

FDA INSPECTOR PERSPECTIVES: GCPs AND INSPECTIONS OF CLINICAL INVESTIGATORS AND SPONSORS

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Abstract: *The Food and Drug Administration (FDA) has a crucial role in the oversight of clinical research. This article provides an overview of FDA's Bioresearch Monitoring Program, with a focus on inspections of clinical investigators and sponsors. The responsibilities of clinical investigators and sponsors for conducting and monitoring clinical trials are outlined. Common deficiencies found during FDA inspections are discussed. Suggestions for preparing for a site inspection and conducting successful studies are provided. (Note: The source of some of this data is from other Agency offices, such as CDER (DSI), CBER, and CDRH)*

The FDA's Bioresearch Monitoring Program

The FDA's Bioresearch Monitoring (BIMO) Program covers inspections of clinical investigators, sponsors, monitors, clinical research organizations (CROs), institutional review boards (IRBs), radioactive drug research committees, in vivo bioequivalence, Good Laboratory Practices, animal studies, and food studies. The compliance programs for all of these areas are available on the FDA's Web site (www.fda.gov), which details what FDA inspectors look for during inspections.

The BIMO Program covers clinical investigators, sponsors, monitors, CROs, and IRBs involved in studies of drugs, including biologicals, and devices. The program's primary focus is the validity and reliability of the study data and the protection of the rights and welfare of study subjects.

The regulatory basis for BIMO inspections is found in the Food, Drug and Cosmetic Act, Section 505.I, which implements the Investigational New Drug application regulations (21 CFR Part 312 covers drugs, 21 CFR Part 50 covers informed consent, 21 CFR Part 56 covers IRBs). Regulations for medical devices are covered in 21 CFR 812 and 813.

Most BIMO Program activities fall under the Clinical Investigator Inspection Program (Compliance Program 7348.811). The objectives of this program are to:

- Obtain compliance of clinical investigators with the regulations, and
- Assure that the data that are submitted to the FDA are substantiated by data integrity, data quality, and protection of study subjects.

The purpose of the Clinical

Investigator Inspection Program is to ensure adherence to the guidelines and the regulations. While FDA inspectors cannot cite clinical investigators for information in the guidelines, they can cite them for not adhering to the regulations. FDA inspectors seek to:

- determine the validity of specific studies in support of products pending approval, by determining if the investigator has adhered to the submitted protocol,
- determine that all adverse events were documented and reported,
- determine the completeness and accuracy of the data,
- ensure that the rights and safety of subjects are properly protected. This is more than just looking to see that there is a signed informed consent form,
- determine that subjects are properly informed about the clinical trial,

- ensure that subjects were not coerced into entering the study, which has been a problem in some studies, and
- determine that subjects were consented prior to the initiation of any study procedures.

The objectives of BIMO inspections for sponsors/monitors are to determine how sponsors verify the validity of data from clinical investigators and to determine the adherence of sponsors, CROs, and monitors to the regulations. The objective of BIMO inspections of IRBs is to ensure the protection of the welfare and rights of research subjects.

Weaknesses in the Clinical Research System

There are some weaknesses in the clinical research system due to volume versus resources. Not having the appropriate resources at a clinical site presents a problem. Doing more with less is one of the problems. Education and staff turnover create a tremendous problem. We have inspected some sites where the clinical investigator has had a complete turnover of site personnel during the study; there was no continuity and records were missing.

Conflicts of interest include financial conflicts of interest. The FDA enacted a Financial Disclosure Act. BIMO inspectors typically do not cover this during a clinical investigator inspection.

The FDA has established initiatives to address these weaknesses. The agency has systems in place to handle complaints from sponsors and the general public about clinical trials. These complaints generate inspections. The FDA has also proposed tighter regulations for sponsor reporting of site falsification, which would generate more inspections.

