

Guidance for OHSU Principal Investigators and Study Teams: FDA Inspection Conduct and Responses

BACKGROUND AND REGULATORY OVERSIGHT

FDA's Bioresearch Monitoring (BIMO) Program inspects clinical investigators, IRBs, sponsors, monitors, contract research organizations (CROs) and other facilities (e.g. laboratories) "to help ensure the protection of the rights, safety, and welfare of human research subjects involved in FDA-regulated clinical trials, to verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications, and to assess compliance with statutory requirements and FDA's regulations governing the conduct of clinical trials."

Clinical Investigators are required to permit FDA to access, copy and verify any records or reports made by the investigator to comply with 21 CFR part 312.68 and 812.145.

This document provides guidance on interactions with the FDA, notifications, and responding to a Form FDA 483 and/or FDA letters after the inspection. The scope of an FDA inspection may differ depending on the role the OHSU PI played in the study and the activities conducted at OHSU (Investigator vs Sponsor-Investigator).

FDA INSPECTION NOTIFICATION

FDA conducts both announced and unannounced inspections of clinical investigator sites. When an investigator is notified of a pending FDA inspection or when an FDA Inspector(s) arrives unannounced, the study team should make the study records requested available to the FDA Inspector.

If the Principal Investigator (PI) is unavailable, inform the Inspector and let FDA decide to postpone or continue with the inspection. The study team should not refuse or delay the audit. If a site refuses or postpones the inspection, the FDA inspector will notify the FDA district office who will address the refusal with the PI. If the PI/Sponsor-Investigator still refuses or there is an unreasonable delay (de facto refusal), FDA may pursue a warrant.

PI NOTIFICATIONS

The PI should notify OHSU departments involved in the study conduct and funders as required by their contracts.

- Notify the industry Sponsor immediately (unless the FDA instructs you not to notify the Sponsor). If you have questions about the requirements for notifying an Industry Sponsor/Funder/Supporter, refer to your contract and contact CTO Contracting.
- Notify the OHSU IRB Chair and IRB Manager, the CTO-Contracting Manager(s), and the OHSU Research Pharmacy if drug is still on site (invdrug@ohsu.edu). Include the eIRB #, protocol title, PI name and the date(s) FDA plans to be at OHSU in the emails.
- If the study is using a central IRB, the PI should also notify the central IRB as required by their policies.
- Notify your departmental contacts as appropriate. This may help you with administrative resources and rooms scheduling.

PREPARATION

The following recommendations will allow the study team to put their best foot forward during the audit and to inform themselves of FDA expectations.

- Review the protocol and consent forms to re-familiarize yourself with the study (especially if it has been a while since the study was conducted).
- Study documentation should be inspection ready at all times. There is a [Clinical Trial Regulatory File Checklist](#) and an [FDA Audit Checklist](#) – checklist available on the [OCTRI Tools, Templates, and Resources webpage](#). The Knight Cancer Institute also has an SOP and an FDA Inspection and Preparation Manual for their investigators on the Knight bridge site.
- Review the FDA Bioresearch Monitoring Program (BIMO) Compliance Program Manual(s) relevant to the upcoming inspection. FDA Inspectors use the manual(s) to conduct the investigation. There are separate manuals for:
 - Clinical Investigators
 - Sponsors, Contract Research Organizations, and Monitors (for OHSU Sponsor-Investigator trials)
- Create a plan for the FDA inspection to help your site appear well organized. This will make the audit go more smoothly.



- Schedule a conference room for the duration of the inspection. The room should have adequate work space for the Inspector, should be away from the flow of office/clinic traffic, and near a copy machine.
- Assign a primary contact for the FDA Inspector, and make sure they are available for the duration of the inspection.
- Notify any subject matter experts that the FDA is going to be here and confirm they will be available (co-I specialists)
- Plan to have additional people with the appropriate access (eIRB, study files) to help retrieve information quickly.

THE FDA INSPECTION

The inspector will verify compliance with the protocol and applicable regulations by reviewing documents and talking to individuals involved in the conduct of the study. The Inspector will record all responses and findings in an Establishment Inspection Report (EIR).

