

FDA Site Inspection Guidance for Investigators and Staff

1 Introduction

The Food and Drug Administration (FDA) Bioresearch Monitoring Program (BIMO) oversees FDA-regulated human research by performing site visits to clinical investigators, sponsors, and Institutional Review Boards (IRBs). BIMO's authority is set forth in [21 CFR 312.68](#): Inspection of Investigator's Records and Reports. The FDA's goals with site visits are to:

- protect the rights, safety and welfare of subjects involved in FDA-regulated clinical trials,
- verify the accuracy and reliability of clinical trial data submitted to the FDA in support of research or marketing applications, and
- assess compliance with FDA regulations governing the conduct of clinical trials.

The FDA conducts inspections to determine if investigators are in compliance with FDA regulations and the protocol. Inspections can be announced or unannounced. Inspections on clinical research can also be study-specific or investigator-specific, and may be for one or multiple studies. Most inspections of clinical investigations are routinely performed to verify data submitted to the FDA (e.g., at sites enrolling the largest number of participants) or for general surveillance. For-cause/directed inspections of clinical investigations can also occur as a result of a complaint or notice of non-compliance made to the FDA, due to sponsor concerns, to verify implementation of corrective actions following a previous inspection, or based upon current and ongoing public health issues.

The Northwestern University IRB Office compiled this guidance to aid investigators and research staff throughout the process of a Food and Drug Administration (FDA) Inspection. This is a general guidance to assist investigators during the FDA Inspection process based on standard inspections and may not be all inclusive of each investigator's experience.

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2 FDA Inspection Notification

Routine inspections are generally announced and usually receive 1 to 14 days' advance notice. For-cause inspections may be announced or unannounced with little or no advance notice. Inspections cannot be postponed without sufficient justification.

2.1 Record Initial Communication and Inspection Requests from the FDA

Take detailed notes on all communication with the inspector once the FDA provides the inspection notification. In regards to the notification itself, this includes:

- Who received the notification and when
- Estimated date and duration of the inspection
 - How long will the inspector(s) be on site?
 - Are the dates flexible?
- FDA inspector(s) contact information
 - Will there be more than 1 inspector?
- Purpose and scope of the inspection
 - Who/what is being inspected?
 - Is it an inspection of a study or of an investigator?
 - Will multiple protocols be inspected?
- Why is the inspection being done? The inspector's requests for the inspection (specific personnel, documents, etc.)
- If any information is needed before the inspection, and if so, by when.

If the inspector does not provide all of the above information, request it or seek clarification. If there is no advance notification of the inspection, request and record this information at the initial meeting with the inspector upon their arrival.

2.2 Notify Others of the FDA Inspection

Promptly notify all of the following stakeholders about the inspection, including the estimated date/duration the inspector will be on-site and the purpose/scope of the inspection, so they can each prepare for the visit as necessary:

- All study investigators and staff
- Department chair
- Northwestern IRB Office (all of the following)
 - IRB Compliance Unit (irbcompliance@northwestern.edu)
 - Piper Hawkins-Green, IRB Compliance Manager (piper@northwestern.edu)
 - *For biomedical studies*: Lisa Linn, Biomedical IRB Manager (Llinn@northwestern.edu) and Main Biomedical Office (irb@northwestern.edu)
 - *For social-behavioral studies*: Braden Van Buskirk, Social and Behavioral IRB Manager (b-vanbuskirk@northwestern.edu) and Main Social and Behavioral Office (sbsirb@northwestern.edu)
- Office for Sponsored Research (if the study is externally funded or grant funded)
 - Department Grants/Contracts Officer or SponsoredResearch@northwestern.edu
- External IRBs (if the study has ceded review to an external IRB or if participating site IRBs have ceded review to Northwestern IRB)
- Directors of clinics or centers (if applicable)
- Other relevant department/clinic/center staff and/or administrators (if applicable)

- Study sponsor or Contract Research Organization (CRO) (if externally sponsored/funded)
- Investigational Pharmacy (if utilized for the study)
 - invdrugser@nm.org
- Feinberg School of Medicine, Office for Research (if the PI is affiliated with FSM)
 - Abby Cosentino-Boehm, Director of Administrative Operations (a-cosentino-boehm@northwestern.edu)
- Staff in clinic spaces that may be visited by the inspector (if applicable)
- Local ancillary support services, such as laboratories, imaging, diagnostic testing, pathology core, electronic systems, etc. (if applicable)

In the notification to each entity above, include whether the FDA has requests related to their function, such as availability of specific people, documents, or a tour of facilities.

3 Before the FDA Inspection

The following steps are recommended in preparation for an FDA inspection.

3.1 Review and Understand Investigator Obligations

The Principal Investigator (PI) should review the following guidance on FDA inspections and their responsibilities for FDA-regulated research.

Inspection guidance from the FDA:

- [FDA Inspections of Clinical Investigators: Information Sheet Guidance](#). This guidance provides information to clinical investigators on how and why the FDA conducts inspections.
- [FDA Compliance Program – Bioresearch Monitoring](#). This document is the detailed guidance for FDA inspectors on how they are to conduct inspections of clinical investigators and sponsor-investigators and the regulations that guide their inspections, and may be useful to anticipate the scope of review.