Clinical Investigator Commitments

FDA Form 1572, which the clinical investigator must sign, lists the clinical investigator's responsibilities:

- conduct the study according to the protocol,
- personally conduct/supervise the study,
- ensure proper consent and IRB review,
- report adverse experiences,
- read/understand the investigator's brochure,
- ensure that associates (including sub-investigators, study coordinators, and others involved in the study) know their obligations,
- maintain adequate and accurate records (this is a key point),
- ensure that the IRB complies with 21 CFR 50 (informed consent) and 21 CFR 56 (IRBs), and does initial and continuing review of the study, and
- promptly report to the IRB all changes in research activity (including the termination of the study).

For device studies, the clinical investigator signs an investigator statement rather than FDA Form 1572. By signing this statement, the clinical investigator in a device study agrees to conduct the study in accordance with 21 CFR 812.100, which outlines the general responsibilities of clinical investigators of device studies.

Inspection Assignments

Inspection assignments are issued by the FDA centers. The primary sources of inspections are the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health. A few inspections are assigned by the Center for Veterinary Medicine and the Center for Food Safety and Applied Nutrition. These centers send inspection assignments out to the districts, which assign the inspectors.

Types of Inspections

Most assignments are routine inspections for pivotal studies that are pending New Drug Application

review. Typically, these assignments are based on the sites with the highest enrollment.

Directed, or for cause, inspections can be generated by suspicion of false or fraudulent data, or data that appear unrealistic, or when the sponsor alerts the FDA of serious problems. When reviewing the data submitted by the sponsor, the medical reviewer may feel that there is something wrong with the data. For example, in one study which generated an inspection, medical and statistical reviewers saw that 70 and 80 year-old Alzheimer's patients who were enrolled in a study all had normal nerve stimulation tests, when many of the subjects should have had abnormal nerve stimulation tests. Unrealistic data could include blood pressure measurements that are all the same. Many inspection assignments are generated by complaints from sponsors.

A routine inspection typically takes three to seven workdays. It could take longer, for example, if the inspection covers more than one protocol. The length of time depends upon the complexity of the protocol and the records, and the availability of the records.

Directed inspections may take seven days or longer, since the inspectors will be focusing on different things. We performed one directed inspection that took three months and resulted in disqualification of the clinical investigator. The duration of a directed inspection depends on the complexity of the assignment.

Inspection Metrics

Metrics for the Center for Drug Evaluation and Research show that the number of inspections of drug studies increased significantly between fiscal year 1992 and fiscal year 2001: from 11 in 1992 to 54 in 2001. The number of complaints about clinical trials also increased, from 76 for fiscal years 1992 to 1998, to about 132 in 2001 alone.

This increase is probably due to the FDA's outreach activities. The largest percentage of complaints comes from IRBs (19%) and sponsors (14%). Subjects and study coordinators are also sources of complaints.

The Qualifications of FDA Investigators

FDA field investigators have a minimum of a four-year college degree, usually in life sciences or related disciplines. Some field investigators have nursing, pharmacy, or medical degrees. Field investigators are trained to conduct inspections of clinical investigators. They go to a national BIMO monitoring course, which reviews all of the regulations and provides training in how to inspect clinical investigators, IRBs, and sponsors. After the course, they return to their districts for on-the-job training.

Inspectional Activities

When the district receives an assignment from headquarters, the inspector calls the site to make an appointment to conduct the inspection. All inspections of clinical investigators are scheduled by appointment. During the opening interview, the inspector issues a notice of inspection (FDA Form 482), provides an information sheet about the FDA, and presents his/her credentials.

The inspector interviews the key staff at the site. He/she is following an FDA compliance program and must provide headquarters with specific information as well as understand what is happening at the site and how the clinical trial was run. Sometimes, headquarters asks the inspector to ask specific questions. The staff to be interviewed could include the clinical investigator, sub-investigators, the study coordinator, and the pharmacist.

The inspector then reviews source documents, case report forms, consent forms, administrative records, drug storage, and other study records.

Regulations do not specify where study documents should be stored; however, it is convenient if they are organized in study binders. The source documents are defined as the recording device(s) on which the study data are first recorded. Thus, if the study data were first recorded on a post-it note, the post-it note must be retained. The original source documents must be available for review. If shadow charts are used, they must be available for review. The inspector will also look at where the investigational drugs or devices were stored.

