Investigator's Guide - Preparing for an FDA Site Inspection

GUIDANCE

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General Instructions

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Overview

Preparation for a site inspection by the Food and Drug Administration (FDA) requires a multi-faceted approach. The agency may conduct site inspections of the Institutional Review Board (IRB) or specific clinical research studies. The purpose of each program is to ensure the protection of research subjects and the integrity of data submitted to the agency. In conducting study-specific site inspections, the FDA reviews materials in order to determine whether the Principal Investigator (PI) is meeting obligations according to the protocol, institutional policies and procedures, and relevant regulatory requirements. The FDA may also conduct Sponsor inspections to determine if the Sponsor meeting obligations for regulatory sponsorship of an Investigational New Drug (IND) or an Investigational Device Exemption (IDE) study.

Initial Contact by the FDA

The time frame between initial contact by the agency and the actual inspection is generally very short. Typically, these inspections should be scheduled within 5 to 7 days from the date of initial contact and when all goes well, the date is mutually agreed upon by the site and the agency representative. When the agency calls, the recipient of the call should request the following information:

- date(s) of planned inspection (may request alternate date within a 5 to 7 day window)
- study(ies) to be inspected
- representative's contact information (name, phone number, e-mail, and office location)

Immediately after the call, the Investigator should contact the following as appropriate:

- Study sponsor (when applicable)
- Office of Research Compliance at orc@email.chop.edu, 267-425-2447 or 267-426-8723
- Institutional Review Board (IRB) at irboffice@email.chop.edu or 215-590-2830
- Investigational Drug Services (IDS) (if investigational product is stored in CHOP pharmacy) at investigationalpharmacy@email.chop.edu or 215-590-4470
- Study team personnel and other ancillary departments, as applicable
- Iron Mountain if records are stored off-site - ***request immediate delivery***
- ***Also, notification of Division Chief is encouraged***

General Instructions (cont.)

Contacts & Additional Information

For questions or additional information regarding preparation for site inspections by regulatory agencies, contact **Karen Burke, Director, Research Compliance, at 267-425-2447 or e-mail ORC@email.chop.edu**.

For additional information related to the FDA's Bioresearch Monitoring compliance program guidance for Clinical Investigators, refer to the *FDA Compliance Program Guidance Manual*.

Inspectional Processes & Investigator Responsibilities

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Introduction

When called upon, the Office of Research Compliance (ORC) will provide the Investigator and clinical team (or Sponsor, if applicable) with guidance and resources to assist in preparing for an FDA site inspection and assuring compliance. In addition, the ORC will review documents and can address the processes and responsibilities below.

Study Records

Study records that ***must*** be available for the site inspection include the following:

- ***current IRB-approved protocol and all previous versions*** (these might be in eIRB)
- ***current Investigator Brochure, and all previous versions***, when applicable
- ***current IRB-approved Informed Consent form(s) and all previous versions***
- ***continuing review(s)***, when applicable
- ***regulatory documents,*** when applicable:
  - regulatory agency correspondence (to/from regulatory agencies)
  - IRB approvals and correspondence (to/from IRB)
  - annual reports to the regulatory agency
  - FDA Form 1572 (all versions)
  - FDA Form 1571 (all versions)
  - FDA Form 3674
  - Investigator CVs
  - adverse event (AE) or serious adverse event (SAE) reports
  - investigational product shipping and accountability documents
  - subject screening and enrollment documentation
  - documentation of monitoring visits
- ***subject study records*** (e.g., source documents, case report forms [CRFs], informed consent forms, lab data, imaging or diagnostic data, as applicable).

Inspectional Processes & Investigator Responsibilities (cont.)

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Data Review & Mock Interview

Upon request, the ORC will review a subset of the files and data and conduct a mock interview with the PI and study team to include the following:

- regulatory review and IRB responsibilities
- investigator responsibilities
- sponsor responsibilities (as applicable)
- discussion of how research consent is obtained and documentation of consent is captured
- translation of consent forms or other study related documents (as applicable)
- accountability of the investigational product and storage
- data management
- electronic records and signatures
- completion and documentation of human subject training or other related education and training
- Standard Operating Procedures (SOPs)
- adverse event documentation and reporting
- data storage and retention of records
- pre and post inspection interview preparedness
- how to respond to FDA verbal and written findings

Preparing for the Inspection

Prior to the inspection, the study team should address the following:

- Reservation of quiet workspace for inspector for duration of visit
- Preparation of a contact list of the study team (PI, Study Coordinator, Research Administration, Pharmacy, etc.)
- Preparation of listing of clinical trials in which the PI is involved (the assigned inspector may give direction as to what should be included in such a listing)
- Identification of scribe to document questions and requests or runner to collect requested documentation
- Invitation to ORC, IRB, and IND/IDE Support Program representatives to attend opening (pre-inspection) meeting

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Inspectional Processes & Investigator Responsibilities (cont.)

