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The Inns and Outs of a FDA Audit

Jeri and Noboru Oishi Symposium & Continuing Education Workshop

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OBJECTIVES

- Understand the federal regulations which involve Clinical Investigators and Clinical Investigator responsibilities.
- Understand how FDA prepares for a Clinical Investigator Inspection.
- Understand what to expect during and after an FDA inspection.
- Identify specific problems seen during recent FDA inspections at clinical sites.

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Careful inspection planning is the key to getting complete information concerning clinical trial conduct

Frances Kelsey, PhD, MD receiving the President's Award for Distinguished Federal Service from President Kennedy 1962, the same year as the passage of the Kefauver Harris Amendment to the FD&C Act.

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What is Bioresearch Monitoring (BIMO)?

- **On-site inspection** by FDA/Office of Regulatory Affairs to evaluate for subject protection, data verification, compliance
- **Compliance Program Guidance Manuals (CPGM)**

http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm

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FDA GCP Regulations

Inspections apply to:	**FDA regulated CLINICAL and non-clinical research**
Regulatory oversight	**Institutional Review Boards (IRBs), Sponsors, CROs/Monitors, Clinical Investigators**
Relevant Regulations include (but not limited to)	**21 CFR** **•Part 50: Protection of Human Subjects** **•Part 54: Financial Disclosure** **•Part 56: Institutional Review Boards (IRB)** **•Part 312: Investigational New Drugs (IND)** **•Part 314: New Drug Applications (NDA)** **•Part 511: New Animal Drugs** **•Part 812: Investigational Device Exemption (IDE)** **•Part 814: Pre-Market Approval Applications (PMA)**

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Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf

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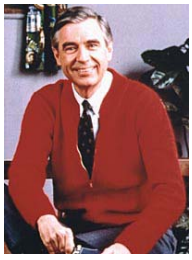
Regulation and Guidance



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Clinical Investigation

- Any experiment in which a drug is administered to human subjects. An experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.
  - 21 CFR 312.3

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Clinical Investigator (CI)

- The individual who actually conducts the clinical investigation
  - 21 CFR 312.3
  - 21 CFR 812.3(i)

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CI Responsibilities

- Responsible for overall conduct of the study at the study site (21 CFR 312.60), including
  - Directing administration or dispensing of test article
  - Ensuring that data are collected and maintained in accordance with the protocol and regulatory requirements

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CI Responsibilities

- Follow the approved protocol or investigational plan.
- Obtain Informed Consent prior to conducting any study-related procedures.
- Maintain adequate and accurate records.
  - 21 CFR 312.62

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CI Responsibilities

- Administer test article only to subjects under control of the Investigator.
- Ensure Adverse Events are appropriately reported.
- Ensure adequate Investigational Review Board (IRB) review.

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CI Responsibilities

- Investigator Agreement
- Statement of Investigator (Form 1572)
- Financial Disclosure
  - 21 CFR 54

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Sponsor-Investigator

- The individual who initiates and also conducts the clinical investigation
- Must comply with regulatory requirements applicable to both sponsors and clinical investigators
  - 21 CFR 312.3
  - 21 CFR 812.3(o)

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FDA INSPECTION

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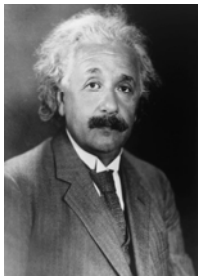
Science and Regulation



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Who conducts the inspection?

- Each FDA Center (CDER, CBER, CDRH, etc.) oversees inspections of research related to the product it regulates.
- Inspections are conducted by FDA field investigators from Office of Regulatory Affairs (ORA).

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How does FDA choose Studies and Sites

- Prioritize important studies
- Is any site "driving" the results
- Safety questions
- Imbalance or outlier in an important attribute-can be too many or too few
- Clinical investigator history
- Regional or country diversity

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TYPES OF FDA INSPECTIONS

- Routine:
  - New Drug/New Animal Drug Applications (NDAs/NADAs) (drugs)
  - Pre-Market Applications (PMAs) (devices)
  - Surveillance

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TYPES OF FDA INSPECTIONS

- Directed:
  - Investigate problems that have been identified at the Investigational New Drug (IND) or Investigational Device Exemption (IDE) stage.
  - Investigate complaints that have been reported to the FDA
  - Compliance follow-up for previous deficiencies.

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For-cause inspection

- Investigate the allegation
- Lack of oversight of study
- Not following protocol
- Inadequate monitoring
- Allegations of falsification create especially challenging inspections

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FDA INSPECTION

Inspection Scope:

- Were the rights, safety and welfare of research subjects protected?
- Were the quality, reliability, and integrity of data ensured?
  - Anticipated and unanticipated adverse events
  - Test article accountability records
  - Study monitoring

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FDA inspection
Pre-announcement – when would be a good time for you?

