



FDA Audit Guidelines

University of Miami

Office of the Vice Provost for
Research



FDA Audit Guidelines

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NOTE: Content adopted from University of Pennsylvania FDA Audit Guidelines



Introduction

The FDA is required to ensure that sponsors and principal investigators (PI) are adhering to all applicable regulations while undertaking clinical research activities. The regulations specifically allow FDA to conduct on-site audits of both sponsor and PI facilities (21 CFR 312.58, 312.68, 812.45). FDA regulations also require audits of manufacturing and laboratory facilities used in the creation of new drugs and the analysis of protocol specific diagnostic tests. The scope of this document is on clinical investigator inspections.

These audits apply to research conducted under an Investigational New Drug application (IND) and Investigational Device Exemption (IDE). The FDA may also audit any research using an FDA regulated product regardless of whether an IND or IDE is required to carry out the research. Meaning research conducted using an FDA regulated product is subject to audit by the federal government.

There are two types of audits:

Routine

An audit conducted to assess the validity of the study data, normally determined by subject accrual rate or amount of data obtained from a given site

For Cause

An audit conducted potentially based upon a complaint of non-compliance or FDA concern over data submitted by a given site

Upon notification of an FDA Audit, the PI must notify the following offices as soon as possible:

- Department Chair
- The Vice Provost for Research (VPR)
- Appropriate Governing Board or Committee (i.e., IRB, ESCRO, IACUC, etc.)
- Office of General Counsel (GC)

Vice Provost for Research Role in FDA Audits

The purpose of the audit is to ensure compliance with the regulations. FDA will do this through documentation review as well as one-on-one interaction with the PI. The Office of Research Compliance Assessment (ORCA) has extensive knowledge and experience in research regulations and can assist PIs and their study teams in the preparation and conduction of an FDA inspection.

Pre-Audit Review

At the time of notification by FDA, the PI must inform VPR. At this point, VPR (or designee) will discuss with the PI's his/her particular interest/preferences regarding VPR support. For example, the Office of Research can assist in coordinating the audit and the location for the audit. In addition, ORCA can provide pre-inspection support in the form of:

- counseling support to help prepare for the inspection
- an FDA Audit Preparation Assessment to prospectively identify gaps that could be proactively resolved

Inspection Facilitation

Based on individual PI's preference, Office of Research (OR) can provide space, resources, and support to host the inspection. A research team member will be identified to accompany the FDA investigator and to oversee the administrative aspects in response to FDA requests (e.g., making photocopies, securing additional documents).

The OR is available to assist in coordinating the scheduling of time with the PI for FDA questions and daily debriefing meetings. This encourages the FDA investigator to consolidate his/her questions into as few interruptions for the PI as possible.



Assist in Response to Inspection Observations

If there are any inspectional observations, the principal investigator (PI) will receive an FDA 483 (a summary of inspectional findings). Although not required by regulation, it is in the PI's best interest to respond to these observations in writing. ORCA can assist in responding to an FDA 483 and also in implementing corrective actions to address the inspectional observations.

Audit Preparation

The Principal Investigator's Role:

In anticipation of an FDA audit, the PI needs to ensure the following:

- Review the [External Audit for Research Policy](#).
- Time and flexibility in his/her schedule to meet with the FDA investigator.
- A controlled environment in which the investigation will be conducted (the Office of Research has dedicated space available).
- The FDA investigator has accessibility to all necessary source documentation (medical and clinical records*), study records (case report forms or electronic data capture systems), and regulatory documentation.

NOTE: FDA investigators may request additional documentation if deemed necessary to assure compliance. These may include appointment books for the PI or patient schedules as well as surgical schedules.

Important information for the day of the audit:

- Always ask for the FDA investigator's identification. They are required to present their identification and you are required to ask for it prior to handing over any confidential documentation for review.
- The FDA investigator will present the PI with an FDA Form 482 Notice of Inspection. The Principal Investigator will sign the 482 and receive a copy.

The PI is highly encouraged to engage ORCA office for preparation assistance. ORCA has in-depth experience and resources available to help you be prepared for the inspection. You may also find that reviewing recent FDA findings and recent warning letters as a helpful resource. This information is publicly available on the FDA website and can provide an education on what other sites are doing wrong regarding their clinical research practices.

<http://www.fda.gov/foi/warning.htm>

Audit Areas

The FDA Consumer Safety Officer (CSO or FDA investigator) must conduct the inspection according to written policy from the FDA's Office of Regulatory Affairs, Compliance, Science and Protection. This procedure for conducting clinical investigator audits can be found on the FDA website [Inspection Guidelines](#). The procedure outlines what specific areas will be reviewed during the inspection.

The following sections describe each inspection area, and include ways to prepare for review of each area.

Protocol

Assure that all versions of the protocol are IRB-approved and that NO CHANGES to the protocol were implemented prior to IRB approval.

Authority and Administration

Review the regulatory documentation, including monitoring log, delegation of responsibility log, CV's, IRB and sponsor communications and lab information to determine:

- How the PI is informed of his/her requirements regarding the study protocol and accountability of the test article.