The PI or most senior member of the study team (if the PI is unavailable) should be present at the beginning of the inspection to meet with the FDA Inspector. The study team should plan for the following:

- The FDA Inspector will show their badge with their credentials and issue a completed Form FDA 482 (Notice of Inspection). Note the FDA Inspector's name and badge # in the site audit records.
- During the initial meeting with the FDA Inspector, be prepared to discuss the Inspection process.
 - Introduce the site primary contact and provide general tour of the facility (bathroom, exits, and work area for FDA Inspector). FDA inspectors are considered escorted guests at OHSU, so plan to have an escort for the FDA inspector everywhere they go on the OHSU campus.
 - Notify Transportation and Parking and provide the FDA Inspectors license plate number so they can be put on the do not ticket log. Questions regarding parking should be directed to ohsuid@ohsu.edu (503)-494-8283.
 - Ask what documentation, resources, and facilities that the Inspector would like to view during the visit.



- Schedule at least one daily check in with the PI and the FDA Inspector. The Inspector should check in/out with the primary contact at the beginning and end of every day.
- Do not offer refreshments or lunch to the Inspector

DOCUMENTATION

All source documents, regulatory documents, and CRFs should be available to FDA Inspector upon request (21 CFR parts 312.68 and 812.145). Do not withhold documentation from the Inspector.

- Ask the FDA Inspector if they want to review the subject medical records (source documents) electronically or on paper. Then complete either the [OHSU Clinical Research Paper Chart Audit Request Form](#) or the [External Research Monitor and Audit Request Form](#) based on the inspector's preference.
- Do not share your login or give the FDA inspector direct access to any OHSU systems (e.g. eIRB, eCRIS, X drive, or Box). Arrange to sit with the investigator while you navigate the system and/or print requested materials needed for the audit. Study research database access should follow study/system SOPs.
- Regulatory records should be printed or viewable by the inspector (note there is no process for granting outside auditors/inspectors access to the eIRB). If utilizing electronic regulatory binders, confirm with the inspector if they want access or require records to be exported/printed for their review.
- Keep track of all documentation provided to the inspector. Redact patient name and MRN on the copy provided to FDA. Discuss the redaction process with the Inspector to ensure subject confidentiality is protected while still providing FDA the documentation they require.
- If the FDA Inspector requests electronic copies of records, provide them on an encrypted flash drive. If you have questions about the appropriate method of providing electronic records, contact OHSU Information Privacy and Security at OIPS@ohsu.edu or call 503-494-0219
- Do not provide documentation (or offer information) the FDA Inspector did not request UNLESS additional documentation explains irregularities (e.g. notes to file, sponsor correspondence related to exceptions/protocol deviations) related to the request.
- Documents not subject to FDA Inspection:



- Contracts and budgets
- Independent Quality Assurance Audit results/reports. This does not exclude sponsor monitoring reports or other quality/safety audits that are required by sponsors/investigators to meet predicate rule requirements.
- Subjects/patients not enrolled in the study being investigated. If the Inspector wants to review other studies you will be notified that the scope of the inspection has changed.

COMMUNICATION

Conversations with the FDA Inspector will be recorded in the Establishment Inspection Report. FDA Inspectors are representatives of the Federal Government and are trained interviewers doing “detective work”; therefore:

- Be truthful in all communications with the FDA Inspector. If you don’t know an answer, don’t guess. State you will get the information requested.
- Do not answer questions that are not related to what you do – refer to other subject matter experts (e.g. pathologist, research pharmacy, etc.).
- Politely correct erroneous information presented by the FDA Inspector.
- Reference documentation (protocol, policy or procedure references) whenever possible while responding to questions.
- Limit conversation to the study being inspected and FDA’s questions.
- Do not be defensive, argue and/or complain (about the sponsor, PI/coordinator, IRB, etc.).
- Keep track of questions asked and documents provided.

END OF THE INSPECTION

At the end of the inspection, the FDA Inspector will conduct an exit interview with the PI/Sponsor-Investigator or most responsible study staff if the PI/Sponsor-Investigator is not available. Attendance should include the PI/Sponsor-Investigator, primary contact during the inspection, and any necessary subject matter experts. Assign someone to scribe the exit interview.

EXIT INTERVIEW

- Follow the same communication guidelines described above: answer honestly, do not withhold information, do not get defensive, politely correct erroneous information

presented by FDA, and provide documentation whenever possible. This is your opportunity to agree/disagree with the findings.

- A 483 will be issued to the Sponsor-Investigator/Principal Investigator at the conclusion of an investigation, if the FDA Inspector has observed any conditions that may constitute violations of the Food Drug and Cosmetics Act and related acts.
- If you receive a 483, review the information on the form, ask questions, provide/refer to documents that show corrective action (retraining, IRB submissions, revised SOPs) if possible. The FDA Inspector can make changes to the 483 during the exit interview, if the information provided warrants a change.
- Request a copy of the Establishment Inspection Report (EIR). They are not automatically provided. This will come at a later date.

