FDA INSPECTIONS

Introduction and Purpose

The U.S. Food and Drug Administration (FDA) conducts inspections to ensure the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials are protected, to determine the accuracy and reliability of clinical trial data, and to determine if the study has been conducted in compliance with FDA regulations. The most common type of inspection is classified by the FDA as a “Routine” inspection and is generally triggered by a marketing approval submission. Clinical sites with the highest enrollment numbers in the pivotal trials are the most likely candidates for a routine inspection. “For Cause” inspections are less common, and generally are conducted to investigate a specific problem that has come to FDA’s attention.

The Office for Human Research Protections (OHRP) within the U.S. Department of Health and Human Services may also initiate and conduct inspections of clinical trials. The responsibilities, notification, conduct and response to OHRP inspections should follow the same procedures and requirements in this SOP, as applicable.

The purpose of this SOP is to outline the processes for the preparation, conduct, and response to an FDA inspection of a clinical trial at the University of Utah.

Definitions and Acronyms

Clinical Research: Clinical research includes all research involving human participants. It does not include secondary studies using existing biological specimens or data collected without identifiers or data that are publicly available.

Clinical Trial: Clinical trials are clinical research studies involving human participants assigned to an intervention in which the study is designed to evaluate the effect(s) of the intervention on the participant and the effect being evaluated is a health-related biomedical or behavioral outcome.

CAPA: Corrective and Preventative Action
ERICA: Electronic Research Integrity Compliance Administration
FDA: United States Food and Drug Administration
GCP: Good Clinical Practice
HIPAA: Health Insurance Portability and Accountability Act
IC: Inspection Coordinator
IDE: Investigational Device Exemption
IND: Investigational New Drug application
IRB: Institutional Review Board
OHRP: Office for Human Research Protection
PHI: Protected Health Information
PI: Principal Investigator
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SOP: Standard Operating Procedure

Procedure

1. Notification and Scheduling an Inspection

1.1. The FDA inspector should contact the study PI to schedule an inspection. If a sub-investigator, study coordinator, clinical research administrator or other individual is contacted with notification of the inspection, immediate notification of the PI must take place.

1.2. The following information should be obtained at the time of initial notification:

- Identity of the clinical trial(s) to be inspected, the scope of the inspection, and the reason or cause for the inspection
- Inspection start date, expected duration, and the number of inspectors
- Name(s) and contact information of the FDA inspectors
- Requests for specific personnel or specific documentation

1.3. The PI or designee will provide notice of the inspection (or arrival of an FDA inspector in case of an unannounced inspection) to the following:

- Institutional Review Board administration
- Clinical Trial Sponsor
- Compliance Services FDA Clinical Research Compliance Officer
- Investigational Drug Services administration
- Department Chair and Clinical Trials/Research Administration leadership as well as any applicable compliance/regulatory and study support staff

1.4. At the time of the notice of inspection, an Inspection Coordinator (IC) should be identified within the department, who will work with the PI to oversee the preparation and conduct of the inspection, as well as the response and follow-up action items post inspection.

1.5. The IC is responsible for the creation and maintenance of a Record of Inspection documenting all conduct of the inspection, from the time of notification through the complete inspection period. The Record of Inspection should document all details pertaining to the inspection.

1.6. In the case of an unannounced inspection, the FDA inspector should be asked to remain in a public area (e.g. lobby) with reception or security personnel until the PI, IC and/or inspection support personnel are contacted and an appropriate office or conference room can be secured for the inspection.
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2. **Preparation for the Inspection**

2.1. The PI, study coordinator, IC, and other essential study personnel will make arrangements to ensure they are available and on site for the planned duration of the inspection.

2.2. The IC will ensure that a conference room or other adequate space is reserved for the planned duration of the inspection. The inspection room should be away from patient clinic space and from research operations in order to avoid disruption, and should be free of documents or materials pertaining to other study or patient records.

2.3. The PI, study coordinator and other appropriate personnel should prepare a summary of the clinical trial(s) selected for inspection, which will include: IRB status, enrollment and participant status, description of protocol amendments and IRB approval dates, consent version log, deviations, serious adverse events and other safety issues.

2.4. A listing of FDA-regulated studies conducted by the investigator in the role of PI for the last 3 years should be compiled and include the IRB number, protocol title, sponsor name, activation date, number of local participants enrolled, IND number (if applicable) and current study status.

