Preparing for and Responding to an FDA Inspection

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About Advarra

➢ North America’s premier provider of IRB, IBC, and global research compliance consulting services

➢ Leverage strengths in technology, regulatory expertise, and customer service to serve increasingly complex research needs
About Advarra

- Combined 60+ years of experience
- Access to over 2,400 unique institutional research sites
- Global consulting services
- The industry’s most comprehensive and efficient technology
About Today’s Presenters

Ellen Liedel-Sargent
Sr. Director, Advarra Consulting

➢ Over 22 years in the pharmaceutical industry
➢ Over 10 years in quality assurance
➢ Masters in Science, Regulatory Affairs, Quality Assurance
➢ BSN
About Today’s Presenters

Robert Romanchuk
Chairperson, Advarra IRB

➢ Over 20 years in IRB and clinical research operations
➢ BSHS, Clinical Research Administration
➢ CIP, CCRC, CRCP
Part I: The Bioreserach Monitoring Program (BIMO) Inspection Program
BIMO objectives

➢ To protect the rights, safety, and welfare of human research subjects

➢ To verify the accuracy, reliability, and integrity of clinical and non-clinical trial data submitted to the FDA

➢ To assess compliance with FDA’s regulations governing the conduct of clinical and non-clinical trials, including regulations for informed consent and ethical review
Inspection Triggers

➢ New drug application
  • 70% of inspections associated with new drug application (NDA)/biologics license application (BLA)

➢ Complaint ("for cause")
  • 30% of clinical investigator inspections follow a complaint

➢ Routine surveillance inspections
  • Concentration on institutional review boards (IRBs) and good laboratory practice (GLP) facilities
Inspection Findings

- No action indicated (NAI)
  - No objectionable conditions or practices

- Voluntary action indicated (VAI)
  - Objectionable conditions or practices
  - Not at threshold to recommend administrative or regulatory action

- Official action indicated (OAI)
  - Serious objectionable conditions found
  - Regulatory action recommended
About OAI

- Regulatory violations uncovered during the inspection is/are repeated, deliberate, and/or involve submission of false information to FDA or the sponsor in any required report.

- Regulatory violations are significant/serious and/or numerous, and the scope, severity, or pattern of violations support a finding that:
  - Subjects under the care of an investigator have been (or would be) exposed to an unreasonable and significant risk of illness or injury.
  - Subjects rights have been (or would be) seriously compromised.
  - Data integrity or reliability has been compromised.

[Link to FDA webpage](https://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133571.htm)
Current BIMO Metrics (2017)
Application-Inspections Overseen by OSI/OSIS* (CDER, FY 2008-FY 2017)

*Based on inspection start date—[Complis database as of December 29, 2017]
OSI = Office of Scientific Investigations; OSIS = Office of Study Integrity and Surveillance; CDER = Center for Drug Evaluation and Research
Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator; GCP = Good Clinical Practice
Bioequivalence (BEQ) Application-Inspections accomplished with 289 FY17 site visits
Good Laboratory Practice and Bioequivalence inspection programs operated by OSIS as of January 2015

Source: [www.fda.gov](http://www.fda.gov)
Referral-Related Clinical Investigator Inspections
(CDER, FY 2008-FY 2017)

*Based on inspection start date: Referrals include Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals—internal and external for All Branches [Complis database as of December 29, 2017]

Source: www.fda.gov
Clinical Investigator Inspections Final Classification
(CDER, FY 2017)

- No Action Indicated: 70%
- Voluntary Action Indicated: 28%
- Official Action Indicated: 2%

418 CI Inspections

Source: www.fda.gov
Part II: Preparing for an FDA Inspection
Objectives – Inspection Preparedness

- Physical set-up for conduction of an inspection
- Preparedness and completeness of study documentation
- Principal investigator (PI) oversight
- Appropriateness of site facilities and equipment
- Handling, storing, and dispensing of investigational product
- Interview skills
**Site Organizational Overview**