Investigator Responsibilities:

- PI obligations per Northwestern IRB policies and procedures for human research detailed in Northwestern's [Investigator Manual \(HRP-103\)](#).
- Delegation of authority (DOA) log:
 - Confirm that the log is up to date, reflecting additions and removals of all staff
 - Review roles and responsibilities for accuracy of tasks performed
 - Ensure appropriate delegation of study-related tasks based on staff qualifications
 - Validate that delegated tasks were initialed and dated by the PI before involving staff in the study
- PI obligations for the IND under [Form 1572](#) (for investigational drug trials only):
 - Will assure that the study will not start prior to review and approval by the IRB
 - Will conduct and personally supervise the study according to the relevant protocol

- Will only change the protocol after notifying the sponsor and obtaining IRB approval prior to implementing the change
- Will seek a properly constituted IRB and obtain initial and on-going review
- Will obtain informed consent of participants and submit progress reports to the IRB at intervals not to exceed 1 year
- Will prepare and maintain adequate and accurate case histories designed to record all pertinent observations for each participant
- Will prepare and maintain adequate and accurate drug accountability records
- Will collect and report the data in a way to accurately and completely reflect the observations noted during the study
- Will report immediately and promptly if adverse events are alarming
- Will assure that the study will not start prior to review and approval by the IRB
- Will conduct and personally supervise the study according to the relevant protocol
- Will only change the protocol after notifying the sponsor and obtaining IRB approval prior to implementing the change
- Will communicate to sub-investigators information on scientific matters of importance related to the investigation
- Will ensure that the drug is administered according to the stated dosing regimen, including dose, route, rate, and duration, and maintains records documenting such facts
- Will certify that the drugs are being tested for investigational purposes and will obtain informed consent of participants or their representative prior to enrollment

For more information on the Form FDA 1572 and making sure it is completed correctly, see the FDA's information sheet [Frequently Asked Questions – Statement of Investigator \(Form FDA 1572\)](#).

- Sponsor-Investigator obligations for the IND under [Form 1571](#) (for investigational drug trials only when the PI is also the IND holder or sponsor):
 - Not begin study until 30 days after FDA's receipt of IND
 - Not to begin or continue studies that are placed on hold
 - An IRB that complies with 21 CFR Part 56 is responsible for the initial and continuing review of the study
 - An agreement to follow all other applicable requirements
 - Name of individuals who are responsible for monitoring the conduct and progress of the study
 - Name of individuals who are responsible for the review and evaluation of safety information
- PI obligations for the **IDE or Abbreviated IDE** (for investigational device trials only):
 - See the FDA's webpage on [IDE Responsibilities](#) for both Investigators and Sponsor-Investigators for both significant risk device studies (conducted under an IDE) and nonsignificant risk device studies (conducted under an abbreviated IDE).

3.2 Review Protocol(s) Identified for Inspection and Related SOPs

Standard operating procedures (SOPs) are written, step-by-step instructions that describe how to perform a routine activity. They should provide enough procedural structure to ensure regulatory and clinical practice compliance and consistency across studies, while remaining flexible to avoid boxing oneself into a corner with too much detail. The FDA does not necessarily judge the quality of an SOP, but will evaluate if an SOP is in regulatory compliance, if study documentation adequately demonstrates it is being followed, and that improvements are made when an SOP is ineffective.

- All study staff should review and understand the current protocol(s), consent form(s), and SOPs
- Ensure the protocol, consent form(s), and/or SOPs are up to date and accurate with the following descriptions:
 - Recruitment process
 - Informed consent process
 - Randomization scheme and blinding procedures
 - Control article (i.e. placebo)
 - Clinical monitoring program
 - Records retention plan and system
- Review the sponsor's SOP on FDA Inspections (if applicable)

Note: The inspector may request to review another study while on-site that was not included in the initial inspection notification, or request a list of the PI's studies. Therefore, it is recommended to make a list or table of all the PI's current and recently archived FDA-regulated studies (see checklist in [Appendix II](#)). If the study teams have the time and resources, it may also be beneficial to review study records for those studies as well.

3.3 Review Study Records

Study records should support the assertion that the PI is upholding all of their responsibilities and obligations. In the eyes of the inspector, if it is not documented, it did not happen.

Investigators are required to permit the FDA to inspect and copy any records pertaining to the investigation. All of these documents should be readily available for inspection. If some of the documents are not immediately available (i.e., offsite storage), obtain them as soon as possible, preferably at least 2-3 days before the scheduled inspection.

The inspector is most likely to review:

- Study record on [ClinicalTrials.gov](https://clinicaltrials.gov)
 - Trial registration
 - Submission of results
 - Adherence to the Food and Drug Administration Amendments Act ([FDAAA](#))
- Regulatory documents
 - Delegation of Authority logs
 - All IRB-approved versions of the protocol and amendments, including associated signature pages
 - All IRB-approved versions of Investigator Brochures and/or package inserts

- All IRB-approved versions (with the IRB watermark/stamp) of Informed Consent Documents
 - All IRB-approved versions of all other documents submitted to the IRB for review (participant-facing documents, recruitment, questionnaires, diaries, etc.)
 - All IRB correspondence (e.g., approvals, continuing reviews, modifications, RNIs, and all other issued letters and relevant correspondence)
 - Including whether all reportable events, such as major protocol deviations, serious adverse events (SAEs), and suspected unexpected serious adverse reactions (SUSARs) have been reported to the IRB when required
 - Applicable [IRB Rosters](#)
 - Correspondence and documents submitted to and received from FDA regulatory agencies, such as:
 - Annual, maintenance, and safety reports to the FDA (Sponsor-Investigators only)
 - [FDA Forms 1571 and/or 1572](#) (drug trials only)
 - Investigator Agreement(s) (device trials only)
 - Financial disclosure forms (sponsor forms, [FDA Form 3454, or FDA Form 3455](#))
 - Screening and enrollment logs
 - Documentation of investigator and staff training and qualifications
 - Investigational New Drug (IND) or Unanticipated Adverse Device Effects (UADE) safety reports
 - Lab accreditation and reference ranges
 - Site visit/monitoring log
 - Pharmacy files
- Participant Files
 - Case Report Forms (printed copies or encrypted flash drive copies of electronic case report forms)
 - Relevant Electronic Medical Records (EMR) (printed copies, encrypted flash drive copies, or over-the-shoulder system review)
 - All supporting source documentation:
 - Clinic or hospital records (those related to the participant's diagnosis/condition, records to support participant eligibility, etc.)
 - Laboratory, radiology reports, EKGs, etc.
 - Device/Drug accountability
 - Adverse Event (AE) logs and Serious Adverse Event (SAE) reports
 - Participant diaries and completed surveys
 - Documentation of protocol deviations (missed procedures, missed visits, etc.)
 - Note: inspectors often review the first and last participants' records and then randomly selects other records to review