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Pre-Inspection Meeting

Upon arrival of the Inspector, the PI and study team can expect the following:

- Site representative:
  - checks credentials of the agency's representative upon arrival
- Inspector:
  - produces the Notice of Inspection (e.g., Form FDA 482)
  - requests business cards from site representatives
  - reviews the site 1572 Investigator Statement with the PI and study team
  - requests information related to delegation of responsibilities
- PI:
  - outlines the roles and responsibilities of each member of the study team
  - reviews of the protocol
  - discusses study conduct
  - discusses data collection procedures and storage

Inspectional Processes & Investigator Responsibilities (cont.)

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Inspector Review and/or Actions

The Inspector will conduct a review of study materials, which may include any of the following:

Regulatory Documents & IRB Responsibilities

- submission of documents for approval prior to start of study
- documentation of IRB approval
- protocol deviations and exemptions
- documentation of progress reports and continuing review
- submission of documentation of unanticipated problems to IRB

Sponsor Correspondence

- exemptions granted from Sponsor
- IRB-approved consent forms sent to Sponsor
- correspondence with Sponsor (approvals, documentation of unanticipated problems, and intercurrent illnesses)
- enrollment of subjects (reasons for early withdrawal or termination documented)
- Documentation of Monitoring visits

Informed Consent Process/ Documentation

- execution of the consent process, including documentation
- use of IRB-approved consent forms
- consent obtained prior to performance of study-specific procedures
- documentation and tracking of consent for use of subject study data or specimens for future use

Test Article Accountability

- acceptable storage: room temperature, refrigerator, freezer, temperature logs are current
- preparation of the test article
- administration of the test article
- destruction of test article and/or return of test article to Sponsor

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Inspector Review and/or Actions (cont.)

Subject Records

- inclusion/exclusion criteria, exemptions
- documentation of all study-related tests/procedures
- source documentation (ChartMaxx, EPIC, study-specific source documents, separate research charts, shadow charts)
- documentation of adverse events
- documentation of concomitant medications
- status of subject from baseline to study completion (alive, active, lost to follow-up)
- exposure to test article (potent/functional product)
- use of electronic records (validation, audit trial, electronic signatures)
- location, storage & retention of study records (on-site and off-site storage policies)
  Note: Records should be retained in accordance with CHOP *Retention and Destruction of Records* policy (A-3-9) and regulatory requirements.
- documentation and accountability of stored specimens (includes specimens stored at CHOP or specimens shipped to applicable research facilities)

Documentation & Reporting of Unanticipated Problems

- completion and submission of safety reports, as applicable
- reporting and documentation of unanticipated problems to the Sponsor, IRB and any applicable regulatory agencies (immediate reporting of serious and unexpected problems)
- documentation of unanticipated problems on CRFs
- classification (grading) of unanticipated problems

Frequently Asked Questions

During the course of the site inspection, the agency's representative may address specific questions to the PI, coordinator and members of the study team. Many questions are prompted to assess consistency and accuracy in response and compare practices and knowledge of investigational procedures. ***Common questions asked during a site inspection include***:

1. Provide an overview of the study including background, objectives, study design, duration of the study, subject population, number of subjects enrolled, etc.
2. What responsibilities were delegated to other members of the research team?
3. How are potential research subjects identified?
4. Who screens and recruits subjects?
5. Were all advertisements used for recruitment IRB approved?
6. Who verifies inclusion and exclusion criteria?
7. Who obtains informed consent/assent?
8. Was written documentation of consent required?
9. Is the informed consent process documented in the medical record?
10. Was assent required? If so, what is the minimum age for which assent is required?
11. Were any research participants wards of the state?
12. Were screening and enrollment logs used and maintained during the conduct of the study?
13. Where was the study conducted? (Inpatient vs. Outpatient)
14. Study start and completion dates?
15. How was data obtained and recorded?
16. Who was responsible for distribution, administration, and accountability of the test article?
17. Is the subject required to return the test article?
18. What are the procedures for destruction of the test article and/or return of the test article to the Sponsor?
19. Is documentation and accountability of stored specimens accurately maintained? Where are specimens stored?
20. Is there a time frame to administer the test article (e.g., if a drug is administered how long does it take to administer the drug)? What is the route of administration (e.g., IV push, intravenous infusion, or oral)?
21. What are the side effects of the test article, if applicable?
22. How is the test article stored? (e.g., room temperature, refrigerated, frozen)

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Questions the FDA May Ask (cont.)

