - Adequate monitoring of the site and communication of the sponsor (monitoring reports)
  - Consent Forms (including the consent process)
The inspector will review subject data to verify that:

- Data entered on the CRF is has been accurately and completely recorded (matches source documents)
- Subjects existed
- Subjects meet inclusion/exclusion criteria
- Clinical laboratory testing was documented by laboratory records
- All adverse events were documented and appropriately reported
- The PI assessed the severity of the adverse event and documented the relationship of the event to the investigational product
- All concomitant therapies and/or inter-current illnesses were documented and reported
After the Inspection

- The FDA inspector will hold an exit interview at the conclusion of the audit to discuss findings and deficiencies.
- Study staff should document the interview, specifically noting observations, comments, and commitments.
- Any deficiencies will be noted on the FDA form 483 and given to the PI.
  - PI can respond to the 483 verbally during the exit interview and/or in writing.
FDA Form 483

- Contact the QI Program for assistance with responding to the Form 483

- Written response should:
  - Determine if a finding was an oversight/single occurrence of if it is a systemic problem requiring a change to the procedure/process
  - Address each specific finding, point by point
  - Describe corrective actions—DON’T OVERCOMMIT!!
  - The response should be sent to the FDA within 15 days
Post-Inspection

- After the inspection, the inspector will write an Establishment Inspection Report (EIR) and submit it to FDA headquarters.

- After the report has been evaluated you will receive one of three letters:
  - No action indicated (NAI): No objectionable conditions or practices were found during the inspection, or the significance of the objectionable conditions does not justify further FDA action.
Post-Inspection

- Post-inspection letters (cont)
  - Voluntary Action Indicated (VAI): Objectionable conditions were found and documented, but the FDA is not prepared to take or recommend further regulatory action because the objectionable conditions are few and do not seriously impact subject safety or data integrity.
  - Official Action Indicated (OAI): Regulatory violations uncovered during the inspection are repeated or deliberate and/or involve submission of false information to FDA or to the sponsor.
Post-Inspection

OAI may result in:

- Warning letter (WL)
  - Violations can be corrected through specific action(s) by the investigator and adherence to the corrective action plan has a high probability of preventing similar or other violations in the future

- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
  - Repeatedly or deliberately failed to comply with the requirements for conducting clinical trials
  - Repeatedly or deliberately submitted false information to FDA or to the sponsor
Results of 2014 Inspections

In 2014, clinical investigator inspections were classified as:

- NAI: 58%
- VAI: 37%
- OAI: 5%
Most Common Findings

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection—failure to report AEs and informed consent issues
Develop compliance plans to ensure proper study management:

- SOP’s: Standard Operating Procedures to achieve consistency
- Source Documentation: Maintain all the applicable original documents, data, and records that correspond with the CRFs
- Checklists/Logs: A way to verify completion of study-related procedures
- Note-to-file: A way to explain and correct unexpected departures from the protocol
Resources

- Study Management Resources
  - Staff signature/delegation of authority log
  - Enrollment log
  - Monitoring log
  - Drug/Device Accountability log
  - Documentation of informed consent checklist
  - Adverse event log
  - Protocol violation/deviation log

QI Program provides electronic templates of the logs and checklists
http://www.partners.org/phsqi/ToolsPage.htm
Resources

International Conference of Harmonisation

Good Clinical Practice Guidelines (GCP)

- Originally intended as guidelines to help standardize international drug studies and speed up new drug approval process (1996)
- FDA has adopted GCP guidelines from ICH
- ICH Guidelines contain a detailed approach to “best practices”
ICH GCP Guidelines

Section 8 Essential documents for the conduct of a clinical trial

- These essential documents individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced
- Documents are the ones typically audited by sponsors and regulatory authorities
Resources

BIMO

- [http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm)

FDA Information Sheets

- [http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm)

Partners Quality Improvement (QI) Program

- [https://partnershealthcare-public.sharepoint.com/Pages/Human-Research-Quality-Improvement-%28QI%29.aspx](https://partnershealthcare-public.sharepoint.com/Pages/Human-Research-Quality-Improvement-%28QI%29.aspx)
Final Thoughts

Document, document, document!!

An ounce of prevention is worth a pound of cure!!