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FDA INSPECTION

The FDA Investigator:

- Pre-announces inspection unless otherwise instructed in the inspection assignment
- Shows FDA credentials to the most responsible person (CI)
- Issues a Form FDA 482 “Notice of Inspection” to the most responsible person;
  - Explains why FDA is there and what records and documents will be reviewed.

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HOW TO PREPARE FOR AN FDA INSPECTION

When the FDA Investigator calls:

- Be sure you understand the specific study that will be inspected.
- The FDA Investigator will tell you what records will be needed.
- The FDA Investigator will tell you how much time will be needed with the CI and/or other study staff.

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HOW TO PREPARE FOR AN FDA INSPECTION

- Have ALL records related to the study available, including:
  - Regulatory records – IRB approvals, protocols, investigator brochure, correspondence
  - Case Report Forms (CRFs), monitoring reports
  - Source records
    - clinic charts, hospital records, x-rays, lab reports, subjects diaries
  - Test article accountability records

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HOW TO PREPARE FOR AN FDA INSPECTION

- Be sure the CI and study staff will be available.
- Reserve a place for the FDA Investigator to work.
- Get the name and phone number of the FDA Investigator.
- Provide specific and clear directions to your site.

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Tips for Successful Study

- Select qualified study personnel
  - Training and GCP experience
  - Provide adequate training up front
  - Stress importance of informed consent process
  - Obtain feedback on protocol requirements

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Tips for Successful Study

- Adopt a “quality system” approach to your study
  - Ensure adequate monitoring
  - Perform routine internal audits
    - Ensure current documentation is used
    - Review clinical data for accuracy
    - Look for unreported and unanticipated adverse events
    - File deviation reports for protocol/regulatory violations
    - Ensure staff understand their responsibilities
    - Hire/train responsible clinical coordinator

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Tips for Successful Study

- Keep files organized at all times.
- Keep ALL correspondence – sponsor, IRB, monitors, study subjects.
  - letters, faxes, e-mails, memos, phone contacts.
- Keep all test article accountability records:
  - Shipping receipts, enrollment logs, dispensing logs.

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Tips for Successful Study

- Know your IRB's requirements.
- Know the sponsor's Adverse Event reporting requirements.
- Know the protocol:
  - Inclusion/exclusion criteria, study windows, study procedures.
- Know each study staff member's roles and responsibilities

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Tips for Successful Study

- Have written procedures:
  - Standard Operating Procedures(SOPs), Quality Policy, training procedures, job descriptions.
- Have a Corrective and Preventive Action Plan.

DOCUMENT!!!

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Inspection Day

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FDA Inspection Procedures

- Show credentials & issue Notice of Inspection
- Investigator asks questions
- Review procedures and records
- Ask more questions
- Schedule close-out meeting
- Discuss findings most responsible person

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FDA Inspection Procedures

- Have most responsible person present at start
- Allow time for opening meeting
- Provide space to work
- Provide access to files and someone who knows where things are in the files
- Provide access or person for copies requested
- Be reachable during the day
- Be available at end of each day for wrap up

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FDA Inspection Procedures

- Inspection of site to “re-create” the trial
- Verification of data submitted to FDA

Source ➡ CRF ➡ Data submitted to FDA

- Human subject protection: IRB review and Consenting process
- Protocol adherence
- Safety reporting

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FDA Inspection Procedures

- What type/how were subjects recruited, enrolled and randomized
- Did the study involve blinded and unblinded staff?
- Who had access to treatment assignment and in what situations?
  - Study staff, pharmacist
  - CRO, Sponsor or other third party

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FDA Inspection Procedures

- **Source documents: what are they?**
  - **“First put pen to paper”**
  - **ALCOA-accurate, legible, contemporaneous, original, attributable**
  - **May be defined in protocol**

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FDA Inspection Procedures

- The FDA Investigator will ask some general questions of the study staff and the CI.
- The bulk of the inspection will involve the FDA Investigator reviewing records.
- Photocopies of some records will be requested.
- Federal regulations allow the FDA to inspect and copy ALL records relating to a clinical investigation.

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FDA Inspection Procedures

- Review of the following
  - Authority and Administration for Studies
  - Protocol
  - IRB
  - Human Subjects' Records
    - Informed Consent
    - Source Documents
    - CRFs

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FDA Inspection Procedures

- Review of the following
  - Other Study Records
  - Financial Disclosure
  - Electronic Records
  - Test Article Control
  - Records Custody and Retention
  - Reports to Sponsor
  - Monitoring

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FDA Inspection Procedures

- Study Files
  - Study protocol
  - Consent form(s)
  - Investigational Brochure
  - Adverse event reports
  - Any advertising
  - All correspondence to/from – CI, IRB, and sponsor

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FDA Inspection Procedures

- The FDA Investigator will schedule a close-out meeting with the most responsible person.
  - Daily and at end of inspection.
- The site inspected may receive a Form FDA-483, ”Inspectional Observations”.
- Observations may also be presented orally.
- The site may discuss all observations and issues with the FDA Investigator at the time of the close-out.