**Site process for inspection visits**

- Determine who is the inspection host—this person should be with the inspector at all times and during all interviews
- Greeting the inspector and credential requests
- Back room support and location—every document reviewed by the inspector should be copied and logged in an inspection log
- Inspection review area—quiet area away from traffic where inspector cannot overhear other conversations
- Copier and printer
- Investigational product and accountability logs
Site Organizational Overview

Organization and reporting relationships

- Organizational charts
- Evidence of PI oversight
- Systems for quality assurance (QA) and quality control (QC)
- Standard operating procedures (SOP) index and SOPs
- Staff qualification and training – GCP and regulatory training
- Number of clinical trials and their nature
- Proportion of time allocated to clinical trial work
- Curricula vitae (CVs) — current, showing affiliation with site(s)
- Medical licenses, as applicable
Study Documents

➢ Form FDA 1572 and financial disclosures
➢ Protocol and amendments
  • Timely approvals and signed protocol pages
  • Investigator’s brochure
  • Study manuals
➢ IRB approvals
  • Protocols and amendments
  • Informed consents
  • Recruiting material
  • Subject information material
➢ Complete source documentation
  • Past medical records, if appropriate
➢ Study specific training documentation

➢ Signed informed consents forms (ICFs)
  • Were all revisions signed at the first available opportunity?
➢ Delegation log—start and stop dates of performing tasks
➢ Screening and enrollment logs
  • Evidence as to why subjects screened failed
➢ Protocol deviations
  • Reported protocol deviations
  • Documented corrective actions
➢ Monitoring visit follow-up letters
  • Evidence that action items were addressed and followed to closure
Facilities

- Building security—facility diagram, if available
- Confidentiality—Health Insurance Portability and Accountability Act (HIPAA)
- Organization and neatness of facility
- Storage of study documentation
  - Security
  - Fire protection
- Electronic systems—controlled access
  - Medical records
  - Electronic case report forms (eCRFs)—timing of data entry, PI review of CRFs
- Study-related equipment and instruments—maintenance and calibration logs
- Investigational product (IP) management and storage
- Appropriate responses to ad hoc questions
Adverse Events

Adverse events
• Appropriate documentation—start, stop, severity, causality
• Assessment by investigator
• Capture of all medication and procedures for event

Serious adverse events
• All documentation of event and supporting documentation from time of event to closure of event
• Complete serious adverse event (SAE) forms
• Prompt reporting to IRB and sponsor
• Correlation of source documents with SAE form and CRF
• Determination of severity and causality by investigator
Investigational Product (IP)

- Full accountability logs—study level and subject level
- Environmental controls for storing and handling
- Evidence of investigator oversight—written order
- If no IP on site, be able to explain how IP was controlled
  - Who was responsible
  - Who dispensed
  - Who prepared
  - How this person was trained and kept up to date with the study progress
  - IP environmental controls
During a Regulatory Inspection

➢ Make sure your ID badge is visible, if applicable to your site
➢ When introducing yourself, state your name, your position, and the study you are responsible for
  • May also present a business card
➢ Be sure the inspection lead or another company representative is with you during the interview
  • An employee must never be alone with the investigator during an interview
➢ Provide the inspector with requested documents in a timely fashion
  • If there is a problem obtaining a document let the inspector know when the document can be obtained; it may be possible to provide the document post-inspection
**Interviews and Document Requests**

- **Provide requested documentation quickly and completely**
  - Be sure to mark as a copy and confidential
  - Be sure to make a copy of everything provided to inspector

- **Be prepared**
  - Know protocol, procedures, who did what
  - Have explanation for protocol deviations: why they occurred and actions taken to prevent future occurrences
  - Know total number and types of studies being conducted at the site
  - Determine who will interface with inspector
    - Principal investigator
    - Sub-investigator if performed most assessments
    - Main study coordinator

- **Interview room should be free from distractions**

- **Concisely answer only questions asked**
  - Be sure you understand the question, can ask for the question to be rephrased
  - If you do not know the answer, state that you will get back to the inspector with the information
    - The study coordinator should not answer questions directed to the PI
    - The PI should not defer questions to the study coordinator (SC)
  - Don’t answer questions outside your areas of responsibility
  - Do not volunteer information if it has not been requested
  - Correct inaccuracies but be nonconfrontational

