Mass General Brigham

Research Compliance Standard Operating Procedures (SOP) and Guidance

Coordination of FDA Clinical Investigator and Sponsor-Investigator Inspections

January 2022

PURPOSE

The purpose of this SOP and guidance is to provide information to Investigators and study staff regarding the FDA Inspection process. Although every FDA inspection is unique, the inspection process and the role of investigators and research staff during these inspections are similar.

BACKGROUND

FDA conducts clinical investigator and sponsor-investigator (herein referred to as investigator) inspections to determine if the investigators are conducting clinical studies in compliance with applicable statutory and regulatory requirements. FDA Inspectors may request to access, copy, and/or verify any records or reports made by the investigator with regard to, among other records, subjects' case histories and the disposition of the investigational product.

FDA conducts both announced and unannounced inspections of investigator sites, typically under the following circumstances[1]:

- To verify the accuracy and reliability of data submitted to the agency
- As a result of a complaint about the conduct of the study at a particular site
- In response to sponsor concerns
- Upon termination of the clinical site
- During ongoing clinical trials to provide real-time assessment of the investigator's conduct of the trial and protection of human subjects
- At the request of an FDA review division; and
- Related to certain classes of investigational products FDA has identified as products of special interest in its current work plan (i.e., targeted inspections based on current public health concerns).

During an inspection, the FDA Inspector typically verifies compliance with the regulations governing the use of investigational products and human subject protections at 21 CFR parts 11, 50, 56, 312, and/or 812 by inspecting records and talking to individuals involved in the conduct of the study.

[1] For complete list see FDA Information Sheet Guidance For IRBs, clinical investigators, and Sponsors: FDA Inspections of Clinical Investigators (June 2010) located at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf.

ROLES AND RESPONSIBILITIES

Designated Official:

The Mass General Brigham Principal Investigator (PI) is considered the 'Designated Official' (DO) at the Institution and is the main point of contact for the FDA. The FDA holds the PI responsible for conducting the clinical research in accordance with FDA, ICH GCP, and IRB regulatory requirements. The FDA expects the PI to be an integral part of the inspection. The FDA Inspector generally communicates directly with the PI, not with institutional officials or representatives.

The DO is responsible for:

1) Immediately informing the Institutional Liaison (IL) (i.e., Mass General Brigham Director of the HRA Compliance and Education Office) of the inspection
2) Scheduling the inspection and reserving space for inspectors and interviews
3) Overseeing inspection preparation, including gathering documents
4) Meeting with FDA Inspectors, ensuring requested documents are provided, documenting FDA questions, and responding to questions
5) Scheduling interviews with study team
6) Responding to FDA observations (Form FDA 483) and FDA Warning letter, if applicable
7) Overseeing post FDA inspection implementation of corrective action plan

Institutional Liaison:

The Institutional Liaison (IL) (i.e., Mass General Brigham Director of the HRA Compliance and Education Office) is the person designated by the institution to monitor the inspection's progress, serve as a resource to the DO and Institution, as well as coordinate key aspects of any written response to the FDA (e.g., response to form FDA 483).

This individual is the institutional point person and is responsible for:

1) Notifying hospital, compliance, and IRB leadership of inspection, tracking progress of the inspection, and keeping hospital, compliance, and IRB leadership apprised of inspection activities and concerns.
    - Notification will be made to: Directors of the IRB, VP of Human Research Affairs, Hospital Sr. Vice President of Research, Hospital Compliance Officer/Director of Research Compliance, Mass General Brigham Chief Research Compliance Officer
2) Coordinating internal review of study materials prior to the inspection
3) Providing FDA regulatory and inspection process expertise to DO during FDA inspection
4) Attending significant interviews and meetings with FDA inspectors (as allowed)
5) Providing FDA inspector or DO with institutional information as needed
6) Coordinating Investigator consultations with the IRB, Office of the General Counsel (OGC), or other institutional departments, as needed
7) Providing guidance to DO regarding implementation of corrective actions as appropriate during the inspection
8) If FDA Form 483 or FDA Warning Letter received, reviewing and editing DO's response, and coordinating internal review of DO's response prior to DO sending response to FDA
9) Working with hospital compliance/research compliance to determine if any applicable

reporting to sponsor regarding FDA inspection is necessary.

