Walkthrough of an FDA Clinical Investigator Site Inspection

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Poll Question

How many times has your facility been inspected by the FDA?

- Never
- Once
- 2-5 times
- More than 5 times

The objectives of FDA's BIMO Program:

- **To protect** the rights, safety, and welfare of human research subjects
- **To verify** the accuracy, reliability, and integrity of clinical and non-clinical trials data submitted to FDA
- **To assess compliance** with FDA's regulations governing the conduct of clinical and non-clinical trials, including those for informed consent and ethical review

OVERVIEW

- Inspection Preannouncement
- Opening Meeting
- Facility Tour/Equipment Overview
- Record Review
- Common Form FDA-483 Observations
- Closeout Meeting
- Updated Guidance Documents

Preannouncement

- Most inspections are pre-announced (however it is not an FDA requirement)
  - Investigator and key study personnel should be available
  - Original source documents available
  - When there are concerns of study integrity or allegations of fraud an inspection may not be pre-announced

- A Sponsor may send a representative to be present
  - The inspection is of the study site NOT the Sponsor
  - Study records and information are expected to be provided by the study site.

Preannouncement - What to Expect

- The FDA Investigator will preannounce up to five business days prior and inform the site of:
  - Explanation of the purpose/scope
  - Protocol to be covered
  - Records to be reviewed
  - Time commitments and need for workspace and record access (if electronic medical records, accompanying personnel to navigate)

Opening Interview

- FDA Investigator will present credentials and issue Form FDA-482
- The interview can consist of:
  - An overview of the FDA inspectional process
  - Clinical Investigator's overview of the study at the site
  - Any significant protocol deviations, SAEs, UADEs, etc.
  - Request for a list of studies conducted by the investigator (to include application number (if known), IRB, and sponsor)

Clinical Investigator Inspections

Typically 3-7 days to audit one study. The time will vary depending on:

- the number of studies
- the number subjects
- the amount of data to be verified
- specific requirements in the assignment
- organization of the study files
- the ability of the site to provide requested copies and information
- availability of CI and staff to address any questions or concerns

What is covered during the inspection?

Inspections of Clinical Investigators include review and assessment of:

- Facilities & equipment
- Regulatory/administrative documents
- Subject case histories and case report forms
- Test article accountability records

Facilities and Equipment

To determine the adequacy of the clinical site the FDA Investigator will ask for a tour and note:

- Number of exam rooms
- Space for laboratory equipment and conduct of procedures
- Storage of investigational product
  - Access/security
  - Temperature monitoring devices
  - Separation of investigational product by study

Review of Regulatory Records

The following should be available for review:

- Protocol (and amendments, if applicable) on site
- IRB correspondence and approval of:
  - Investigator
  - Original protocol and amendments
  - Informed consent forms
  - Recruitment materials, etc.
- Sponsor Correspondence
  - E-mail communication, newsletters

Regulatory Records [cont.]

- Monitoring reports
- Statement of Investigator (FDA-1572)/Investigator Agreement
- Financial Disclosure Forms
- All informed consent forms used during the study
- Staff resumes/curricula vitae/licenses
- Training records
- Laboratory Certifications and reference values

Investigator Responsibilities

- Investigators who conduct clinical investigations under 21 CFR Part 312 and/or 21 CFR Part 812, commit themselves to personally conduct or supervise the investigation ensuring:
    - Initial and continuing IRB approval
    - Informed consent is obtained per 21 CFR Part 50
    - The study is conducted in accordance with the protocol
    - Control of the investigational product
    - Accurate, complete, and current case histories are maintained
- The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

What Is Appropriate Delegation of Study-Related Tasks?

- A qualified physician should be responsible for all study-related medical decisions and care.
- Licensure vs. Protocol requirements
- Clinical / Medical Judgment – (*i.e.,* global assessments, adverse events)
- Examples of Inappropriate Delegation:
  - Screening (Medical Histories & Eligibility)
  - Physical Exams
  - Adverse Event Evaluation/Classification
  - Assessments of Study Endpoints
  - Obtaining Informed Consent

Delegation of Significant Study Tasks

- Documentation should be maintained describing:
  - Task to be performed
  - Individual assigned to the task
  - Dates these tasks are assigned (start/stop)
  - Training received to qualify individual to perform assigned tasks.

Review of Subject Case Histories

Records for all subjects enrolled should be available for the FDA Investigator to assess:

- Documentation of each subject's informed consent prior to the conduct of study procedures
- Clinical Investigator's compliance with inclusion/exclusion criteria
  - Medical history, laboratory results, study specific tests, etc.
- Compliance with protocol specific tests, dosing of enrolled subjects, use of concomitant meds

Review of Subject Case Histories

- Documentation of adverse events and reporting of serious adverse events, when appropriate
- Clinical Investigator oversight
- Data validation
  - If sponsor-provided data is included for verification, the FDA investigator will compare the data to original case histories
    - Primary efficacy endpoints, safety endpoints, adverse events, etc.

Subject Selection

- It is typical to audit a sufficient number of subjects enrolled from the beginning, middle, and end to provide indicator of compliance
- The total may vary considerably based on the nature of the study and health profile of the target population (sicker subjects = more AEs/concomitant meds)
- The depth of coverage can vary once engaged in comprehensive reviews of enough subjects' files to get a sense of compliance.

