FDA INSPECTION GUIDANCE

This document has been created by the FDA Regulated Research Oversight Program (henceforth referred to as the Program) to help investigators and research staff throughout the process of a Food and Drug Administration (FDA) Inspection.

I. Inspection Notification

1. Complete the FDA Inspection Intake Form
2. Notify Program staff via email: inspection-notification@lists.wisc.edu
   - Member(s) of the Program will be in contact with you following receipt of the email. Program representative(s) will help your study team prepare for the visit and will remain available and in contact throughout the inspection process.
3. Download the FDA Compliance Program Guidance Manual from the FDA website: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm
   - The FDA Compliance Program Guidance Manual, Guidance for FDA staff is the most helpful document to download and review as it is intended to be the manual used by the FDA auditors to conduct the inspection.
4. Gather documents requested for review
   - Make sure that all requested documents are available for inspection.
   - If some of the documents are not immediately available (i.e., offsite storage), get them as soon as possible, at least 2 – 3 days before the scheduled inspection.
   - Maintain an itemized list of the documents with the status of any missing documents.
5. Reserve meeting room(s)
   - The room should be conveniently located, should NOT contain any other study or medical records, other than the study records that the Inspector has requested, and can be locked when the Inspector leaves the room.
   - The Inspector generally will not want the person coordinating the investigation in the room while s/he works, but this person should be readily available to the Inspector at all times.
   - It is also recommended to select a room that is located away from the research area to avoid other research activities and related conversations.

II. Inspection Preparation

1. Designate a person to oversee the inspection
   - 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.
2. Review the sponsor's SOP on FDA Inspections (if applicable)
3. Notify the study team members, Sponsor, and your Department Chair of the inspection
   - If your sponsor is Industry Sponsored, they may send representatives to assist you in preparing for the audit. If the sponsor representative wishes to be present during the inspection, notify the FDA auditor and invite the sponsor representative to observe and take notes, but ask that they not communicate with the auditor unless asked specific question(s).

4. Notify ancillary services, other groups or entities who may be involved, including, but not limited to: Institutional Review Board (IRB), Pharmaceutical Research Center (PRC), etc.
    - Health Sciences IRB Office: (608) 263-2362
    - Pharmaceutical Research Center (PRC): (608) 263-8863
        - If your study is utilizing PRC services, it is recommended to reach out to PRC as soon as possible (immediately following any contact or discussion of an FDA audit) to schedule a meeting. It is standard for the FDA auditor/inspector to meet with the PRC manager during their visit for a tour of the PRC facilities and to ask questions regarding the study drug accountability processes.
5. Review the protocol
    - The Principal Investigator (PI) and all members of the study team should review the current protocol.
6. Identify and locate, if necessary, any records that the FDA is most likely to review
    - FDA-related documents: Form 1572 and/or Investigator Agreement(s)
    - Regulatory documents: Delegation of Authority logs, all IRB approved versions of Informed Consent Documents, all IRB correspondence (e.g., approvals, continuing reviews, current consent, enrollment/screening logs, etc.)
    - Subject Related Documents: Case Report Forms (print copies of any electronic case report forms) and all supporting source documentation:
        - Clinic or hospital records (those related to the subject's diagnosis/condition, records to support subject eligibility, etc.)
        - Laboratory, radiology reports, EKGs, etc.
        - Device /Drug Accountability Logs
        - Adverse Event Logs and Serious Adverse Event Reports
        - Subject diaries
        - Documentation of protocol deviations (missed procedures, missed visits, etc.)
7. Review study records
    - The Self-Audit Tools are designed to help ensure that your study records are complete and organized, with a focus on documents and areas the FDA may review.
    - Identify any weaknesses 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 Note to File (NTF). Assure that PI has signed all NTF's, and retrospectively add them (with current date) if they are missing.
    - Correct items that can be corrected using appropriate correction methods. Line through data to be corrected/changed, initial and date (with the current date) any changes or corrections. Retain originals and never use white-out.
    - Identify any items noted during prior audits or monitoring visits and ensure that those items have been appropriately addressed.
    - Develop and implement a written corrective and preventive action (CAPA) plan to address identified problems (template available in the Study Conduct tab of the Clinical Research Toolkit webpage). Be prepared to provide a copy of the plan to the FDA Inspector to demonstrate that you are proactively addressing potential concerns.