Sr. Chair of the Mass General Brigham IRBs & Mass General Brigham Director of the Compliance and Education Office

The Directors of the IRBs are responsible for:

1) Providing FDA regulatory and IRB review process expertise to DO during inspection
2) Following IRB External Reporting Policy
3) Evaluating FDA inspectional observations and determining non-compliance based on approved protocol
4) Working with OGC, Sr. VP of Research, IL, and Research Compliance to determine corrective and preventive action plans
5) Ensuring appropriate documentation regarding inspection is maintained in IRB protocol file (e.g., Form FDA 483, Warning Letter, Investigator responses)
6) Ongoing oversight of corrective actions if requested by IRB committees.

Mass General Brigham Chief Research Compliance Officer:

The Mass General Brigham Chief Research Compliance Officer is responsible for:

1) Tracking and maintaining statistics on FDA inspections for each hospital and system-wide for periodic reporting to the Mass General Brigham Research Compliance Committee, Mass General Brigham Board of Directors Audit and Compliance Committee, and other Mass General Brigham or hospital senior management groups
2) Providing oversight to ensure Mass General Brigham and hospital senior leadership (i.e., Sr. VP for Research, Chief Financial Officer (CFO), Compliance, OGC, etc.) are involved appropriately
3) Ensuring that findings of non-compliance are addressed in accordance with appropriate Mass General Brigham policies
4) Working with hospital Research Compliance or Corporate Compliance staff following an inspection to monitor compliance with corrective action plans and application of lessons learned across the Mass General Brigham system

Hospital Research Compliance Director/Corporate Compliance Officer

The Hospital Research Compliance Director/Compliance Officer is responsible for:

1) Providing training to the research community on this SOP
2) Notifying CTO of inspection findings and working with CTO to determine if additional reporting to sponsor is necessary
3) Working with CTO, Grants and Contracts, and Institutional SVP on sponsor reporting

Hospital Sr. Vice President for Research (or equivalent position)

The Hospital Sr. Vice President for Research is responsible for:

1) Reviewing FDA's inspectional observations (Form FDA 483) and Warning Letters, and determining whether a hospital response or other institutional action is merited
2) Ensuring and enforcing remediation, implementation of corrective action plan, reporting to sponsor, and all other steps necessary to close the matter

INSPECTION PROCESS

Notification

The FDA Inspector will contact the PI via email or telephone to schedule a routine inspection. The inspector will arrive unannounced for inspections that are for-cause or directed. If the PI is unavailable at the time of the call or the unannounced arrival, the Inspector may ask to speak to the primary study staff member or an administrative assistant. The FDA will want to schedule the inspection promptly; however, it is reasonable to ask the FDA Inspector(s) to accommodate the investigator's travel/clinic schedule.

The PI or person who speaks with the FDA Inspector should record the following information:

- FDA Inspector name & contact information
- Date/time of call
- Study to be inspected
- Reason for inspection
- Date and expected duration of inspection
- List of personnel FDA might want to meet with
- How many inspectors will be on-site
- Any additional details given

If the Inspector requests to receive documents prior to the site inspection, ask the Inspector to confirm in writing (e-mail) the exact documents they wish to receive, the address of the FDA office to which they are to be sent, to whom addressed, and deadline for receipt. Prior to providing documents, consult with IL. Any subsequent phone calls should be recorded on a paper log or electronically.

Pre-Inspection

The DO is responsible for overseeing preparation for the inspection. The DO should do the following after notification of FDA inspection:

1) Notify IL and Industry Sponsor (if any) of the FDA inspection
2) Secure a conference room or office for the FDA Inspector(s) for the duration of the inspection. The room should be private and free of other research study materials. The room should have access to the Internet and a photocopier should be nearby (if possible)
3) Inform the study team and gather study materials including: all regulatory documentation, IRB correspondence, and subject files (including consent forms, source documentation and

case report forms). If materials are stored offsite, they should be retrieved.

4) Prepare a list of all (active and inactive) FDA-regulated studies on which the DO is the Principal Investigator – the FDA will request such a list. It should include:
    - protocol #
    - protocol title
    - role in study
    - product name
    - name of sponsor, and
    - study start/end dates

5) Meet with the study team to review protocol, study procedures, and documentation practices.
6) Designate a member of the study team to take notes during significant interviews and meetings as well as maintain a list and copies of all documents provided to the inspector.
    - This person should also be responsible for obtaining an encrypted flash drive on which copies of all documents requested by the inspector will be saved. The flash drive will be taken by the inspector at the end of the inspection. Contact the Mass General Brigham HRA Compliance and Education Office (C&E Office) for information regarding the preferred flash drive for FDA inspections.
7) Review observations noted during prior monitoring visits, audits or inspections of this study or other FDA- regulated studies to ensure that they have been appropriately addressed.