After completing the inspection, the inspector schedules an appointment for an exit interview with the clinical investigator and anyone else who the clinical investigator would like to interview. If there are deviations from federal regulations for Good Clinical Practice, an FDA Form 483 may be issued.

Table 1 outlines critical issues in inspections. These cover items confirming that: study entry is recorded, subjects exist and have

the disease under study, drug accountability is documented, raw data exist, the IRB approved all significant stages of the study, and informed consent was conducted appropriately.

At the exit interview, the inspector discusses inspection findings and may issue an FDA Form 483. If an FDA Form 483 is issued, the inspector will ask for a verbal response.

Post-inspection, the inspector writes the Establishment Inspection Report. This report is sent to the center that assigned the inspection and is reviewed by the medical reviewers at FDA headquarters. Headquarters sends the clinical investigator a letter.

Common Deficiencies

Table 2 outlines common deficiencies at clinical sites. These deficiencies cover the protocol, concomitant therapy, records, adverse events, drug accountability, the IRB, and informed consent. Examples follow.

Examples of protocol non-adherence include problems with inclusion/exclusion criteria, dosing subjects

TABLE 1
Critical Issues during Inspections

- Is study entry recorded?
- Is there a subject/diagnosis?
- Is drug administration documented?
- Is there raw study data?
- Did an IRB approve all significant stages?
- Did each subject provide proper informed consent prior to study admission?

TABLE 2
Common Deficiencies at Clinical Sites

- Protocol non-adherence
- Failure to report concomitant therapy
- Inadequate and inaccurate records
- Failure to report adverse events
- Inadequate drug accountability
- IRB problems
- Informed consent

on time, and obtaining the required ECGs as scheduled. During one inspection, the inspector found that the inclusion/exclusion criteria were not followed: “A subject started Ziac containing a beta blocker and was screened and randomized. The protocol inclusion criteria does not allow for a subject who requires beta blockers.” During another inspection, the inspector wrote: “The protocol treatment plan was not always followed in that subjects x and x received the first and second doses 10 days apart and not 8 days apart according to the protocol.” A third protocol-related deficiency was: “Baseline ECGs not performed as required by the protocol at screening or randomization visit, but performed after randomization visit as follows..” This scheduled activity was not completed according to the protocol.

One inspection revealed a deficiency related to a failure to report concomitant therapy: “Subject underwent hand surgery, given Lidocaine, Marcaine, Keflex, Biaxin and was taking other drugs. None were reported as concomitant medications on case report forms.” Concomitant medications should be reported.

Lack of supporting documentation for entries found in case report forms (CRFs) is one example of inadequate and inaccurate records. During one inspection, “Source documents could not always be found for the following subjects...” Another deficiency is source documents that revealed that the CRFs were inaccurate: “Lab report shows sample drawn at 14:55, but case report form shows sample taken at 07:53.”

One inspection revealed a failure to report adverse events: “Adverse events were not always reported to the sponsor as follows: Patient diary records leg cramps. This adverse event was not reported in the case report form.” This was probably just an oversight.

Inadequate drug accountability deficiencies include: “Drug accountability records reported in the case report forms do not always agree with patient diaries as follows: diary shows all doses taken, but CRF shows 2 doses missed....” Which is correct? Another inspection showed inadequate drug storage: “Daily temperature records show the study drug was held in the refrigerator at or below freezing until drug was dispensed on days....”

IRB problems include failure to obtain the proper approvals: “Subject administered a consent not approved for the surgery site, referenced another IRB for questions, and the consent was not documented as IRB approved.”

Deficiencies related to informed consent include signing the informed consent form too late and signing the wrong informed consent form.

Examples include:

- “Six subjects signed the informed consent form after treatment commenced.”
- “Subject x signed the wrong consent form (for protocol x) on x, received the first treatment on x under protocol x, and signed the correct consent for protocol x on x.”

The Most Common Deficiencies

Failure to follow the protocol and failure to maintain adequate and accurate records continue to be among the most frequently encountered findings (Table 3).