2.5. Study documents that are likely to be inspected will be collected and reviewed for organization and completeness. These documents include:

- Regulatory Binders containing all IRB approvals, current and previous versions of the study protocol and informed consent form, FDA 1572, FDA safety reports, investigator and staff credentials (including Curricula Vitae and medical licenses), financial disclosure, laboratory accreditation, investigator’s brochure, monitoring reports, etc.
- Subject Screening and Enrollment logs
- Delegation of Authority logs and protocol training records
- Informed consent forms (100% of study participant consent forms should be reviewed in preparation of the inspection)
- Case report forms and all supportive source documentation
- Study participant charts should contain all source documentation to demonstrate compliance to each eligibility criterion, each protocol requirement, and provide evidence for validation of each case report form entry, as detailed in the University of Utah Study Records Management SOP (UUSOP-06).
- Pharmacy and drug accountability records
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- Investigational device inventory and accountability records
- Department and Cross-Departmental Standard Operating Procedures for research conduct

2.6. Review of the records identified above is conducted to ensure:
- The documents and charts are complete, accurate and well organized
- There are no links to other clinical trials, or to other subjects in the study participant charts, and that all sticky notes and other extraneous information not considered source data is removed
- All past monitoring and inspection findings have been resolved and processes have been implemented to ensure major deficiencies to not continue to occur

2.7. Deficiencies and errors discovered during the review of study documents should be corrected using GCP guidelines. Errors should be lined through, initialed and dated. White out and other ways to obliterate original records should never be used. Notes, if appropriate, should be added to explain or clarify any corrections made.

2.8. A HIPAA-compliant process will be devised to allow review of the electronic medical records and/or study database in case this is requested by the FDA inspector.

2.9. The clinical trial sponsor may send representatives to help in the review and preparation for the FDA inspection. Sponsor personnel will be allowed and encouraged to help in the preparation of the inspection, but should not be allowed to participate in the inspection or interact with the FDA inspectors.

2.10. The PI, sub-investigators and all other applicable study staff should be informed of the results of the pre-inspection review, including any relevant findings or concerns prior to the inspection.

3. Conduct of the Inspection

3.1. Upon arrival for the inspection, the IC should ask to see the inspector’s credentials and take note of the badge identification number and expiration date. The FDA inspector will present a Notice of Inspection (FDA 482) to the PI. The identification number and expiration date from the inspector’s credentials and a copy of the FDA 482 will be maintained in the Record of Inspection.

3.2. The IC will escort the inspector to the reserved conference room and contact Information Technology/Services to ensure the computer connection ports in the room are properly secured.
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3.3. The inspector may be offered bottled water, but individuals involved in the study inspection should not offer any food or other refreshments and should not interact socially with the inspector for the duration of the inspection.

3.4. An initial meeting should be held with the FDA inspector, PI, IC, and other applicable personnel to establish the agenda and timeline for the inspection and to discuss the scope, purpose and aims of the inspection.

3.5. All study records reviewed in preparation for the inspection should be available, but should not be provided to the inspector until specifically requested. Only the records requested should be provided for review.

3.6. The IC or an appropriate support staff member will act as scribe and document comments and questions made by the FDA inspector, responses by the PI or study team member, and will keep a record of all documents requested for review and that are photocopied. This will serve as an internal document as the Record of Inspection.

3.7. The FDA inspector may wish to conduct a physical inspection of the research facilities, clinical spaces, investigational pharmacy, infusion center, or other location where trial-related functions were conducted. The inspector should be accompanied at all times, and any questions or comments made by the inspector (and answers or responses provided) will be recorded for the Record of Inspection.

- FDA inspectors should be discouraged from taking photographs or other recordings of the research facilities that may capture patient or study subject protected health information (PHI), or result in a possible breach of confidentiality.

3.8. The inspector may request interviews with sub-investigators, coordinators, or any relevant study or clinical staff to ask specifically about aspects of the trial, or about institutional clinical research practices and procedures.

- If asked a question from an inspector, the interviewee should answer honestly and completely to the best of their knowledge. Answers should be clear and concise, answering the direct question but should not volunteer additional information. If the answer to a question is not fully known, the answer should be sought as soon as possible from someone who has the correct information. The interviewee should not guess, speculate or argue with the inspector.

- The Record of Inspection should document all questions and answers during the course of the inspection.

3.9. The FDA inspector will request study documentation for review, including regulatory binders, study participant charts, drug or device accountability
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records and other study records. The inspector may request to make copies of certain documents to retain with their files.

- Each record or document provided to the inspector should first be reviewed and verified by the IC, PI, or other appropriate study team member.
- If the inspector requests a copy of a document for their files, any paper copies provided should be stamped as “Copy” prior to being given to the inspector. An additional stamped “Copy” should be made for inclusion in the Record of Inspection.
- FDA inspectors may supply encrypted flash-drives and request electronic copies be placed within those devices. These devices are considered property of the federal government and should be handled with care and returned to the inspector timely complying with the request to load the drive with copies of electronic study record. The University of Utah may not supply the flash drive to the inspector. It is required that the inspector supply an encrypted device to the study team for use.
- The FDA provided flash drives should be permitted if requested, in lieu of or in addition to, the request for paper copies.

3.10. If the inspector requests to review the electronic medical record system or other electronic system used to create or store study information, they will be guided by the IC, study coordinator, or another study member to ensure access is limited to appropriate study participant records only.

3.11. The IC and PI should request a daily summary meeting with the inspector to discuss findings or observations, and to determine whether there are any concerns or questions that may be addressed. Any clarifications or corrective action plans that can be made should be implemented by the following day or at least by the closeout of the inspection.