Locate and review the above list of study records using:

- Northwestern University IRB post-approval monitoring (PAM) checklists: these checklists are designed to help ensure that study records are complete and include most of the aforementioned regulatory and participant documents and areas the FDA may review.

- [HRP-429 - CHECKLIST - Biomedical Research](#)
- [HRP-427 - CHECKLIST - Drug or Device Clinical Trial](#)
- [HRP-428 - CHECKLIST - Participant File](#) (for all participants)
- [HRP-1406 - CHECKLIST - Studies Under External IRB Review](#) (if applicable)
- [HRP-1407 - CHECKLIST - Site File](#) (if applicable)
- FDA Site Inspection Supplemental Checklist (see [Appendix II](#)): this supplemental checklist includes study records the inspector is likely to review that may not be on the post-approval monitoring checklists as they are typically outside of the IRB's scope. It is recommended to use this supplemental checklist during study record review in addition to the IRB post-approval monitoring (PAM) checklists listed above.
- [E6\(R2\) Good Clinical Practice: Guidance for Industry](#): all clinical trials should be in compliance with Good Clinical Practice (GCP) standards described in this document.
- [Electronic Source Data in Clinical Investigations](#): recommendations for the capture, review, and retention of participants' electronic source data in FDA-regulated clinical investigations.

3.4 Organize Study Records

Make sure documentation is easy to follow and review by others. The inspector should be able to locate certain documents and easily follow the regulatory and participant files.

Create Note-To-Files (NTFs) to describe where documentation can be found if it is stored in another location or stored only electronically. This way the inspector can ask for the documentation they need instead of thinking it does not exist. For example, if all investigational product accountability documents are stored in the Investigational Pharmacy, then file a NTF in the study records to state this along with the pharmacy location. For another example, if certain participant files are only stored electronically and a paper copy will not be printed for the inspector's review, then file a NTF to document what documents are stored electronically and where.

Study teams may also use the IRB's [Study Support Resources and Templates](#) to aid in organization of study files.

3.5 Reconcile Missing and Incomplete Documentation within Study Records

Not only should study teams make sure they have all of study records available and organized, they should also reconcile records where appropriate. It is important for files to be clean and organized, but essentially the inspector wants to view the study as-is, so try to limit major corrections and updates. Study teams can reconcile study records prior to an inspection by:

- Identifying weakness or gaps (i.e., source documents not included in the research record, incomplete or out of date delegation log, etc.).
 - Pay close attention to protocol variances, as these could be explained through the use of a NTF.
 - Assure that PI has signed all NTFs, and retrospectively add them (with the current date) if they are missing.
- Correcting minor issues that can be corrected using appropriate correction methods.
 - Line through data to be corrected/changed so the original entry is still visible, then initial and date (with the current date) the changes or corrections.
 - Retain originals

- Never use white-out
- Identifying any items noted during prior audits or monitoring visits and ensure that those items have been appropriately and fully addressed.
- Understanding the scope of remaining issues.
- Developing and implementing a written [corrective and preventive action \(CAPA\) plan](#) to address identified problems. Be prepared to provide a copy of the plan to the FDA inspector to demonstrate that the PI is proactively addressing potential concerns.
- Creating an itemized list of missing documentation, protocol amendments needed, and missing or inaccurate study data.

Note: Best practices are to regularly review and reconcile study records throughout the life of the study. Making many documented updates or corrections right before an inspection may raise a red flag for the inspector, even if just cleaning up the records. Therefore, it is not recommended to submit any protocol amendments to the IRB, submit corrections to study data, etc. immediately prior to an inspection, as this may lead to misunderstandings and additional findings from the inspector. Instead, document these items internally and address those types of changes and corrections after the inspection.

Per the [FDA's annual inspection metrics](#), common audit findings are areas to pay close attention to for reconciliation before the inspection, including:

- Failure to follow the protocol or regulations, or both (protocol deviations)
- Failure to comply with Form FDA 1572 requirements
- Inadequate and/or inaccurate study records and/or source document and Case Report Form (CRF) mismatch
- Failure to report adverse events (i.e. safety reporting violation)
- Inadequate investigational product accountability
- Failure to comply with [21 CFR part 56](#) (IRB) requirements and/or inadequate communication with the IRB
- Failure to obtain FDA and/or IRB approval prior to study initiation
- Improper informed consent process and/or inadequate subject protection
- Failure to report concomitant therapy
- Inadequate training records
- Inadequate monitoring

3.6 Make Administrative Arrangements for the Inspection

- The PI should designate an inspection coordinator (or multiple inspection coordinators).
 - This person will oversee the entire inspection process (before, during, and after).
 - This person will be the general contact person/liaison to the inspector.
 - This person should be knowledgeable about the study activities and records, and be able to coordinate with the study PI and other study personnel both prior to and during the course of the inspection.
 - This person is usually the primary study coordinator.
- Designate another person to be the inspection assistant (or multiple inspection assistants).
 - This person will accompany the inspection coordinator during the visit and is dedicated to taking notes, making copies, locating personnel, etc.

