FDA Conduct of Clinical Investigators Inspections

Nancy A. Bellamy
Bioresearch Specialist/ BIMO Monitor
US Food & Drug Administration
Office of Regulatory Affairs
Detroit District Office

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OBJECTIVES

• What to expect in an FDA inspection of Clinical Investigators
• Preparing / Responding
• Common FDA-483 Observations
• Resources
• Recent BIMO Metrics

FDA’s BIMO Program

• Protect the rights, safety, and welfare of subjects in FDA-regulated trials
• Determine the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications for new products
• Assess compliance with FDA’s regulations governing the conduct of clinical trials, including those for informed consent, ethical review and control of research articles
FDA’s BIMO PROGRAM AREAS – Bioresearch Monitoring

• Good Clinical Practice (GCP)
  – Institutional Review Boards (IRBs)
  – Clinical Investigators (CIs)
  – Sponsor-Monitors, CROs

• Good Laboratory Practice (GLP)
  – Nonclinical (animal) laboratories

• In Vivo Bioequivalence (Beq)
  – Analytical Laboratories
  – Phase 1 clinical research facilities

INSPECTION ASSIGNMENTS ARE ISSUED BY FDA’s CENTERS

• CDER- Center for Drug Evaluation & Research
• CDRH- Center for Devices and Radiological Health
• CBER- Center for Biologics Evaluation and Research
• CVM- Center for Veterinary Medicine
• CFSAN- Center for Food Safety and Applied Nutrition

INSPECTION ASSIGNMENTS

– Routine/Surveillance:
  • Studies conducted to support marketing permits: NDA, BLA, PMA, ANDA or research permits: IND (drug), IDE (device)

– Directed/For Cause:
  • Data appears unrealistic/ suspicious
  • Follow up: - to reports of possible misconduct received from outside sources (Sponsors, IRBs, employees, study subjects)
  • --to previous inspectional deficiencies
PREPARING FOR AN FDA INSPECTION

• FDA will call to pre-announce the inspection
  – Routine inspections, no more than 5 days notice
  • PDUFA and MDUFMA mandate deadlines for agency review
  – Will provide the specific study to be inspected, records for review and time needed with the CI and/or other study staff
  – Obtain the FDA Investigator’s name and contact info
  – Provide specific and clear directions to your site

PREPARING FOR AN FDA INSPECTION

• Reserve workspace for the FDA Investigator
• Be sure the CI, Study Coordinator and others knowledgeable about the study will be available
• Set time aside for the duration of inspection
  – Approximately 3-7 days
  – Duration may depend on volume of records and/or FDA Investigator findings

PREPARING FOR AN FDA INSPECTION

• Have ALL records related to the study available, including:
  – Regulatory records – IRB approvals, protocols, investigator brochure, correspondence file
  – CRFs, monitoring reports
  – Source records – clinic charts, hospital records, x-rays, lab reports, subjects’ diaries
  – Test article accountability records
COPIES REQUESTED BY FDA

- Protocol and amendments
- Informed Consent and revisions
- IRB approvals –amendments/Continuing Reviews
- CVs for primary personnel
- Any publications from the study
- List of other Clinical Studies for the past 3 years

INSPECTIONAL ACTIVITIES

- Initial interview
  - FDA credentials, Notice of Inspection
  - Interview staff
- Facility walkthrough
- Review study records
- Obtain documents
- Daily summary
- Exit interview/Close out meeting
  - Inspectional findings (Form FDA-483, verbal observations)

INSPECTIONAL ACTIVITIES

- In the Opening meeting, the FDA Investigator will ask questions of the Clinical Investigator and possibly the study staff
- The bulk of the inspection will involve the FDA Investigator reviewing records
- Copies of some records will be requested
- Federal regulations allow the FDA to inspect and copy ALL records relating to a clinical investigation (312.68) HIPAA does not apply
CRITICAL ASPECT OF INSPECTION

Data comparison

Source documents/Raw data vs.
Case Report Forms vs.
Summary Data submitted to the FDA

STUDY COVERAGE:
General

• Responsibilities of staff and training received
• Contract Research Organizations (CRO’s) – labs, monitors, etc.
• How study data obtained and recorded
• Adhered to protocol and investigational plan
• Protocol deviations reported

STUDY COVERAGE:
General

• Study subjects:
  – Source, exist, have disease being studied, meet inclusion/exclusion criteria
• Study Records
  – CRFs completed, agree with source data, consistent with protocol, electronic records (21 CFR Part 11)
• Drug/Device Accountability:
  – Complete records covering shipping, receiving & dispensing
  – Disposition of unused test article (return/destruction)
  – Stored in secure location at proper conditions
STUDY COVERAGE:
Degree of Delegation

- Delegation of authority
  - Established & documented by clinical investigator (For Drug studies list primary on Form FDA-1572)
  - Delegate to qualified and well-trained study staff
  - CI is still responsible for the adequate supervision of study activities

STUDY COVERAGE:
INFORMED CONSENT FORM

- ICF and Procedures:
  - ICF content (21CFR 50.25 Basic and Additional elements)
  - Signed/dated ICFs on file
    - Prior to study-specific activities
    - Revisions
  - Informed Consent Process (CI or delegate)

STUDY COVERAGE:
IRB Communications

- IRB approvals
  - Protocol (original and amendments)
  - ICF (all versions)
- IRB submissions
  - Required reports submitted
  - Timely
STUDY COVERAGE:
Sponsor & Monitor Communications
• Signed Agreement (devices) or FDA-1572 (drugs)
• Financial disclosure
• Required reports submitted
• Monitor’s communications & evaluations
• Corrective actions to issues identified by the Sponsor & Monitor