Statement of Investigator FDA-1572

- Sponsors are required to collect the 1572 from investigators; however, FDA does not require the form to be submitted to the agency.
- FDA 1572's are only required prior to the first shipment from the Sponsor. They do not have to be resubmitted for changes to sub-investigators, laboratories, etc.
- Each co-investigator (responsible for fulfilling all of the obligations of an investigator) must sign a separate 1572.
- Individuals who make direct and significant contributions to the study data should be listed as sub-investigators.
- Must be maintained on file at the site
- An Investigator Agreement will be found in the conduct of device studies

Common FDA 483 Deficiencies

- Failure to follow investigational plan
  - e.g. subject eligibility, protocol-specified tests/assessments performed at the prescribed intervals and reported accurately, inappropriate delegation as a failure to conduct/supervise, etc.
- Failure to prepare or Maintain Adequate or Accurate Case Histories
  - including Adverse Events (*i.e.,* any deviation from baseline, hospitalizations, etc.)

Common Observations [cont.]

- Inadequate investigational product disposition records
- Failure to obtain informed consent or informed consent improperly documented
- Failure to report to the IRB unanticipated problems involving risk to human subjects

Closeout meeting:

- FDA investigator will summarize what was covered during the inspection
- Form FDA 483, if appropriate, will be issued
  - Voluntary written response to be submitted within 15 business days (name & address will be provided)
- Discussion of verbal observations
- Discuss potential actions
- Explanation of review process and classification letter

When the inspection is over…

- Respond to the Form FDA 483 within 15 business days
- Begin implementing corrective actions
- Wait patiently to receive a copy of the report

In Summary…

- Follow your investigational plan
- Document, document, document (if it's not documented…)
- Don't wait for FDA to show up to your site to get ready for an inspection
- Provide the FDA investigator with the required records to complete their inspection and be cooperative

Resources

Places to go for answers:

FDA - GCP start page: **www.fda.gov/gcp**

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

Information Sheets:

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219433.htm

Bioresearch Monitoring Information page:

http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm

Guidance for Industry

Investigator Responsibilities
Protecting the Rights, Safety, and Welfare of Study Subjects

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

Bioresearch Monitoring Compliance Programs

https://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograMManual/ucm255614.htm

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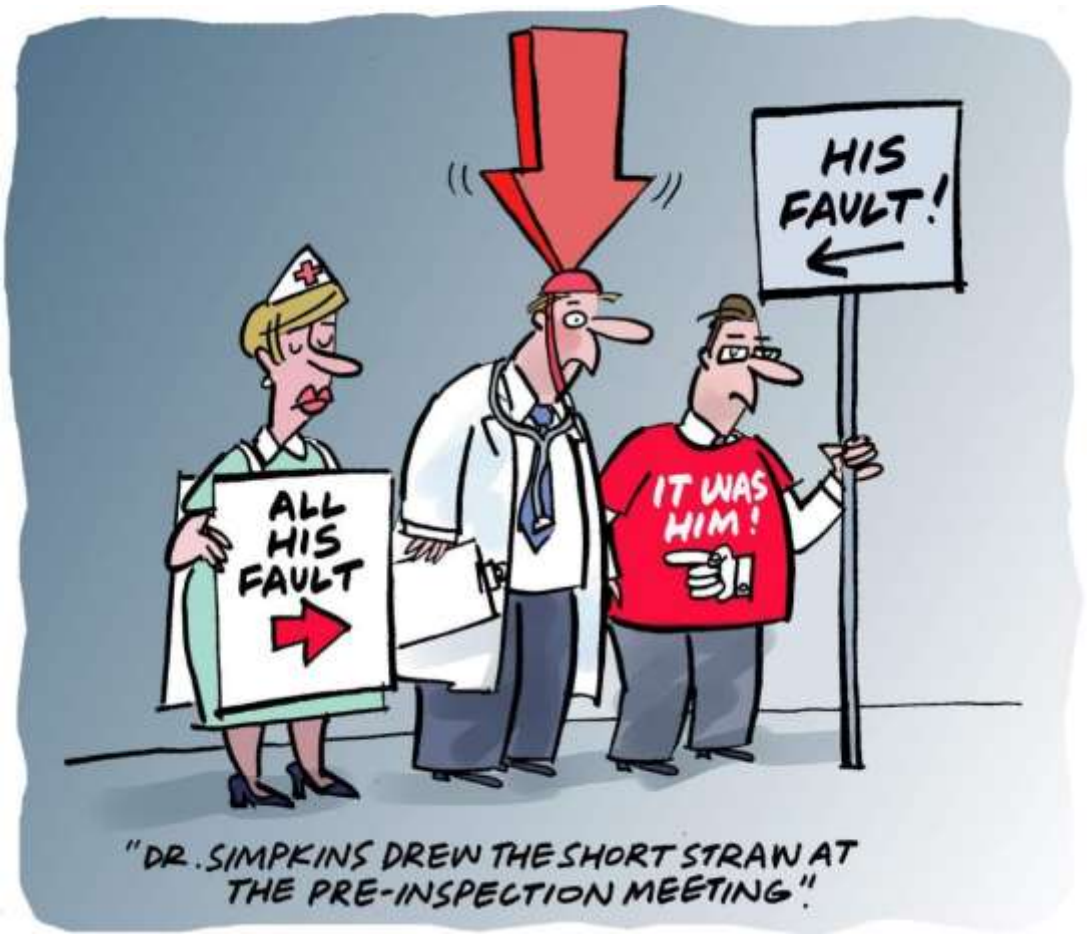
Questions?



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