23. Was a temperature storage log or documentation maintained?
24. Are quality control checks routinely done to ensure the temperature of the investigational product is appropriately maintained? If so, how often and by whom?
25. What systems are in place if there is a power outage to ensure temperature stability of the test article?
26. Where is the investigational product stored (e.g., in pharmacy, research department, OR)?
27. Were there any changes in the protocol or study design?
28. Were there any protocol deviations or approved exemptions?
29. How is the investigational product received (e.g., shipped directly from manufacturer or Sponsor to CHOP main pharmacy or satellite pharmacy)?
30. What is used as source documentation (e.g., EMR, study-specific source documents, separate research chart, shadow chart, CRFs, lab data, imaging, or diagnostic data)?
31. Are electronic records used?
32. How are electronic records validated? Is there an audit trail? Were electronic signature implemented?
33. Where are research documents stored (e.g., on-site, off-site, long-term storage)?
34. How long are research records retained?
35. Was the study routinely monitored?
36. Is there documentation of each monitoring visit?
37. Was a pre-study, site initiation visit completed?
38. Is documentation of training noted?
39. How often was the study monitored? Was the study team satisfied with the overall monitoring of the study?
40. Is there documentation of the monitor's communications with the PI or other members of the study team?
41. Is there documentation of the monitor's evaluations of the progress of the study?
42. Did any unanticipated problems occur?
43. Were the unanticipated problems reported to the IRB, Sponsor, and applicable regulatory agencies in a timely manner?
44. Were the unanticipated problems related to the test article?
45. Did the subject require any intervention as a result of the adverse event? What was the intervention?
46. Were there any study specific SOPs written for the study?
47. Is the study an applicable clinical trial and registered in the ClinicalTrials.gov database or equivalent registry?

Inspectional Processes & Investigator Responsibilities (cont.)

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Exit Interview Preparedness

- Reserve a meeting room and contact institutional officials in preparation for the exit interview. ***The following Research Administrators should be informed of the pending exit interview***:
  - Chair, Committees for the Protection of Human Subjects (IRB)
  - Director, Human Subjects Research (IRB)
  - Vice President, Research Compliance and Regulatory Affairs
- During the exit interview the agency's representative will discuss the findings from the inspection and notify the PI if deficiencies were found. This is the opportunity for the PI to provide information and clarification regarding any queries or concerns raised during the review and inspection.
- Form FDA 483, "Inspectional Observations," will be issued when deviations from regulations are observed.
- Inspector will advise on when to expect the regulatory agency follow-up letter.
- Inspector will advise on any circumstances requiring re-inspection by the regulatory agency.

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Post Inspection

FDA's Establishment Inspection Report (EIR) and classifications:

- **NAI** – no action indicated; no findings were found during the inspection.
- **VAI** – voluntary action indicated; objectionable conditions or practices noted but administrative or regulatory actions are not indicated.
- **OAI** – official action indicated; serious conditions found during site inspection and regulatory and/or administrative actions will be recommended. Examples of administrative or regulatory actions include:

  - issuance of a warning letter
  - study is not acceptable in support of safety and efficacy data
  - Sponsor inspection warranted
  - initiation of disqualification procedures
  - seizure of investigational product
  - injunction
  - prosecution

Responding to FDA Verbal & Written Findings

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ORC Assistance

To support the Investigator in constructing a written response to the agency's verbal or written findings (e.g., Form FDA 483 or the EIR), all draft responses must be reviewed by the ORC. The ORC will coordinate reviews with other offices as necessary (e.g., Office of General Counsel, IRB) and will provide feedback to the PI.

See *Site Inspections by Regulatory Agencies* for specific requirements.

Timeframe, Recipients, & Method of Delivery

- CHOP requires a prompt response to findings observed by the regulatory agency.
- The Study Coordinator, Sponsor/CRO, and applicable Research Administration personnel must be copied on the response.
- If submitting a hardcopy response by mail, letter must be sent by registered mail or shipping carrier such as FedEx®. Alternatively, email may be used.

Additional information

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Related Policies & Procedures

- *Site Inspections by Regulatory Agencies*
- *Clinical Research Essential Documents*

References

- *FDA's Compliance Program Guidance for Clinical Investigators*
- *Freedom of Information Act*

Document Contact

Karen Burke, Director, Research Compliance

Publication Authorization

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Director, Research Compliance

Version History

Reassessment of this guide will occur at least once every 24 months. The table below documents the version history for this guide. A cumulative history for this document is maintained for seven years.

Approval Date	Version	Version Summary
01/07/10	V1.0	Initial documentation/publication.
01/25/12	V2.0	Re-assessment and republication.
04/22/13	V3.0	Re-assessment and republication.
08/08/16	V4.0	Re-assessment and republication.
10/11/18	V5.0	Re-assessment and republication.
09/08/20	V6.0	Re-assessment and republication.