# FDA Inspections: What to Expect when you're about to be Inspected

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# Learning Objectives

Why you're here:

*To learn about FDA inspections of Johns Hopkins Investigators and Sponsor-Investigators using Investigational New Drugs (INDs) or Investigational Device Exemptions (IDEs)*

- ✓ Types of inspections and frequency
- ✓ What FDA inspectors review
- ✓ Preparation strategies
- ✓ What are the outcomes of the inspections
- ✓ The Compliance Monitoring Program: a resource for PIs and study staff

# FDA Inspections: Purpose and Scope

- The FDA's Office of Regulatory Affairs (ORA) under the Bioresearch Monitoring (BIMO) program, ensures

  *"the protection of the rights, safety, and welfare of human research subjects involved in FDA-regulated clinical studies..."*

- BIMO is authorized by law to inspect

  *"...clinical investigators, sponsors, sponsor-investigators, monitors, contract research organizations (CROs), institutional review boards (IRBs), [etc.]"*

- FDA "regulated research" means that an investigation is subject to applicable FDA regulations (laws) when using an investigational drug, device, or biologic:
  - ➢ 21 CFR 312 (IND) – includes drugs and biologics
  - ➢ 21 CFR 812 (IDE) – for investigational devices

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# FDA Inspections of Research: Primary Terms

- IND – "Investigational New Drug"
- IDE – "Investigational Device Exemption"
- CI – "Clinical Investigator" (the principle investigator); the person who carries out the clinical investigation
- Sponsor – "[a person or company] who initiates the clinical investigation"' the "holder of the IND or IDE"
- Sponsor-Investigator – "a person who both initiates and conducts the clinical investigation"; the person responsible for all associated regulatory requirements
- Form FDA 1571 – The IND application (also for supplemental submissions)
- Form FDA 1572 – The Statement of the Investigator

# Types of FDA Inspections for PIs

- "For cause":
  - ✓ When FDA receives a complaint or report of non-compliance or serious safety incidents
  - ✓ When a study sponsor identifies an investigator that
- "Routine Records":
  - ✓ When a New Drug Application (NDA) is submitted to FDA (after a study has been concluded)
  - ✓ Often high enrolling or high profile sites will be selected for inspections
- Typically, at Johns Hopkins, FDA inspections are "routine," and occur on average 2-3 per year

# FDA Inspection Basics – Before the Visit

1. You receive notification from FDA (e.g., an email from FDA or the sponsor)

2. Notify the IRB (CMP), sponsor, and IDS

3. Once scheduled, begin site preparation

    a. Regulatory Record (e.g., IRB approvals, informed consent, safety reports to the IRB, study personnel documentation, etc.)

    b. Research Record (e.g., executed consents, data, source documentation (EMR), notes-to-file, etc.)

    c. FDA Record (e.g., 1572s, 1571s, IND Safety letters, IP accountability, monitoring reports, etc.)

4. Set aside work-space for the inspector

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# FDA Inspection Basics: During the Inspection

1. Day 1: The arrival of the inspector:
   a. CMP confirms inspector credentials and reviews the Notice of Inspection (FDA Form 482)
   b. Introductions
   c. Short presentation of study background, progress, and status

2. Day 1+
   a. The inspector may ask for a list of all FDA regulated studies of the PI
   b. Provide the inspector and all requested study materials
   c. For source documents/data review (do not give the inspector unproctored access to EPIC; print or provide "over the shoulder" access)

# FDA Inspection Basics: Interacting with the Inspector

How to interact with the inspector:

1. Be honest and transparent
2. Do not "give away the farm"
   a. Answer only questions that are asked
   b. Do not volunteer information about other studies or PIs
3. Do not accept from or provide any gifts to (including lunches) the FDA inspector
4. Any questions you have or inquiries from the inspector you are unsure about contact
   a. Clemmie Miller (cmill116@jhmi.edu)
   b. Fred Luthardt (fluthar1@jhmi.edu)
5. Feel free to update the CMP representative throughout the inspection