- Minutes should be recorded of the daily summary meeting by the IC or designated scribe for inclusion in the Record of Inspection. A copy of the daily summary meeting minutes should be sent to the Compliance Services FDA Clinical Research Compliance Officer and to other departmental leadership as appropriate.

3.12. At the conclusion of the inspection, if the FDA inspector has formal observations, they will be presented formally to the PI in an Inspectional Observations report (form FDA 483).

- All observations should be reviewed and discussed in detail so that the PI, IC, and other individuals participating in the inspection closeout meeting
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are clear on the inspector’s intent which will assist in the response and implementation of corrective actions.

- The IC or scribe will take detailed notes during the inspection closeout meeting and include details of the inspector’s suggestions or discussion items.
- Unless correcting significant factual errors during the open discussion, any rebuttal should be saved for the written response. It is appropriate to ask what specific actions or changes will satisfy the observation.

3.13. No study personnel (PI, sub-investigator, study coordinator, etc.) should acknowledge or sign an affidavit issued and requested by an FDA inspector. If this situation arises, immediately notify department leadership and contact the Office of General Counsel who must provide legal guidance, oversight and interaction with the inspector on behalf of the University of Utah for this process.

4. Post Inspection

4.1. At the conclusion of the inspection, the IC will review the Record of Inspection to ensure it contains all the appropriate information, copies of documentation provided to the inspector, notes, minutes of daily summary meetings, etc. to adequately encapsulate the conduct of the inspection.

- If appropriate, an inspection summary report should be generated, which would include the following details: name of the FDA inspector(s), dates of the inspection, purpose and scope of the inspection, summary of the comments, questions and discussions between the inspector and PI/study personnel. The summary should also include a list of all records reviewed, copies that were given to the inspector, and corrective actions started during the inspection. If any follow-up dates were agreed to with the inspector, they should also be included in the summary report.

4.2. A copy of the FDA 483 (Inspectional Observations) should be provided to the IRB administration, clinical trial sponsor, and the Compliance Services FDA Clinical Research Compliance Officer for review and feedback in compiling a response to FDA.

4.3. The PI is responsible for a complete response to all inspectional observations in the FDA 483 within 15 business days (unless another timeline provided by the inspector).

- The IC will oversee the drafting of the response. Information, details, and responses to specific findings may be compiled from multiple individuals, depending on the nature of the observation and their expertise or
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knowledge of the study and events.

- The written response should address each observation separately and point-by-point, and should include the specifics related to each observation. Responses should be factual, clear and include any verifiable evidence to any observation where disagreement may exist.

- Corrective and preventative action (CAPA) plans should be carefully developed so that when implemented, they address the root cause of the problem and prevent further occurrence. Realistic timelines should be included for implementation of corrective actions. The CAPA should include evaluation components and timelines to demonstrate efficacy.

- As appropriate, the response should also include a statement of commitment from senior Department and/or University of Utah leadership.

4.4. Corrective actions should be tracked and documented as completed, when appropriate. This documentation may be needed to respond to a future inspection request for proof of previous actions completed as promised in the written response.

4.5. The FDA 483 and final written response should be submitted to the IRB via ERICA Report within 10 business days of submission to the FDA.

4.6. If/when acknowledgement of the response is received from the FDA or Department of Health and Human Services, this should be submitted to the IRB via ERICA as a Follow-up Informational Report, and a copy provided to the Compliance Services FDA Clinical Research Compliance Officer.

4.7. If the PI receives additional communication in the form of an Informational Letter (NAI – no action indicated, or VAI – voluntary action indicated), or a Warning Letter (OAI – official action indicated), it should be submitted to the IRB via ERICA Report. In addition, a copy of the letter should be sent to General Counsel/Compliance Services FDA Clinical Research Compliance Officer and promptly assessed in order to provide an appropriate response within the scope and time frame required in the letter.

Materials Required

- Notice of FDA Inspection (FDA 482)
- Study records and documentation (study participant charts, regulatory binders, etc.)
- Notes of FDA inspector comments, requests for copies, etc.
- Duplicate copies of all documents and records copied for the inspector
- Inspectional Observations (FDA 483)
- Other FDA communications and PI/institution responses, as applicable
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References
- 21 CFR Part 312.62: Investigator Recordkeeping and Record Retention
- 21 CFR Part 312.68 Inspection of investigator’s records and reports
- 21 CFR Part 812.145 Inspections (devices)
- ICH Guidance for Industry E6(R2): Good Clinical Practice 1.29, 6.10
- FDA Information Sheet Guidance, June 2010: FDA Inspections of Clinical Investigators
- CRCE Procedure: Governmental Agency Audits

Document Approval

Andrew Weyrich, Ph.D.
Vice President for Research, University of Utah

7-15-2020

Revision History

<table>
<thead>
<tr>
<th>Version Date</th>
<th>Change Summary</th>
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<tbody>
<tr>
<td>15Aug2018</td>
<td>Original Version</td>
</tr>
<tr>
<td>09Aug2019</td>
<td>Version #2 – definition section and SOP number updated</td>
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<tr>
<td>26Jun2020</td>
<td>Version #3 – SOP number updated in 2.5</td>
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