The Mass General Brigham HRA Compliance and Education Office (C&E Office) can assist the DO and site in preparing for inspection. If time allows staff from the C&E Office can assist with onsite review of study files and suggest corrective actions as appropriate. Contact information can be found on the C&E Office website on Research Navigator. It is possible that the study sponsor may also send a team to assist in preparation for the FDA inspection.

Access to electronic research records and medical records:

Inspectors are not permitted by the FDA to sign confidentiality agreements required to use certain electronic systems at Mass General Brigham. If documents are stored electronically, then inspectors will complete over-the-shoulder review of documents with a member of the study team.

- Electronic Data Capture system (EDC): Check with the study sponsor or CRO that manages the EDC to see if a temporary user account can be created for the FDA Inspector. If the study team uses REDCap, Inspectors will do over-the-shoulder review of data in REDCap.
- Medical records: Inspectors will usually do over-the-shoulder review of the electronic medical record (Epic) with a member of the study team.
- IRB documents: Inspectors will do over-the-shoulder review of the IRB submission documents, approval letters, and related correspondence in Insight, LabArchives, Dropbox, or shared drive.

Inspection

Arrival of Inspectors

Upon arrival, the FDA Inspector will present their credentials and issue a completed Form FDA 482 (Notice of Inspection) to the PI. The PI should request to see the Inspector's credentials and receive a completed Form FDA 482 if not provided upon arrival.

The PI should

- Document the FDA Inspector'(s)' names and credentials (Note: FDA Inspectors will generally not allow you to photocopy their official badge – write down their name and identification number).
- Escort Inspector(s) to the assigned conference room.
- Gather key study personnel and IL, if allowed, for introductory meeting with the FDA Inspector(s).

The FDA Inspectors will

- Explain the purpose and scope of the inspection.
- Interview Investigators and study staff as needed.
  Note: Investigators and study staff should answer questions to the best of their knowledge (do not speculate or guess). Be concise and only answer questions that are asked. Assert facts and correct any factual inaccuracies, but do not be argumentative.
- Identify which study materials they would like to see.
  Note: Investigators and study staff should provide Inspectors only with information requested. If the requested information is not directly related to the clinical trial being inspected, consult the IL.
- Review study data.

FDA Inspectors will verify[1]

- The extent of delegation of authority and PI oversight.
- Who performed various aspects of the protocol (eligibility, consenting, etc.) and their qualifications.
- How study staff were oriented/trained on the protocol and investigational product
- That the Investigator followed the study protocol approved by the IRB.
- Where specific aspects of the protocol were performed
- How and where data were recorded
- If the Investigator is a Sponsor-Investigator, the FDA inspector will also verify:
  - The overall organization of the clinical research activities and monitoring of the selected trial(s).
  - Determine who is responsible for final evaluations and decisions in the review of adverse and safety information.

Note taking during inspection

The IL should be present at all significant interviews and meetings, as allowed, with the FDA Inspector. If the IL is unavailable, the IL will designate an appropriate individual, for instance the Hospital Research Compliance Director. In addition to the PI and any other study staff present, the IL will take notes to document all questions, responses, and promises made to the FDA. The IL will not actively participate in interviews/meetings.

Copying documents

FDA inspectors may make copies of documents as necessary but are not permitted to remove original documents from the hospital or Mass General Brigham office. If the Inspector requests copies of study documents:

- Copy the documents yourself. Stamp the copy Confidential.
- Make a copy of the documents for your records. Stamp your copies. Copy.
- Keep a log of requested/provided documents for reference. The log should include:
    - Date of request
    - Requestor
    - Name of Document
    - Initials of study staff providing document

FDA request to sign documents, including affidavits

The Inspectors may ask the DO to sign documents (e.g., affidavit) regarding the inspection. Do not sign any affidavits. The DO should feel comfortable asking for time to read, ask questions, consult with institutional representatives, and seek legal counsel prior to signing any document. If the DO has questions or concerns about the documents they are being asked to sign, the DO should contact the IL who can assist in connecting the DO with the appropriate resource for legal advice.