AFTER THE INSPECTION

The FDA Inspector has 30 days to submit their EIR, the records collected during the inspection, to the FDA district office. If there are no findings during the inspection it is unlikely there will be an additional communication with FDA. However, if a Form 483 is issued FDA will consider all of the information collected when determining whether additional action is needed.

NO FINDINGS

If a Form 483 is not issued, no further action is required. The PI should consider scheduling a study team debrief on the inspection and make any procedure changes based on the FDA feedback you received during the Inspection. If changes are made to study procedures/departamental standard operating procedures (SOPs), training should be completed and documented.

483

The FDA Form 483 notifies the PI of objectionable conditions at the sites. The 483 is not intended to be a comprehensive list of all of the potential objectionable findings, therefore, FDA can add additional findings after all of the materials are reviewed by the district office.

It is strongly recommended that the PI/Sites respond in writing and implement corrective action in a timely manner. If a 483 is issued, the PI should do the following:

- Respond no later than 15 business days. Responses submitted after 15 days are not considered when FDA makes their determination regarding additional action.

- Do not ignore the 483, delay responding, or provide an argumentative and/or unsupported response.
- Update relevant departmental SOPs to address deficiencies noted in the 483. Staff training on the revised SOPs should be completed and documented.
- Take any actions suggested by FDA to affirm the validity of the data called into question (e.g. additional validation testing /internal audits/ collecting additional documentation).
- Get input from all departments involved in the findings (e.g. IRB, Research Pharmacy) to include in your response. Do not promise changes to OHSU policies without input/buy-in from those departments.
- See ‘Corresponding with the FDA’ section below for guidance on drafting your response to the Form 483.
- Send the study Sponsor (if industry sponsored) the Form 483 immediately, if required under the contract. The sponsor may be able to help you with a response. The sponsor should be allowed to review the response before it is submitted to the FDA, but the sponsor can’t require edits to the response.
- Submit a Reportable New Information (RNI) report to the IRB with the inspection findings within 5 days (per RNI policy) of receiving the 483. Submit a copy of the 483 response in the eIRB when it is available.
- Notify the IRB Chair and IRB manager via email when you receive the 483 (regardless of the study status in the eIRB) and when you submit your response. Work with the IRB regarding responses to the FDA, particularly if they involve the IRB review or approval.
- You can ask Research Integrity/Legal to review response prior to sending it to the FDA.
- Prepare all studies for re-inspection. If you successfully respond to the 483, you may find that you are selected to be audited on another trial to make sure the corrective actions are working.

CORRESPONDING WITH FDA

When responding to the 483 remember that the information provided will impact FDA’s decision regarding any additional action they may take. If 483 observations are significant and/or you do not respond accordingly, the FDA can take further action. FDA 483 observations should be taken very seriously and should be addressed and responded to thoroughly and professionally.

AUDIENCE

When responding to FDA, remember your audience. 483 responses are available to the following:

- FDA Inspector, the FDA District Office, FDA Headquarters
- OHSU and any other overseeing IRBs
- Study funder(s) (industry and federal)
- Public – available via Freedom of Information Act requests. Warning letters are published on the FDA website.

ADDRESSING FDA 483 FINDINGS

The quality and thoroughness of your 483 response is very important. If the FDA reviewers do not agree that you addressed their concerns or if your response is not properly supported, FDA may escalate your issues to a warning letter.

Respond to all observations on the 483 in a way that is easy for the FDA to follow. Each response must address the central issue(s) raised in the observations and provide factual objective evidence that permits evaluation and aids in understanding the response. A 483 response needs to contain clear, factual, well-supported descriptions of events, systems, procedures and data relevant to each observation. All the information needed to answer an observation can be contained in a narrative presentation that is easy to follow and that allows you to structure the answers in a way that places the site in the best light.