- **Respect the silence**

- **Leave the room when questioning stops**
Things may be uncovered that were not per protocol or regulation
  • If mistakes were made, admit the mistake but demonstrate steps taken to ensure no reoccurrence

Obtain missing documentation from contract research organization (CRO) or sponsor if not on site but in the TMF

If something can be corrected, fix it immediately

Do not get defensive or point fingers to others

Do not back-fill in data

View the inspection as a learning experience
Part III: Responding to Forms FDA 483
General Guidance on Responding to a Form FDA 483

During the inspection

> “Investigators should make every reasonable effort to discuss all observations with management...as they are observed, or on a daily basis, to minimize surprises, errors, and misunderstanding when the FDA 483 is issued”

Investigations Operations Manual (IOM) 2018, section 5.2.3

- Confirm a daily debrief to respond immediately if possible
- Respond at exit interview
- If you disagree with any of the findings, state so with rationale and documentation
- Request a copy of the establishment inspection report (EIR)

> In order to have your responses considered in the final determination, your response must be submitted within 15 days
General Guidance on Responding to a Form FDA 483

**Overall style**

- Acknowledge accountability, assure compliance
- Avoid shifting blame or responsibility
- Stick to the facts
- Be specific
- Don’t make it personal
- Avoid negative comments regarding the field investigator
- Avoid soapboxes and high horses
- Demonstrate commitment
- We “will” rather than we “hope to” or “plan to”
Format

- Start with the citation
  - Restate in bold
- If you disagree, state so and provide supporting documentation or state position clearly
- If you agree—state so
- Identify root cause and apply corrective action/preventive action (CAPA) to each finding individually
  - Include milestones and timelines
- Close with a statement of commitment
- Attach new/revised SOPs, training records, other relevant documentation
Root Cause Analysis (RCA)

1. Define the problem clearly
2. Gather related documentation
3. Identify contributing factors
   - E.g., the “5 whys” method
4. Identify root cause
   - Focus on process, not person
5. Devise solutions to address root cause
   - E.g., process revisions, SOPs
Corrective Action, Preventive Action (CAPA)

Corrective action: an action to eliminate the cause of a **detected** nonconformity (fix it)
- Correction, documentation, notification
- Demonstrate reasonable steps to correct the deviation

Preventive action: an action to eliminate the cause of **potential** nonconformity (make it so it won’t happen again)
- Revision/creation of SOPs, process changes, retraining
- Include deliverables and timeline
- Include documentation of retraining
Follow Up

FDA response: “As a general rule, a Warning Letter should not be issued if the agency concludes that a firm’s corrective actions are adequate and that the violations that would have supported the letter have been corrected”

• A “closeout” letter (or a Warning Letter) will follow in up to 6 months
Exercise #1

- FDA inspector has completed inspection and issues a Form FDA 483 with the following finding:
  - The investigation was not conducted in accordance with the signed statement of investigator and investigational plan
    - Specifically, subject 990-01 screening lab revealed a liver function test (LFT) value significantly above the limit set by exclusion criteria #4
Exercise #1

Background

• Investigation reveals that the LFT was noted by the PI who assessed this as not-clinically-significant
• He phoned the medical monitor who gave the verbal OK to enroll
• No written documentation of this exists
Exercise #1

What will be your written response?

• Restate citation and finding
  - Acknowledge and agree
• Provide root cause(s)
  - Documentation of medical monitors response was not assured
  - Deviation from the protocol was undertaken without IRB approval and without clinical need
• Corrective action
  - Study is closed but the deviation was reported to the IRB
• Preventive action
  - SOP was revised to require documentation of such verbal correspondence
  - Training was undertaken and training log is attached
Exercise #2

A field investigator has completed his investigation and issued a Form FDA 483 with the following finding:

- Informed consent was not properly documented
  - Specifically, the IRB approval date for the informed consent form (ICF) and related correspondence documented the approval date as 4/13/14
  - The subject’s signature and source documentation record a signature date of 4/10/14
Exercise #2

Background

- The clinical research coordinator (CRC) conducted the informed consent (IC) discussion and obtained “verbal” consent but did not complete written documentation (i.e., obtain signatures) at the screening visit.