FDA Form 482 observations for one study with four failed sites illustrate these deficiencies. The study was a randomized comparison of surgery to drug. Protocol violations included:

- the protocol listed stage C or D disease as inclusion criteria, but 20% of the patients at this site did not have stage C or D disease,
- 33% of the patients at this site never received classification of their disease, and

- the protocol requires exclusion of patients who fail to sign the informed consent form, but informed consent forms were not used at this site.

Inadequate randomization included:

- there are no records to explain the method of randomization,
- there are no records to demonstrate that the method of randomization was accomplished, and
- only two of the last 29 (7%) patients entered in the study received surgery; 27 patients received the study drug.

Inadequate documentation of the study included:

- no medical records (progress notes, laboratory results, etc.) were available for 29% of the patients, and
- there were no pathology reports to demonstrate patient eligibility for 33 of the charts audited.

Discrepancies between source documents and the CRFs included:

- the electronic case report form for patient #20 indicates that he died in June 1985; the medical records for this patient indicate that as of April 1996, he was swimming and going to the gym twice a week.

These observations were responsible for a decision not to accept the study data. These deficiencies could have been prevented by the clinical

TABLE 3
The Most Common
Deficiencies at Clinical Sites

Failure to Follow the Protocol

- Violation of inclusion/exclusion criteria, and
- Failure to perform required tests.

Failure to Maintain Adequate and Accurate Records

- Absence of supporting source documents, and
- Inaccurate or incomplete source documents.

investigators and the sponsor. They could have been detected through adequate monitoring.

Compliance Classifications

Inspections are classified as “No Action Indicated (NAI),” “Voluntary Action Indicated (VAI),” or “Official Action Indicated (OAI).” An NAI classification means that the clinical investigator is in compliance and there are no inspection observations. VAI represents marginal compliance; an FDA Form 483 has been issued and corrective action is required. OAI is used for serious non-compliance issues that require regulatory or administrative action. For OAI inspections, a warning letter to the clinical investigator or disqualification of the clinical investigator may be recommended.

Most inspections are classified as VAI. In 2001, 59% of inspections were classified as VAI, 3% as NAI, 2% as OAI, and 36% as pending. From January to May 2003, five warning letters were issued to clinical investigators (three from the Center for Devices and Radiological Health and one each from the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research).

Sponsor/Monitor Inspections

Sponsor obligations for a clinical study are to:

- label investigational products,
- initiate, withhold, or discontinue clinical trials,
- not commercialize investigational products,
- control distribution and return of investigational products,
- select qualified investigators,
- assure that investigators are appropriately informed,
- select qualified monitors,
- evaluate and report adverse experiences,
- maintain adequate records of studies, and
- submit progress reports and final reports.

The FDA’s sponsor/monitor inspection program has two objectives: to determine how sponsors verify the validity of data from clinical investigators, and to determine the adherence of sponsors, CROs, and monitors to the regulations.

During sponsor/monitor inspections, inspectors compare the practices/procedures of the sponsor and the CRO to submission commitments and the regulations. During sponsor/monitor inspections, the inspector looks at:

- the Investigational New Drug (IND) application, the Investigational New Abbreviated Drug (INAD) application, or the Investigational Device Exemption (IDE) application,
- the protocol or the investigational plan,
- safety reports for adverse and unexplained events,
- standard operating procedures for monitors,
- signed investigator statements,
- monitoring reports, and
- receipt, shipment, and disposition.

The number of sponsor/monitor inspections for drug studies has increased from 8 in 1998 to 27 in 2001.

Table 4 outlines typical sponsor deficiencies. Examples of sponsor deficiencies from FDA Form 483s follow. Deficiencies related to improper selection of investigators and monitors include:

- “The sponsor failed to select a qualified clinical investigator for the study site: the investigator for this site failed to obtain written informed consent for two subjects, two subjects were not qualified to enter the study, and no subjects intended to be controls were acceptable, since the clinical investigator had also performed the control procedures.”