Post Inspection

Exit interview

At the end of the inspection, the FDA Inspector will conduct an exit interview. The DO, IL (or designee), and other staff the DO invites should be present. The Inspector will discuss the observations made during the inspection and, if inspectional observations of regulatory significance were made, will issue a written Form FDA 483 (Inspectional Observations) to the DO after the exit interview.

The DO should seek to correct any errors in the observations prior to the issuance of the FDA 483 if possible.

Responding to Form FDA 483

A copy of Form FDA 483 should be given to the IL immediately upon receipt. The IL will review the PI's draft response in consultation with the Compliance and Education Office, IRB Directors, Research Compliance and/or OGC as necessary. The response to Form FDA 483 should include the following:

- Point-by-point response to each observation
- Root cause analysis
- Determine if finding was an oversight/one-time occurrence or systemic where a procedural change is necessary
- Corrective action plan (what, when, how)
- Preventive action plan (how the investigator will prevent observation in future studies)
- Training plan and timeframe; tools and/or written documentation of staff training
- If the investigator disagrees with an observation, a factual response or correction providing verifiable evidence

The response to Form FDA 483 should be directed to the address listed in the upper left corner of the Form. The PI has 15 business days to respond to the inspectional observations identified in Form FDA 483.

The DO should work with the IL and hospital compliance/research compliance to notify the sponsor of the issuance of an FDA 483 and, with compliance, should also review other clinical trial agreements and grant documents for any requirements regarding notification to other sponsors whenever inspection of an unrelated study results in issuance of an FDA 483.

FDA Review of Establishment Inspection Report

The FDA Inspector who conducted the inspection prepares a written Establishment Inspection Report (EIR) to the FDA central office. The EIR, Form FDA 483 (if issued), copies of any materials collected during the inspection, and the PI's response are forwarded to the appropriate FDA Center for further evaluation and final classification of the inspection outcome. The FDA will then make one of the following final classifications for the inspection:

- No action indicated (NAI)
- Voluntary Action Indicated (VAI)
- Official Action Indicated (OAI)

The FDA will typically send one of the following letters to the clinical investigator:

- A letter that FDA observed basic compliance with regulations. Note that this letter will not always be sent when FDA observes no significant deviations.
- An *Informational* or *Untitled Letter* that identifies deviations from regulations that do not meet the threshold of regulatory significance for a Warning Letter.
- A *Warning Letter* that identifies significant deviations from the regulations. Significant deviations can lead to enforcement action if not promptly and adequately corrected. Warning letters include a request for correction and written response to the FDA.
- A *Notice of Initiation of Disqualification Proceedings and Opportunity to Explain* (NIDPOE). FDA may initiate a process to disqualify the clinical investigator from receiving investigational drugs, biologics, or devices if the investigator has deliberately or repeatedly submitted false information to the sponsor or FDA. For more information see FDA's Information Sheet Guidance, "Clinical Investigators Administrative Actions – Disqualification."

The FDA posts final clinical investigator inspection classifications, as well as warning letters, on its website: Clinical Investigators - Disqualification Proceedings | FDA

The DO should share a copy of any letter received by the FDA with the IL upon receipt for consultation with the SVP, Research Compliance, the IRB, and/or OGC in preparing a response, if needed. The DO should adhere to the FDA's instructions.

FDA Inspection Close Out

An FDA Inspection close out letter may be issued when FDA has completed the inspection of the clinical site and is satisfied with corrective and preventive actions.

A Note on Corrective and Preventive Actions:

The DO is responsible for ensuring that any corrective and preventive actions promised to FDA are fully implemented. Ongoing oversight of corrective actions, if requested by IRB committees, will be provided by the Compliance and Education Office on behalf of the IRB. The Hospital Research Compliance Officer will provide monitoring of corrective action plans specific to financial management and hospital policy. FDA may revisit clinical sites to ensure promised actions have been implemented.

Additional Resources:

FDA Bioresearch Monitoring Program - Compliance Program Guidance Manual For FDA Staff

- Clinical Investigators & Sponsor-Investigators: https://www.fda.gov/media/75927/download
- Sponsors & Contract Research Organizations (CROs): https://www.fda.gov/media/75916/download

FDA Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf