Walkthrough of an FDA Inspection

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The objectives of FDA's BIMO Program:

- **To protect** the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials
- **To verify** the accuracy & reliability of clinical trial data submitted to FDA in support of research or marketing applications
- **To assess compliance** with FDA's regulations governing the conduct of clinical trials.

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
- The 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 EMRs, accompanying personnel to navigate)

Opening Interview

- FDA Investigator will present credentials and issue Form FDA-482
- The interview can consist of:
  - Clinical Investigator's overview of the study at the site
  - Any significant protocol deviations
  - Overview of FDA inspectional process
  - 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 of your facility 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 IP by study

Review of Regulatory Records

The following should be available for review:

- Protocol (and amendments, if applicable)
- IRB correspondence and approvals 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 21 CFR Part 812, commit themselves to personally conduct or supervise the investigation and ensuring:
  - Informed consent is obtained in accordance with 21 CFR 50.20
  - The study is conducted in accordance with protocol
  - Control of the investigational product
  - Initial and continuing IRB approval
  - 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, administration of the test article, use of concomitant meds

Review of Subject Case Histories

- Documentation of adverse events and reporting of serious adverse events, when appropriate
- Clinical Investigator oversight
- Validity of study data
  - If sponsor-provided data is provided 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 for an FDA investigator to audit a sufficient number of subjects enrolled from the beginning, middle, and end
- The total number may vary considerably based on the nature of the study and health profile of the target population
- The depth of coverage can vary once engaged in comprehensive reviews of enough subjects' files to get a sense of compliance

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, investigational accountability/dosing records

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

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

“General Responsibilities”

Guidance for Industry

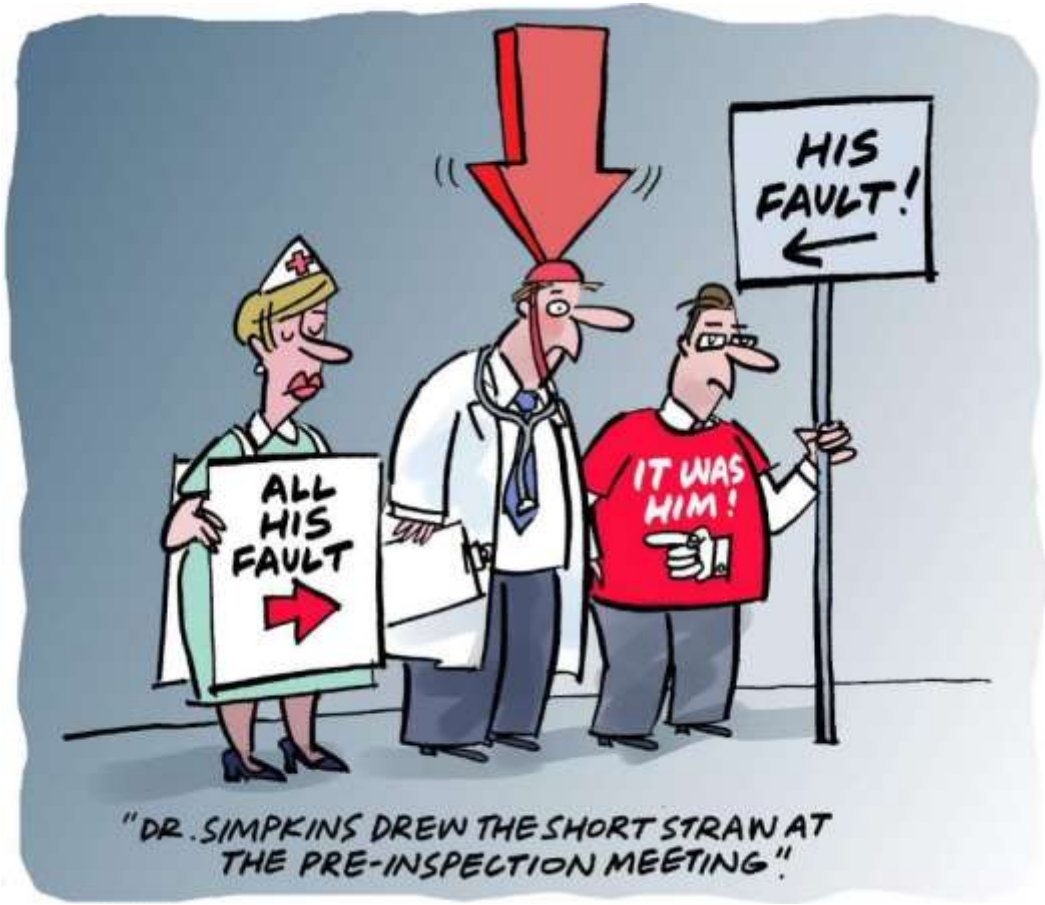
Investigator Responsibilities
Protecting the Rights, Safety, and Welfare of Study Subjects

Draft – May 2007

Final – October 2009

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

Questions?



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