- If there is more than 1 inspector, it is recommended to have at least 1 inspection assistant per inspector.
 - It may also be useful to have other designated inspection assistants to:
 - manage all the study files and be ready to pick up and drop off files the inspector requests or finishes reviewing.
 - be document runners (make and deliver copies).
 - escort the inspector to the restroom or water cooler.
 - be a “system driver” for over-the-shoulder review of electronic medical record (EMR) or electronic data capture (EDC) systems.
- Reserve a room for the inspector to use for the duration of the inspection.
 - The inspection room must contain no records or information, including clinical or research-related, other than the records the inspector has requested.
 - It is recommended that the room be on a different floor or located away from the research area and offices to avoid other research activities and related conversations, but still with convenient access to study staff.
 - The room should be able to be locked when the inspector leaves.
- Consider also reserving a separate “staging room” or “document room” for internal use only. This can be a central area for all study documents to be kept during the inspection, so that study files/binders can be “checked out” or “checked in” throughout the inspection. It can also be useful for private study team meetings and conversations during the inspection.
- Notify all relevant study staff of their inspection responsibilities and ensure they are trained on interacting with FDA inspector.
 - All staff should keep all documents off desks, counters, printers, etc., and be mindful of hallway, elevator, and bathroom conversations.
- Notify the PI, inspection coordinator, inspection assistant, and any primary team members who will meet with the FDA inspector upon their arrival the location, date and time of the initial meeting.
- Inform the FDA Inspector where to arrive for the initial meeting at the specified day and time, and any other pertinent information they may need for their arrival (such as parking, etc.).
- If the study is industry sponsored, the sponsor/CRO may send a representative to assist in preparing for the audit. If the sponsor/CRO representative wishes to be present during the inspection, notify the FDA inspector. If the FDA inspector approves the request, explain to the representative that they may observe and take notes but they are not to communicate with the inspector unless asked specific question(s).

3.7 Final Preparations for the Inspector’s Arrival

- Prepare and share with study staff an internal inspection plan, including any [inspection tracking logs](#) and an inspection file location and process in order to maintain real-time documentation of the inspector’s requests and responses provided throughout the inspection.
- Prepare a summary of the study, the study site (i.e. Northwestern University), and study facilities, including a planned tour of the study site facilities to give the inspector a basic idea of the flow of a participant visit. Provide basic information that is not too detailed, and be prepared to inform facility staff ahead of time of when the tour may take place.

- Ensure all study documents are readily available and accessible for inspection.
 - If over-the-shoulder review will not be used, print out or prepare an encrypted flash drive of any electronic files, such as participant EMR or eCRFs, to which the inspector cannot have direct systems access.
- Remind all staff in the area of the inspection when and where the FDA will be in the facility, and that they should put away all documents and limit conversations in shared areas and near the inspection room.
- Do a sweep in the area near the inspector's room to make sure no study documents, participant charts, sticky notes with passwords, medications, etc. are visible.

4 During the FDA Inspection

4.1 Basic Guidelines

- Be calm, courteous, and professional.
- Ensure that ALL members of the research team and any other individuals helping with the inspection know that the FDA is in the facility. It is recommended the inspection coordinator or assistant email relevant staff a notice of the inspector's arrival and departure each day.
- **Limit idle business conversation by ALL staff.**
- Refrain from social conversations with the inspector.
- The inspection coordinator should also coordinate all FDA requests, accompany the FDA inspector at all times on facility tours, and see that the inspector's questions are answered.
 - The inspector will generally not want someone in the inspection room at all times, but someone should always be readily available to the inspector.
- The inspection assistant should take detailed notes of all requests, questions, answers, etc. throughout the duration of the inspection.
- The PI should set aside time each day to talk with the inspector, as well as be available in person or by phone for questions that may arise.

4.2 Arrival of the FDA Inspector and Initial Meeting

- Greet the FDA inspector at a previously specified location and take them to the reserved inspection room for the initial meeting and to meet the PI.
 - The inspection coordinator should greet the inspector, or otherwise make sure front desk staff know what to do when the inspector arrives.
- At the beginning of the initial meeting, the inspector **must** present their badge/credentials to the PI to verify that they are in order.
 - Document all information from the inspector's identification (however, making copies of identification badges is prohibited).
 - **Ask the inspector to see their credentials if they do not present them. The inspection should not commence if the inspector does not present their credentials.**
- The inspector will then present a Notice of Inspection (**Form 482**) to the PI. This notice authorizes the inspection and its presentation officially begins the inspection. Retain a copy of the Form 482.

- Ask the inspector to provide the Form 482 – Notice of Inspection if they do not present it.
 - If the inspector declines to provide the notice in writing, the inspection may be part of a criminal investigation and require a search warrant. Contact the University’s [Office of General Counsel](#) immediately.
- The inspector will explain the intended purpose and scope of the inspection. Make sure to clarify whether the inspection is routine or for-cause.
- The inspector may ask the PI to summarize the study, the study site, and their study responsibilities.
- Request that the inspector provide a summary of observations at the end of each day.
- Inform the inspector on who to contact and how if they need anything. If there are multiple people, providing a list of contacts may be useful.
- The inspector may ask for a tour of the facilities. The inspection coordinator or assistant should stay with the inspector at all times during any tour. Inform other staff when the inspector will be on a tour of the facility.