- Consider a cover memo with a list of attachments and accomplishments toward the corrective actions. Your cover memo should include the following:
 - Reason for the letter
 - Define any terms used later in the letter
 - Include a commitment of the PI to resolving the issues identified by the FDA 483s and/or warning letter
 - Address any issues that relate to Sponsor-Investigator/PI responsibilities
 - Identify any points of disagreement (see note on disputes below)
 - Introduce the appendices
 - Consider listing what you have already accomplished toward correcting the findings



- Designate the cover letter and response as including confidential information not subject to disclosure under the federal Freedom of Information Act (FOIA) exemption 4.
- Define the planned response timeline (i.e. once per month or every 6 weeks) and make a commitment for the next update response if you are unable to address all of the findings within the 15 days.
- Include PI and site contact information
- The response should include the findings verbatim from the 483 followed by your response. If your response includes documents to show corrective action or to contest the findings, include an appendix with the appropriate documentation attached.
- Include your determination of the root cause of the problem(s). Implement corrective action for each finding. Your plan should specify:
 - Root cause analysis
 - Immediate corrections required/performed
 - Corrective action plan to prevent recurrence. This may include revising standard operating procedure, retraining staff, revising protocols, changes in workflow/documentation and additional monitoring.
 - Include a plan for monitoring the success of your corrective actions.
 - Assignment of responsible individual (if applicable)
- Avoid repetition in your responses. If the 483 includes related observations, simply reference your responses to other findings if the same corrective action applies.
- Provide a justification/documentation to support why the data from your site should be considered reliable and how subjects were protected during the course of the study, if applicable.
- If you can't implement the required corrective action(s) within the 15 day response timeframe, include a timeframe in the response and a date you plan to provide an update/corrective action plan to FDA.
- If you dispute the 483 observation and you can support this with factual objective evidence, then it is appropriate for your 483 response to point this out. The response should not ignore FDA's claim. Responses should provide the facts and explanation needed to explain why the observation is not accurate.



FDA RESPONSES/ACTION

After reviewing the 483, the EIR and your 483 response, FDA will determine if further action is required. The PI/Sponsor-Investigator will be notified of FDA's determination in one of the following letters:

- NAI – No Action Indicated. There is no need to respond to the NAI letter.
- VAI – Voluntary Action Indicated. Respond to the letter using the guidance for responding to the 483 above and address any additional information included in the letter. The VAI letter may not be the FDA's final determination. FDA will use your response to determine if additional action by the agency is required.
- OAI – Official Action Indicated – The PI/Sponsor-Investigator must respond to an OAI letter. The PI/Sponsor-Investigators should consider having OHSU Legal assist with the response.

Notify OHSU departments and the study Sponsor as outlined in the 483 section above when you receive FDA's determination letter.

ADDRESSING AN FDA OFFICIAL ACTION INDICATED (OAI) "WARNING" LETTER

If the PI/Sponsor-Investigator receives an OAI "warning letter" a response to FDA is required. The PI should complete the following:

- All observations/findings in the warning letter should be addressed in the same manner as a 483. Provide documentation of corrective actions taken since the 483 was issued.
- Submit an RNI to the IRB as outlined above and also email the IRB chair and IRB manager.
- Notify the Industry sponsor immediately, if required by the contract.
- Notify the funding NIH Institute(s) or Center(s) within 72 hours of receiving (or receiving notice) of the Warning Letter, if the study receives NIH funding.
- Notify OHSU Legal for assistance in responding.
- The IRB will also provide assistance for IRB related findings.

FDA will use the PI/Sponsor-Investigator's response to a warning letter to determine if further action is required, such as disqualification proceedings.

RESOURCES AVAILABLE

Oregon Clinical and Translational Research Institute's (OCTRI) Regulatory Knowledge and Support (RKS) program is available to answer questions regarding this guidance document (adamsb@ohsu.edu). RKS also provides consultations on IND/IDE study conduct, documentation, and other regulatory requirements. To request a consultation, contact the OCTRI Research Navigator (OCTRI@ohsu.edu) and request a regulatory consultation.

REFERENCES

Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors¹ FDA Inspections of Clinical Investigators June 2010

<https://www.fda.gov/media/75185/download>

Bioresearch Monitoring Program (BIMO) Compliance Programs

<https://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614.htm>

Bioresearch Monitoring Inspections in Vitro Diagnostic Devices

<https://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074893.htm>

FDA Form 483 Frequently Asked Questions:

<https://www.fda.gov/ICECI/Inspections/ucm256377.htm>

FDA Office of Regulatory Affairs (ORA) Inspection Observations

<https://www.fda.gov/ICECI/Inspections/ucm250720.htm>

Notice to NIH Grantees/contractors Regarding Letters or Notices from the Food and Drug Administration (FDA) <https://grants.nih.gov/grants/guide/notice-files/not-od-00-053.html>

<https://grants.nih.gov/grants/guide/notice-files/not-od-00-053.html>