- Proper delegation of various study related tasks.
- Discontinuation of a study before it is completed.
- Name and address of the laboratory facility and its ability to perform study-specific tasks.
- List of individuals performing such tasks and their positions.

Preparation

Verify a complete and well-organized regulatory binder.

Subject Records

The FDA audit includes inspection of subject records to determine:

- The existence of all subjects.
- Validity of data (case report form data versus source documentation).
- Proper documentation of AEs/SAEs.
- Accurate documentation of concomitant medications and patient history.
- Subject eligibility (inclusion criteria met, no subjects meeting exclusion criteria were enrolled).
- The handling of subjects who are no longer eligible to participate in the study (i.e., come to meet exclusion criteria, failure to comply with study requirements, etc.).
- Complete and accurate records were kept on the subject throughout their study participation.
- The sponsor was notified of all study dropouts.

Preparation

- Assure informed consent was obtained and documented on all subjects prior to study entry.
- Include documentation of consent in the subject's source record.
- Assure CRF data is complete, accurate, and can be verified against source records.

Consent of Human Subjects

Required verification that informed consent was obtained from all subjects prior to study entry and in accordance with the regulations (21 CFR 50). The FDA will review consent forms on subjects enrolled and screened.

Preparation

- Always obtain proper informed consent from all subjects screened for entry into the study.
- Ensure that the proper (most current) IRB approved version of the consent form is used.
- Maintain original informed consent documents in the study record or in a separate study file.
- File all IRB approved versions of the informed consent form in the regulatory binder.

IRB Communications

Review of the PI's reports and communications with the IRB. This may include submission of reports, protocol amendments, informed consent amendments, advertisements, and adverse events.

Preparation

All IRB correspondence should be kept current and filed in the regulatory binder. For further assurance in anticipation of an FDA audit, the PI may request a copy of the study's IRB file to review against the IRB correspondence section in the regulatory binder.

Sponsor Communications

The PI's communication with the study sponsor will also be inspected to ensure that both sponsor and PI have met all regulatory obligations. The inspection will include review of:

- The IRB-approved consent form.
- Period reports from the PI.
- Adverse events (within the required timeframes).



- On-study illness and concomitant medication information.
- Timely CRF submissions.

In addition, the FDA will be verifying that the sponsor conducted adequate monitoring of the study's progress.

Preparation

Review study records (case report forms) against source data to ensure that all adverse events were captured and reported and that all concomitant medications were recorded accurately. Also, all sponsor/PI communication should be filed accordingly in the regulatory binder.

Test Article Accountability

The accountability of the test article is an important aspect of the FDA audit. Maintenance of investigational product inventory and records is critical in verifying accountability. Proper documentation of test article accountability includes:

- Receipt dates and quantity.
- Dates and quantity dispensed with subject ID.
- Distribution of test article to subjects enrolled in the study.
- Verify quantity, frequency, duration, and route of administration.
- Study article disposition (what was received from, used, and sent back to the sponsor).
- Compare receipt and usage against shipping records.

Test article accountability also includes proper storage of the test article with adequate security in a controlled environment. FDA investigators will also determine if unqualified or unauthorized individuals administered or dispensed the test article.

Preparation

Ensure adequate documentation of accountability for receiving, storing, and dispensing of the test article.

Electronic Records/Record Retention

21 CFR Part 11 provides specific regulations surrounding the use of electronic records. It consists of a complex set of standards that usually require the use of a third party system or computer consultant with expertise in developing systems that comply with Part 11. Specifically, Part 11 is required for any data that would be submitted in support of a marketing application to FDA. However, compliance with Part 11 is also required if the source documentation at your site is maintained on an electronic database.

Records Retention

For paper case report forms and/or source documentation the FDA investigator will need to assure that records are secure from tampering, and that they can be maintained for the required period of time after the conclusion of the study.

Preparation

If you are using some type of electronic data capture in your study and you're not sure if your system is required to, or meets Part 11 compliance, consult with ORCA or your sponsor as soon as possible.



Inspection Outcomes

The PI is required to forward all outcome related documentation to the Vice Provost for Research and IRB through the HSRO.

The FDA has three classifications for inspectional outcomes.

- **No Action Indicated (NAI)** There either were no observations of non-compliance or minimal findings which were addressed during the inspection.
- **Voluntary Action Indicated (VAI)** The PI has voluntarily agreed to implement corrective actions.
- **Official Action Indicated (OAI)** FDA directed corrective actions must be implemented.

The FDA Audit findings will be communicated in one of two ways:

Form FDA 483: Inspectional Observations

The FDA documents any observations of non-compliance on FDA Form 483 and provides this to the principal investigator upon completion of the inspection. Although not required by regulation, it is in the PI's best interest to respond to these observations in writing.

Warning Letter

If the FDA investigator observes significant non-compliance during an audit or if a PI has consistently failed to address previous FDA inspection observations, the FDA may issue a warning letter. The PI is asked to respond to each issue. Both the FDA warning letter and the response letters are publicly available through the FDA's Freedom of Information Reading Room (<http://www.fda.gov/foi/warning.htm>).

It is important to know that if the FDA issues a warning letter, it is posted in the public domain and able to be reviewed by potential industry and government sponsors.