4.3 Inspection of Study Documents

- Ensure all study documents are readily available when the inspector arrives.
- Do not offer up information or documents that are not specifically requested. Always wait for a specific request to provide information.
- The inspector should not have free access to areas where files are kept. Standard procedure is for the inspector to request files for review, starting with the “general” study materials including the regulatory documents binders, then all signed informed consent forms, followed by a sampling of specific participant records. Bring the requested documents to them.
- If the requested documents are electronic source documents in the EMR that will not be printed out or transferred to an encrypted flash drive, a study staff member or the PI should login and use an over-the-shoulder approach to show the inspector the requested records.
 - FDA inspectors are generally not permitted to receive direct log-in credentials for EMR systems.

It’s the study team’s responsibility to know which documents and data they must provide FDA and which are optional. Inspectors will not provide that information. It also isn’t uncommon for inspectors to ask for documentation that is not under their authority to review. In these cases, study teams may point out that it’s their understanding the FDA policy says inspectors will not routinely look at those documents ask the inspector to reconsider their request. Most of the time, they will retract their request.

Here are examples of documents and data that are required vs. optional to provide to the FDA during an audit:

Required	Optional	Reference
Research data relating to new/investigational products	Research data NOT related to new/investigational products	Food, Drug and Cosmetic (FDC) Act, Section 704(a)

Personnel data as it pertains to training/qualifications	Personnel data not related to their training/qualifications	Food, Drug and Cosmetic (FDC) Act, Section 704(a)
Investigational product/device shipment data	Investigational product/device financial data, sales data, and pricing data	Food, Drug and Cosmetic (FDC) Act, Section 704(a)
Study documents including regulatory files and contracts related to PI obligations/responsibilities	Study documents related to billing, budgets, finances, or internal audits	Food, Drug and Cosmetic (FDC) Act, Section 704(a)
Participant data, signed informed consent forms and information related to the study	Participant names (unless the records of particular individuals require a more detailed review, or unless there is reason to believe that the records do not represent actual case studies or do not represent actual results obtained)	Good Clinical Practice (GCP) regulations in 21 CFR Part 312.68
Participant medical records demonstrating participant eligibility and whether or not a particular adverse event (AE) is considered a suspected or unexpected serious adverse event (SAE)	Participant medical records that precede their study participation and are not related to study inclusion/exclusion criteria	Good Clinical Practice (GCP) regulations in 21 CFR Part 312.68

4.4 Document Copies

- Provide copies only of documents specifically requested by the inspector.
- A record of all documents provided to the inspector, in paper or electronic format, should be maintained.
 - It is recommended to keep a log of all documents requested by the inspector. Study teams may reference or use of the IRB Office’s Inspection Request Tracking Log template found on the IRB website.
 - It is also recommended to track which documents are copied by making an extra copy for an FDA inspection file (i.e. “shadow binder”). If electronic copies of documents are requested, provided PDF versions of requested documents and maintain an electronic shadow binder. A shadow binder may be a combination of a physical binder and electronic file if necessary.
- When making copies for the inspector:
 - Redact any participant identifiers from any copies given to the inspector using a black permanent marker.
 - If the inspector requests that identifiers remain on the records, the HIPAA Privacy Rule at 45 CFR 164.512(b)(1)(iii) permits this.
 - The copies given to the Inspector should be marked or stamped “Confidential”.
 - Duplicate copies for the FDA inspection file (shadow binder) should be marked or stamped “Copy”.

- Study teams may need to obtain participant records from the hospital or clinic to supplement or corroborate the research records.
- Copies should be provided without charge to the FDA.

4.5 Interviews and Inspector Questions

During the inspection, keep a log of interview requests and all questions asked by the inspector. Study teams may reference or use the IRB Office's [Inspection Request Tracking Log](#) template found on the IRB website for this purpose.

The inspector may interview the PI, study coordinator, and members of the study team and ask questions in order to:

- Obtain a brief summary of their role in the study.
- Assess for consistency and accuracy in response.
- Assess how tasks are performed and compare knowledge and practice of study procedures.
- Assess for PI oversight, involvement, and knowledge of day-to-day or routine activities.

For examples of questions frequently asked by the FDA inspectors, see [Appendix I](#).

Answer questions concisely, honestly, and clearly, using the following tips:

- Listen carefully to the question. If you do not understand the question, ask the inspector to explain. Do not interpret (or misinterpret) the meaning of the questions being asked.
- Be truthful – answer the question that was asked in an honest manner.
- Be clear in your response.
- Be concise – stop when you have fully answered the question. Use “yes” or “no” when sufficient.
- Answer only the question the inspector asks. Do not go off on tangents.
- When possible use documents already provided for support of answers.
- Be positive and confident.
- If you do not know the answer to a question do not be afraid to tell the inspector. Write down the question and refer it to the correct person.
- There is nothing wrong with silence. Once you have answered, wait for the next question.

When answering questions, avoid the following:

- DO NOT guess or speculate.
- DO NOT volunteer information.
- DO NOT lie.
- DO NOT argue.
- DO NOT panic.
- DO NOT sign affidavits.
 - If the inspector presents an affidavit (**Form 463** or special purpose affidavit) for signature, politely decline to sign and tell the inspector that you must first consult with the University's [Office of the General Counsel](#).

4.6 End-of-Day Meetings

It is recommended that the inspection coordinator or PI request a meeting with the inspector at the end of each day. During these meetings:

- ask for a summary of the day's activities or feedback on items of concern,
- clarify any issues that were raised and try to resolve them immediately, and
- ask for the next day's agenda.