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FDA Inspection Procedures

- Any deficiencies or observations found during the inspection will be discussed during the inspection and at the close-out.
- The CI or Study Coordinator should be available to answer questions and to provide records during the inspection.

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Definitions

- Violation-not being in compliance with the regulation
- Observation-finding during inspection that may be violation pending FDA Center review
- Form FDA 483-Inspectional Observations issued when violations are noted
- EIR-Establishment Inspection Report describing findings of inspection
- CIS-Clinical Inspection Summary

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Post Inspectional Process at FDA

- Write Establishment Inspection Report (EIR)
- Submit to HQ for evaluation
- HQ usually issues post-inspection letter to IRB/institution
- Copy of EIR issues to IRB from district when process is complete

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Post Inspectional Process at FDA

- The Principal Investigator should respond to the 483 observations in writing.
  - **WITHIN 15 DAYS**
- The study site should take corrective actions for any deficiencies, if possible.
- Provide documentation of the corrective and preventive actions with the response.

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Post Inspectional Process at FDA

- The FDA Investigator will write an Establishment Inspection Report (EIR) that contains all the information collected during the inspection, including attachments and exhibits.
- This report is forwarded to the Center that issued the assignment for review and final classification.

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Form FDA-483 "Inspectional Observations"

- Significant deviations from Regulations.
- Observations are based only on the FDA Investigator's review of available records and information during the FDA inspection.

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Inspection Classifications

- **NAI-No action Indicated**
  - No objectionable conditions or practices
- **VAI-Voluntary Action Indicated**
  - Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any further actions
- **OAI-Official Action Indicated**
  - Serious objectionable conditions warranting action (advisory, administrative, or judicial)

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Inspection Classifications Examples

- NAI: following the protocol
- VAI: assessments not completed appropriately
- OAI:
  - assessments not conducted AND the records are falsified to cover this up
  - Repeated or deliberate failure to comply with the regulations

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Inspection Classifications Examples

- OAI:
  - Falsification of data
  - Lab test inadequate to determine prohibited medication
  - Electronic Data Capture for Patient Reported Outcomes
  - Procedures inadequate to accomplish task

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Post Inspectional Process at FDA

- The inspected site will receive a copy of the EIR after the inspection is classified.
- The assigning Center will send a follow-up letter to the CI.

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FDA Actions

- Possible consequences:
  - Untitled Letters
  - Warning Letters
  - Notice of Disqualification Proceeding and Opportunity to Explain (NIDPOE)
  - Rejection of the study
  - Prosecution

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FDA Actions

- Stop or suspension
  - Investigator Disqualification 21 CFR 312.70
    - Repeated and deliberate failure to comply with the requirements
    - FDA provides notice of matter to investigator and provides opportunity to explain (informal hearing)
    - Opportunity for formal hearing
    - May result in ineligibility to receive investigational drugs

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Warning Letters

- http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

FDA Debarment List

http://www.fda.gov/iceci/enforcementactions/fdadebarmentlist/default.htm

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Outcomes of FDA Inspections

- Acceptance or rejection of study data
- Product approval or complete response to sponsor
- Letter or Warning Letter or Enforcement Action (Disqualification Proceedings) for Clinical Investigator
- Results posted on Clinical Investigator Inspection List (CLIIL), updated quarterly
- Education of study site

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BIMO CI Domestic Inspections Classified FY2014

- Center
  - CBER 109
  - CDER 472
  - CDRH 203
  - CFSAN 1
- Total 785

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BIMO CI Domestic Inspections Classified FY2014

- NAI 57%
- VAI 38%
- OAI 5%

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Most Common CI Domestic Deficiencies

- Failure to follow the investigational plan
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with IRB
- Inadequate subject protection – failure to report Adverse Events (AEs) and informed consent issues

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BIMO CI International Inspections Classified FY2014

- Center
  - CBER 22
  - CDER 116
  - CDRH 17
- Total 155

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BIMO CI International Inspections Classified FY2014

- NAI 57%
- VAI 40%
- OAI 3%

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Most Common CI International Deficiencies

- Protocol deviations
- Inadequate accountability for the investigational product
- Inadequate subject protection – failure to report Adverse Events (AEs) and informed consent issues

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Final thoughts…

- *Have procedures for what you do*
- *Follow your procedures*
- *Use your resources – including FDA*
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Thank You

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