# FDA Routine Records Inspection: What they look for ...

- Delegation of authority documentation and supporting information (CVs)
- Informed consent process and documentation confirmation
- IRB communication and approvals
- Verification of compliance with the IRB approved protocol

## ...What they find

- Out-dated/inconsistent accounting for study-team members
- Inadequate research documentation or inadequate verification with source documentation/data (from EPIC)
- Deficient in maintaining "adequate and accurate case histories" [research records]

# Site Documentation: Regulatory Checklist

- ✓ All regulatory documentation (e.g., IRB approvals; IRB approved materials, such as IBs, consents, recruitment materials; DSMB reports, acknowledgments from event reports, etc.)
- ✓ All FDA documentation for your site (e.g., FDA Forms 1572, 3454, etc.); you can include sponsor communication/correspondence here, too.
- ✓ Prepare a list of FDA regulated research conducted by the PI, if asked by the FDA inspector.
- ✓ Study Team documentation (e.g., your CV and license, delegation of authority log, other licenses/certifications for study team members, etc.)
- ✓ Study article (IND Drug or IDE Device) accountability records (i.e., documentation demonstrating control of the product, lot #s and expirations dates; chain-of-custody; receipts; dispensing records; IDS information, if they're managing the product, etc.)
- ✓ Notify the IDS if the IND product is being managed by them, as necessary, to request records and to notify them if the FDA inspector plans to visit
- ✓ Monitoring reports (and reconciliation documentation) from the sponsor's monitors
- ✓ Participant Enrollment/Screening log

# Site Documentation: Research Record

- ✓ Signed and dated Informed Consent Forms
- ✓ Eligibility assessments (plus source documentation/data, where necessary)
- ✓ Data (Case Report Forms, databases) and supporting source data/documentation, if necessary, for verification/validation and demonstration of protocol compliance
- ✓ Adverse Event and protocol deviation logs
- ✓ Notes-to-File regarding issues or conduct/performance issues related to each participant's time in the study

# FDA Inspection Basics: After the Inspection

1. Notify the CMP representative about the close-out meeting
2. Log any copies provided to the inspector
3. If a FDA 483 (for actionable observations) is issued, contact the CMP for how to proceed
4. Once received (in approx. 30 days), please forward the "Establishment Inspection Report" to the CMP
5. If a *Warning Letter* is issued, contact the CMP for further instructions.

# Outcomes of FDA Inspections

- <u>No observations</u>
- <u>Form FDA 483</u>: Inspector observations indicating incidents of non-compliance with FDA regulations
- <u>Warning Letter</u>: Issued by FDA that identifies major regulatory violations, which further requires corrective actions and may result in "enforcement actions"
- Inspection Results:
  - ✓NAI – "No Action(s) Indicated"
  - ✓VAI – "Voluntary Action(s) Indicated"
  - ✓OAI – "Official Actions Indicated"
- <u>EIR</u> – "Establishment Inspection Report" is a final letter from FDA that presents a full narrative of what occurred during an FDA inspection

# FDA Inspections and the Compliance Monitoring Program

- The CMP is responsible for reviewing
  - ✓ The ID/credentials of the FDA inspectors
  - ✓ The Form FDA 482 "Notice of Inspection"

- The CMP is able to assist with
  - ✓ Preparation and organization strategies for regulatory and research record documentation
  - ✓ Advising investigators and study team members on interacting with the FDA inspector(s)
  - ✓ Coordinating response(s) to FDA, with other IRB entities (e.g., Compliance)
  - ✓ Corrective action plans (CAPs) before or after an inspection

# FDA Inspections: Additional Points

- The inspector will not go through eIRB
- Work with your study sponsor for specific preparation activities, but note the sponsor must not engage or interfere with the Inspector
- Keep a log of documents that are copied for and collected by the inspector
- Even corrected problems can result in a 483 or Warning Letter
- Source documentation/data from EPIC can be printed, reviewed "over the shoulder," or via accessed via CareLink ("technically")

# FDA Inspections: Questions and Contacts

- Thank You!
- Contact Information:
  - Fred Luthardt: fluthar1@jhmi.edu
  - Suzanna Roettger: sroettg1@jhmi.edu
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