After the inspector departs each day, notify all staff of the inspector's departure and convene a meeting of study team members to brief them on the day's activities and plan for the following day.

4.7 Other Guidance, Reminders, and Recommendations

- It may be useful to practice responses to [frequently asked questions](#) and specific areas of concern for the study/investigator under inspection.
- The IRB Office staff are available throughout the inspection process should the PI have any IRB-related questions or receives IRB-related requests from the inspector.
- If a sponsor representative wishes to be present during the inspection, invite them to observe and take notes, but ask that they not communicate with the auditor unless asked specific question(s).
- The inspector may request a reasonable quantity of samples of retained participant specimens. Make sure to pull identical samples to retain and to ask the inspector to issue a Receipt for Samples (**Form 484**).
 - A Form 484 does not apply to items or materials examined but not removed, labels, promotional material, photographs, or any record taken by the inspector.
- If the inspector insists on taking photographs or video/audio recordings, take and retain duplicates at the same time for the inspection file/shadow binder.
- While on site, the inspector may ask to review records for other studies.
- It may be advisable to inform the inspector of typical office hours, in order to set an expectation for how early or how late the inspector can arrive or stay each day.

5 Conclusion of the FDA Inspection

The FDA inspector will usually hold an exit interview at the conclusion of the inspection. If the inspector does not initiate the meeting, the PI should request one.

5.1 Exit Interview

The inspector will discuss findings and notify the PI if deficiencies were found. Remember, they almost always will find something – it's their job! This interview is an opportunity for the PI to provide information and clarify any questions or concerns raised during the inspection.

The following should be notified of the time and place of the exit interview so they can attend:

- PI
- Inspection coordinator(s)
- Inspection assistant(s)
- Other primary study or department staff as appropriate

During the exit interview:

- Record any discussion of observations, recommendations, comments, and commitments
- Clarify and seek to correct any errors in the findings
- If possible, respond to any deficiencies
- Do NOT argue if your opinion differs from the inspector, but instead ask them to indicate the regulation or guidance prompting their assertion

The outcome of the inspection communicated during the exit interview may be one of the following:

- No Action Indicated (NAI) – no objectionable conditions or findings
- Voluntary Action Indicated (VAI) – objectionable conditions or findings, but not serious enough to recommend regulatory action
- Official Action Indicated (OAI) – FDA Form 483 issued with serious objectionable conditions and regulatory action recommended

5.2 Issuance of an FDA Form 483

If serious deficiencies have been found during the inspection, a [Form 483](#) – List of Observations will be issued during the exit interview. A Form 483 is an official list of inspectional observations or deficiencies, but does not represent a final agency determination. It should be used as a guide for corrective action; however, specific recommendations are typically not listed.

The PI can (and should whenever possible) respond to issues listed in the Form 483 during the exit interview. Corrective actions or procedural changes done in the presence of the inspector are regarded as positive indications of the PI's concern and desire to voluntarily correct discrepancies.

6 After the FDA Inspection

6.1 Draft an Inspection Summary Report

Immediately after the visit, no matter the outcome, the PI, inspection coordinator(s), and inspection assistant(s) should write a detailed internal report from the inspection notes. The report should be kept with study documents and include:

- A summary of questions and discussions between the inspector and each employee
- List of all studies or facilities/departments visited
- List of all records reviewed
- Copies of all documents duplicated for the inspector
- Note of all samples taken, and receipt for samples
- Note of all commitments made (include completion dates if set with FDA)
- Comments of the inspector related to the inspection

6.2 Response to the FDA Inspection Report or Form 483

If a Form 483 is issued by the FDA, the PI or a designee must send a written response **within 15 working days**. If the FDA requests voluntary actions, the PI or a designee should still send a written response to address each action.

The written response should include the following:

- Address each particular observation or finding, point-by-point.
- Consult with the appropriate individuals if the response requires additional input.
 - For example, consult with the Investigational Pharmacy if the response is related to study drugs.
- If the PI disagrees with an observation, respond factually, providing clear and verifiable evidence.
- Determine if a finding was an oversight/one-time occurrence or systemic, and if a change of procedure is indicated.
- Delineate corrective and preventative actions (CAPA), including a justification of why the proposed response will remediate the issue and a realistic timeline for correction.
 - See the Northwestern IRB website for guidance on writing a comprehensive [Corrective and Preventative Action \(CAPA\) Plan](#)
 - Reach out to the IRB Office Compliance unit directly (irbcompliance@northwestern.edu) for assistance as needed for determining appropriate corrective or preventative actions
- Keep a copy of the final signed response in the study files along with all attachments.

The response should be submitted to the FDA in paper format, accompanied by an electronic copy on a jump drive, using a secure delivery method (e.g. FedEx or UPS) with a requested receipt of delivery. The inspector may request the response be submitted by email, but even so it is highly recommended to also submit in paper format what is submitted via email.

The FDA should issue an acknowledgment letter to confirm receipt of the response and may ask for additional information or indicate that the corrective actions are not adequate.

6.3 Notify the IRB

No matter the outcome, the PI must provide notice of the FDA inspection findings or outcome to the Northwestern IRB.