- At the next visit, the CRC obtained written consent using the newly distributed ICF approved on 4/13/14, but asked the subject to date it as 4/10/14 (i.e., “backdating”).
Exercise #2

What will be your written response?

• Restate citation and finding
  - Acknowledge and agree with finding
• Provide root cause(s)
  - The CRC conducted the IC discussion and obtained verbal consent but did not complete written documentation (obtain signatures) at the screening visit
  - At the next visit the CRC obtained written consent using the newly distributed ICF approved on 4/13/14, but asked the subject to date it as 4/10/14
• Corrective action
  - Study is closed but the deviation was reported to the IRB
  - The subject was informed of the event and invited to respond
• Preventive action
  - CRC and all staff were retrained on appropriate documentation of IC and attributable, legible, contemporaneous, original, and accurate (ALCOA) practices
  - CRC is being monitored during all consent discussions and will not resume independent IC discussions until compliance is assured
  - Training log is attached
A field investigator has completed his investigation and issued a Form FDA 483 with the following finding:

- You failed to prepare or maintain adequate and accurate case histories
  - Specifically, you documented that you assessed 4 subjects during study visits on 4 dates that, according to your staff and clinic schedule, you were out of town or otherwise not available as follows
Exercise #3

Background

• Investigation reveals that the PI was indeed not available on the dates listed but had delegated the ICF to a CRC
• Upon return to the office some time later, when presented with a stack of papers to sign, he dated the ICF on the same date as the CRC
Exercise #3

What will be your written response?
• Restate citation and finding
  - State agreement with the finding
• Provide root cause(s)
  - The PI inadvertently signed the ICF assuming he had reviewed and approved the subject’s enrollment and incorrectly entered the date of enrollment
• Corrective action
  - A note to file was included in the study files to document the error
  - The matter was reported to the IRB
• Preventive action
  - The PI and all staff were retrained on appropriate documentation of IC and ALCOA practices
• Training log and delegation of authority log are attached
FDA inspections are inevitable for sites planning to conduct research for up to 5 years or longer

Well-prepared investigators/sites decrease their likelihood of receiving a Form FDA 483

The response to findings, not the findings themselves, often determine whether a warning letter will follow
Resources

- Regulatory Procedures Manual

- FDA Investigations Operations Manual (IOM)
  - https://www.fda.gov/ICECI/Inspections/IOM/default.htm

- BIMO CPGM-Clinical Investigator Inspections
  - https://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133571.htm
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IRB Inspections Final Classification*

Includes 2 RDRC (VAI)

- NAI: 77%
- VAI: 21%
- OAI: 2%

n= 124*

*Inspections classified in FY17 by all Centers with jurisdiction over studies involving human subjects. Some inspections may have occurred in a different FY.

Source: www.fda.gov
Common IRB Deficiencies

- Inadequate initial and/or continuing review
- Inadequate written procedures
- Inadequate meeting minutes, membership rosters
- Quorum issues
- Prompt reporting of non-compliance, suspension or termination
- Subpart D deficiencies
- Lack of or incorrect SR/NSR determinations

Source: www.fda.gov
Sponsor/Monitor/CRO Final Classification

- NAI: 64%
- VAI: 30%
- OAI: 6%

n = 104*

*Inspections classified in FY 17 by CBER, CDER and CDRH. Some inspections may have occurred in a different FY. Includes Sponsor-Investigator inspections.

Source: www.fda.gov
Common S/M/CRO Deficiencies

- Inadequate monitoring
- Failure to bring investigators to compliance
- Inadequate accountability for the investigational product
- Failure to obtain FDA and/or IRB approval prior to study initiation.

Source: www.fda.gov
GLP Final Classification

- NAI: 65%
- VAI: 35%
- OAI: 0%

n = 34*

*Inspections classified in FY17 by CDER and CDRH. Some inspections may have occurred in a different FY.

Source: www.fda.gov
Common GLP Deficiencies

- Organizational and/or Personnel inadequacies
- Incomplete/inadequate/no study records
- Inadequate archiving
- Inadequate/no SOPs
- Protocol deviations