- “The sponsor shipped investigational devices to a study site prior to receiving a signed investigator agreement and prior to verification of IRB approval.”

A deficiency related to failure to report adverse events is: “The sponsor did not report the following unanticipated adverse effects to FDA within the 10 day time frame: x.” An example of lack of required records is: “The sponsor failed to maintain records of study devices used under protocol #x. The sponsor did not have records of shipment to the study site, and final disposition of used and unused devices.” The sponsor must keep these records.

There are many possible outcomes to sponsor inspections:

- warning and untitled letters,
- re-inspection,
- termination of an exemption (IND, IDE, INAD),
- refusal to approve or license,
- withdrawal of approval (PMA, NDA, NADA),
- determination that a device is not substantially equivalent or the rescinding of a 501(k) application,
- implementation of the Application Integrity Policy,
- initiation of stock recovery,
- seizure of test articles,
- injunction,
- prosecution, or
- referral to other Federal, state, and local agencies.

TABLE 4
Typical Sponsor Deficiencies

- Improper selection of investigators and monitors
- Failure to report adverse events
- Lack of required records
- Failure to conduct proper monitoring of the investigator(s)

In 2001, 48% of sponsor inspections for drug studies were classified as NAI, 30% as VAI, 3% as OAI, and 19% as pending.

Inspection reports are automatically sent to the inspected party once headquarters classifies the inspection. Once the inspection reports are released to the inspected party, they are also available through the Freedom of Information Act.

Tips for Conducting a Successful Study

Table 5 outlines tips for conducting a successful study. Make sure that the protocol design is as simple as possible. Focus on essential data points to avoid ambiguity and vagueness. Fully understand protocol limits and the importance of strict compliance.

Understand the elements of data quality. All records should meet the ALCOA test: attributable, legible, contemporaneous, original, and accurate.

Minimize the need for transcription. Moving things from one piece of paper to another introduces errors. Do not throw away anything, especially originals.

Understand the regulatory responsibilities. Communicate with the IRB, the sponsor, the monitor, and the regulatory authorities.

Preparing for a Site Visit

FDA investigators follow Compliance Program CP 7348.811 (Clinical Investigator Inspections) and Compliance Program CP 7348.810 (Sponsor/Monitor/CRO Inspections), as well as the Code of Federal Regulations. These compliance programs are available on the FDA's Web site (www.fda.gov/oc/gco/default.htm).

Have the following available for the inspector:

- all study documents,
- a person who is knowledgeable about the study,

- a place for the inspector to review records, and access to a photocopier.

TABLE 5
Tips for Conducting a Successful Study

Enhancing Protocol Adherence

- Protocol design should be as simple as possible, promoting collection of quality data without compromising study objectives
 - Focus on essential data points (explain significance in terms of study objectives [efficacy/safety] or subject protection)
 - Avoid ambiguity and vagueness in inclusion/exclusion criteria and adverse experiences
- Fully understand the protocol limits and the importance of strict compliance
 - How much latitude is available for clinical treatment (e.g., concomitant therapy)?
 - Is it okay to use the hospital or clinical protocol to perform routine procedures (e.g., chemotherapy)?
 - Is it okay to skip procedures that are not medically necessary (laboratory tests, PEs, biopsies)?
 - Which protocol procedures can be performed by non-physician study support staff?

Understand the Elements of Data Quality

- All records should meet the ALCOA test:
 - Attributable
 - Legible
 - Contemporaneous
 - Original
 - Accurate

Enhancing Record Quality

- Minimize the need for transcription
- Do not throw away anything, especially originals

Understand the Regulatory Responsibilities

- Read the following before signing on to conduct a study:
 - International Conference on Harmonization GCP Consolidated Guideline
 - FDA GCP Regulations
 - FDA Information Sheets for IRBs and Clinical Investigators

Communicate with the IRB, the Sponsor, the Monitor, and the Regulatory Authorities

- With the IRB:
 - Protocol changes
 - Continuing review
- With the sponsor and the monitor:
 - Openly address problems
- With regulatory authorities:
 - Understand expectations
 - Honor reporting obligations