- If the FDA issues a Form 483: the PI must submit a copy of the Form 483, the PI's draft or official response, and CAPA plans to the Northwestern IRB via a Reportable New Information (RNI) application.
- If the FDA does **not** issue a Form 483, but the inspection identified information that indicates participants were placed at increased risk of harm or that participants' rights or welfare were adversely affected: the PI must submit a copy of the inspection report, the PI's draft or official response, and CAPA plans to the Northwestern IRB via a Reportable New Information (RNI) application.
- If the FDA does **not** issue a Form 483 **and** the inspection did **not** identify information that indicates participants were placed at increased risk of harm or that the participants' rights or welfare were adversely affected: the PI must inform the IRB Office of the outcome via email with a copy of the final report or written communication from the FDA inspector. Direct this email to the same IRB Office contacts to whom the initial notification was sent (see [section 2.2](#)).

The IRB may decide to take additional action based on the outcome or findings of an FDA inspection of a study or investigator.

6.4 Notify the Sponsor

The PI should notify the sponsor of the study of an issuance of a Form 483 and provide a copy of the PI's formal written response.

The PI should also should review their 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 a Form 483.

6.5 Warning Letter

Failure to respond or failure to respond adequately to the Form 483 may result in escalation to a Warning Letter. The FDA publishes Warning Letters [on their website](#) on a monthly basis. **If the PI receives a Warning Letter, they must respond in writing within 30 days.**

Notify the IRB Office immediately upon receipt of a Warning Letter. Follow the same instructions outlined in [section 6.2](#) to respond to a Warning Letter.

6.6 Inspection Closeout

An inspection is closed out after the conclusion of any follow-up by the FDA to Form 483, Warning Letter, or other actions arising from the inspection. The FDA inspector will file an Establishment Inspection Report (EIR) after they close out the inspection. If the EIR is not sent to the PI, the PI can ask the inspector about obtaining it or file a [Freedom of Information Act \(FOIA\) request](#).

In addition, basic information about the inspection will eventually be posted online following an inspection closeout, which will include the final outcome (NAI, VAI, or OAI) after any responses to findings are reviewed (<https://www.accessdata.fda.gov/scripts/inspsearch/> and <https://www.accessdata.fda.gov/scripts/cder/cliil/index.cfm>). Typically, if a Form 483 is issued and the PI's responses are deemed appropriate the final outcome will be NAI or VAI.

7 References

- 7.1 "Investigator/Staff Guidance for FDA Inspections." Ohio State University Office of Responsible Research Practices. <https://orpp.osu.edu/irb/investigator-guidance/fda-inspections/>
- 7.2 "Site Inspection Guide." University of Iowa Human Subjects Office and Institutional Review Board. Version 1, Jan 19, 2016: <https://hso.research.uiowa.edu/food-and-drug-administration-fda-site-inspection-guide>
- 7.3 "FDA Inspection Preparation Guide." UT Southwestern IRB. Version 1.0, Nov 2012.
- 7.4 "FDA Inspection Guide." University of Wisconsin-Madison Madison's Institute for Clinical and Translational Research (ICTR) Study Monitoring Service - FDA Regulated Research Oversight Program. Nov 13, 2019.
- 7.5 "FDA Inspection Intake Form." University of Wisconsin-Madison Madison's Institute for Clinical and Translational Research (ICTR) Study Monitoring Service - FDA Regulated Research Oversight Program. Nov 13, 2019.
- 7.6 "The Right to Refuse: Information That FDA Inspections Can't Request." WCG Center Watch. Jan 24, 2020: <https://www.centerwatch.com/articles/24528-the-right-to-refuse-information-that-fda-inspections-cant-request>
- 7.7 M. K. K. Sobcinski and S. Wiskow. "BIMO Inspections: Recommendations for Sponsors," Clinical Researcher. Volume 33, Issue 6, Jun 2019: <https://acrpnet.org/2019/06/11/bimo-inspections-recommendations-for-sponsors/>
- 7.8 "Frequently Asked Questions (FAQs)." Children's Hospital of Philadelphia Office of Research Compliance and Regulatory Affairs, as cited in reference 7.2.
- 7.9 S. Tendolkar. "Successful FDA Inspections at Investigative Sites for Clinical Trials of Drugs and Biologics," Journal of Clinical Research Best Practices: Vol. 9, No. 1, Jan 2013.
- 7.10 A.P. Schwartz. "FDA Inspections: How to Respond to a Request for an Affidavit." Med Device Online. <https://www.meddeviceonline.com/doc/fda-inspections-how-to-respond-to-a-request-f-0001>
- 7.11 A. Choudhary. "FDA Forms General Used in Pharmaceutical Inspection." Pharmaceutical Guidelines. <https://www.pharma guideline.com/2014/11/fda-forms-issued-in-inspections.html#gsc.tab=0>
- 7.12 J.R. Hills. "FDA Inspections of Investigator Sites: Preparation and Conduct." PowerPoint presentation for the Research Compliance Network. Mar 9, 2020.
- 7.13 C. Malcolm. "12 Items Auditors Look for When Reviewing an Investigator Site File." Advarra Blog. Jul 8, 2020: <https://www.advarra.com/12-items-auditors-look-for/>