STUDY COVERAGE:
Adverse Events
• Adverse Event Reporting: (adverse effects, unanticipated adverse device effects, etc)
  – Assessment of relationship to test article
  – Documented and reported to sponsor (and IRB – if required)
  – Reported within required timeframes
  – Follow up with subject and required parties

ISSUES IDENTIFIED
DURING THE INSPECTION
• 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
CLOSE OUT MEETING

- Held with the Principal Investigator and staff
- FDA Investigator discusses findings
  - Verbal discussion/observations
  - If applicable, issuance of a Form FDA-483
- FDA-483, Inspectional Observations
  - Significant deviations from FDA regulations.
  - Based on the FDA Investigator's review of available records and information

COMMON OBSERVATIONS for CLINICAL INVESTIGATORS

- Protocol Deviations-Inclusion/Exclusion; schedules- dosing, lab tests, return visits; meds.
- Failure to report Adverse Events
- Poor recordkeeping: missing source docs
- Informed Consent issues-wrong version
- IRB issues-Approvals; reports SAEs/deviations
- Test Article Accountability (CI responsible)
- CI's failure to adequately supervise the study:
  -- staff errors, training lapses

Responding to the Inspection

- The Clinical Investigator should respond to the 483 observations in writing within 15 days to be evaluated with the FDA investigator's report.
- The study site should take corrective actions for any deficiencies or plans for future studies
- Provide documentation of the corrective and preventive actions with the response
AFTER THE INSPECTION-FDA

- FDA Investigator will write an Establishment Inspection Report (EIR) that contains all the information collected during the inspection
- The EIR is sent to the Center that issued the assignment for review and final classification
- The assigning Center will usually send a follow-up letter to the Clinical Investigator
- The inspected site will receive a copy of the EIR after the inspection is classified (NAI/VAI)

AFTER THE INSPECTION: CLASSIFICATION

The assigning Center will classify the inspection as:

- NAI = no action indicated
- VAI = voluntary action indicated
- OAI = official action indicated

AFTER THE INSPECTION: REGULATORY ACTION

- Possible consequences:
  - Untitled Letters
  - Warning Letters
  - Rejection of the study or remove site data
  - Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
  - Prosecution
Tips for Successful Research Studies

- Understand protocol requirements & limitations
- Train all employees & document training
- Use the latest version of the ICF - control copies
- Keep ALL records – sponsor, IRB, monitors, subjects
  - letters, faxes, e-mails, memos, phone contacts
- Keep all test article accountability records
  - Shipping receipts, enrollment logs, dispensing logs
- Keep complete, organized & adequate records:
  Attributable, Legible, Contemporaneous, Original & Accurate (ALCOA)

Tips for Success (cont)

- Know your IRB’s requirements - Continuing Review; ADEs; amendments; recruitment ads;
- Know the sponsor’s Adverse Event reporting requirements
- Protocol deviations are not protocol revisions.
- Be very open about errors - one line through, initial, date and reason for change. Document and report deviations, record the sponsor decisions
- Know each study staff member’s roles and responsibilities – the CI is ultimately responsible
- Establish & document delegation of authority

Bioresearch Monitoring (BIMO) Metrics – FY-2012
Most Common CI Deficiencies

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product (Reconciliation of received, used, returned)
- Inadequate Communication with the IRB
- Inadequate subject protection – including informed consent issues
### Common FDA Acronyms

- **BIMO** = Bioresearch Monitoring
- **IND** = Investigational New Drug application (allows clinical research)
- **IDE** = Investigational Device Exemption (allows clinical research)
- **NDA** = New Drug Application (allows marketing of drug)
- **PMA** = PreMarket Approval (allows medical device marketing)
- **BLA** = Blood License Application (allows biologics marketing)
- **NADA** = New Animal Drug Application (allows veterinary drug marketing)
- **FY** = Fiscal year (Oct 1st – Sept 30th)
- **CI** = Clinical Investigator
- **IRB** = Institutional Review Board
- **RDRC** = Radioactive Drug Research Committee
- **GLP** = Good Laboratory Practices (animal/preclinical studies)
- **BEQ** = Bioequivalence
- **Spon/Mon** = Sponsor/monitor

### Resources on www.fda.gov

- Guidance Documents (examples)
  - Financial Disclosure by Clinical Investigators (Feb.’13)
  - Q&A on Informed Consent Elements (Feb.2012)
  - Electronic Source Documentation in Clinical Investigations (Nov’12)
  - IRB Responsibilities for CI Qualifications, Adequacy of Sites, and Whether an IND/IDE is needed (Mar.’13)
  - Investigator Responsibilities—Protecting Rights, Safety, and Welfare of Study Subjects (Oct. ’09)
  - Adverse Event Reporting to IRBs—Improving HSP (Jan. ’09)

  Compliance Programs: 7348.811- Clinical Investigators, 7348.809- IRBs; 7348810- Sponsors; 7348.001- BEQ

### BIMO REGULATIONS (Code of Federal Regulations)

- 21 CFR 50: Protection of Human Subjects
- 21 CFR 56: Institutional Review Boards
- 21 CFR 58: Good Laboratory Practice for Non-Clinical Laboratory Studies
- 21 CFR 361 Radioactive Drug Research Committees
- 21 CFR 511 Animal Clinical Studies (Vets)
BIMO REGULATIONS
(Code of Federal Regulations)

- 21 CFR 314: New Drug Applications (NDA)
- 21 CFR 312: Investigational New Drug Exemption (IND)
- 21 CFR 814: Pre-Market Approval Applications (PMA)
- 21 CFR 812: Investigational Device Exemption (IDE)