8 Appendix I: Questions Frequently Asked by FDA Inspectors

- 8.1 Provide an overview of the study including background, objectives, study design, duration of the study, participant population, and number of participants enrolled.
- 8.2 What responsibilities are delegated to other members of study team?
- 8.3 How are potential participants identified?
- 8.4 Who screens and recruits participants?
- 8.5 Were all methods and materials used for recruitment IRB approved?
- 8.6 Who verifies inclusion and exclusion criteria?
- 8.7 Who obtains consent/assent?
- 8.8 Was written documentation of consent required?
- 8.9 Is the informed consent process documented in the medical record?
- 8.10 Was assent required? (Include age of assent)
- 8.11 Were there any research participants who were wards of the state?
- 8.12 How are screening/enrollment logs used and maintained during the conduct of the study?
- 8.13 Where were study procedures conducted? (e.g., inpatient or outpatient)
- 8.14 What are the study start and/or completion dates?
- 8.15 How do you communicate protocol or study design changes to study staff, pharmacy, and/or ancillary department staff?
- 8.16 How do you obtain, record, secure, and retain data?
- 8.17 What do you use as source documentation (study specific source documents, separate research chart, shadow chart, CRFs, lab data, imaging or diagnostic data)?
- 8.18 Do you use electronic records?
 - How are records validated?
 - Do you use electronic signatures?
 - What are the data security/controls?
 - Is there an inspection trail?
- 8.19 Was data transferred or transmitted outside the institution?
- 8.20 What is your record retention policy?
- 8.21 Were there any protocol deviations or exemptions?
- 8.22 Who is responsible for receipt, distribution, administration and accountability of test articles?
- 8.23 Who are the investigational pharmacists?
- 8.24 How is the test article stored?
- 8.25 Describe procedures for destruction and/or return of the test article.
- 8.26 Where and how are specimens stored?
- 8.27 Describe your procedure for maintaining and documenting storage of specimens.
- 8.28 Describe maintenance of temperature logs and how you deal with temperature excursions, including:
 - Frequency of temperature monitoring (manual check or electronic monitoring)

- Frequency of quality control checks
- 8.29 Was the study routinely monitored?
- Documentation of monitoring communications and evaluations
 - Frequency of monitoring
 - Was the study team satisfied with overall monitoring of the study?
- 8.30 Did study team receive study-specific training?
- Documentation of training
 - Study team training, pharmacy
- 8.31 Did any unanticipated problems occur (AEs, SAEs or deaths)?
- Were events reported to the IRB, Sponsor, IRB, regulatory agency in a timely manner?
 - Were the events related to the test article?
 - Did the participant require any intervention/treatment as the result of the event?
 - What was the intervention/treatment?
- 8.32 Are there any study specific standard operating procedures (SOPs) for this study?
- 8.33 Is the study registered with Clinicaltrials.gov or equivalent registry?

9 Appendix II: FDA Site Inspection Supplemental Checklist

This supplemental checklist includes study records study teams should review or prepare for an FDA Inspection in addition to documentation listed on Northwestern University IRB's [post-approval monitoring \(PAM\) checklists](#).

1. Administrative

Item #	Documentation Item	On File & Current (or N/A)	Location Filed	Not Available/ Missing	Comments
1.1	List or table of the PI's closed and active FDA-regulated studies (including study title and IND numbers, sponsor(s) and relevant dates)				
1.2	A list of facilities and personnel providing laboratory, imaging, ECG and other services and external procedures for the study				
1.3	List of all electronic systems used to generate, collect or analyze data or used to generate electronic signatures; and evidence of Part 11 computer system compliance				
1.4	Chain of custody SOP for participant documentation and/or specimens				

2. Investigators and Research Staff

Item #	Documentation Item	On File & Current (or N/A)	Location Filed	Not Available/ Missing	Comments
2.1	Signature log (may be combined with delegation of authority log)				
2.2	Good Clinical Practice (GCP) training				
2.3	Protocol training				

2.4	Any additional staff training				
2.5	Conflict of Interest management documentation				
2.6	CV and license of investigational pharmacist				

3. Protocol

Item #	Documentation Item	On File & Current (or N/A)	Location Filed	Not Available/ Missing	Comments
3.1	Randomization log				
3.2	Pharmacy manual				
3.3	Laboratory manual				
3.4	Sponsor and/or CRO correspondence				
3.5	Any other correspondence pertinent to the study				
3.6	Corrective and preventative action plans for identified issues				

4. Monitoring

Item #	Documentation Item	On File & Current (or N/A)	Location Filed	Not Available/ Missing	Comments
4.1	Monitoring visit log				
4.2	Monitoring letters and reports				
4.3	Documentation of all AEs, SAEs, and participant deaths				
4.4	Evidence of AE, SAE, and participant death reporting to the sponsor within required timeframe				
4.5	Evidence of investigator review of AEs and SAEs				

	in timely manner, with reporting to the IRB as necessary within required timeframe				
4.6	Participant deaths that were not anticipated and possibly related to study participation reported to the IRB within 24 hours				
4.7	Safety Reports/Memos				
4.8	Submission of Safety Reports/Memos to the FDA and/or IRB, as necessary				
4.9	Protocol deviation log				
4.10	Evidence of protocol deviation reporting per sponsor and IRB requirements				
4.11	Temperature logs for applicable equipment				
4.12	Calibration and maintenance records for applicable equipment				

5. Participant Source Documents

Item #	Documentation Item	On File & Current (or N/A)	Location Filed	Not Available/ Missing	Comments
5.1	Applicable participant medical records				
5.2	Documentation of the informed consent process for each participant prior to study procedures, including for re-consent(s)				
5.3	Documentation of meeting inclusion/exclusion criteria for enrollment participants				

5.4	Documentation of reason for screen-failed/excluded/withdrawn/early terminated participants				
5.5	All visits conducted within protocol windows (or otherwise recorded as protocol deviation)				
5.6	All laboratory reports and other diagnostic test reports on file and graded and/or signed by the PI or designee				
5.7	Concomitant/prohibited medication log for each participant				
5.8	Record of dose modifications				

6. Investigational Product

Item #	Documentation Item	On File & Current (or N/A)	Location Filed	Not Available/Missing	Comments
6.1	Investigational product shipping receipts				
6.2	Investigational product accountability log				
6.3	Investigational product destruction documentation and/or SOP				