III. Inspector Arrival

1. Escort the Inspector to the appropriate meeting room. The PI should be available when the Inspector first arrives.
2. The Inspector will present his/her credentials to the PI to verify that they are in order. Ask the Inspector to see his/her credentials if he/she does not present them. Document all information from the inspector's identification as no copies of the identification badges can be made.
3. The Inspector will then present a Notice of Inspection (Form FDA 482) to the PI authorizing the inspection; its presentation officially begins the inspection. The FDA Inspector will explain the intended purpose and scope of the inspection.
4. The FDA Inspector will then ask the PI for the list of the PI's currently active studies and will request the PI to summarize and discuss the study identified for inspection. The FDA Inspector may also ask the PI to summarize his/her responsibilities with respect to the study.
5. Ensure that ALL members of the research team know that the FDA is in your facility. Limit idle business conversation by ALL staff.

IV. During the Inspection

During the inspection, the person coordinating the inspection should oversee all FDA requests and take notes to be written up at the conclusion of the inspection.

Remember: Investigators (PIs) are required to permit the FDA to inspect and copy any records pertaining to the investigation, including PHI.

1. The Inspector may ask for a tour of the facility. The designated escort should stay with the Inspector at all times.
2. Providing Documents for Review
   - 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 patient records. Study finances (budget, contract, etc.) and personnel records are not included in the standard inspection, and should be excluded from the files shared with the inspector.
     - The Inspector may ask for a copy of the contract, if it includes details of the investigator's contractual obligations/responsibilities for the study. In this case, only the contract should be provided; budget information should be removed/redacted.
   - When documents are copied for Inspectors, make an extra copy for the site's FDA inspection file. <u>It is very important to keep a copy of every record/document that is provided to the Inspector during the inspection in a "shadow binder".</u> Copies are provided without charge to the FDA. Except for training/qualification records, the FDA Inspectors ordinarily will not request to see personnel records, financial records, and records of internal audits (section 704(a) FDC Act).
     - If the Inspector prefers, electronic copies of requested documents may be provided. It is recommended that the study team provides pdf versions of requested documents and maintains a list (i.e. folder) of documents provided.
     - A record of all documents provided to the Inspector, in paper or electronic format, should be maintained.

- Remove any subject identifiers from any copies given to the Inspector. The copies given to the Inspector should be marked or stamped "Confidential" and the site copies (shadow binder) should be marked or stamped "Copy."
- **Only documents specifically requested by the Inspector should be provided for review.**
    - If the requested records are electronic source documents in the EMR, the coordinator (or designee) should login to Health Link and use an over-the-shoulder approach to show the Inspector the requested records.
    - Patient records may need to be obtained from the hospital or clinic to supplement or corroborate the research records.
    - Documents may need to be removed from the subject files (e.g., if the Inspector asks to see all informed consent forms)

3. Principal Investigator Availability During the Inspection

- The Principal Investigator should set aside some time each day to talk with the Inspector. In the event that the Inspector does not initiate an end of day summary and discussion, the PI should request the meeting.
- The Principal Investigator should plan on being available to the Inspector, either in person or by phone, in order to answer any questions that may arise.

4. Answering the FDA Inspector's Questions

- During the inspection, the person coordinating the inspection should keep an exhibit log that includes a list of ALL questions asked by the Inspector.
- Answer questions as if you were in a deposition.
    - Listen to the question carefully. 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 concise – stop when the question is fully answered and wait for the next question.
    - Answer only the question that is asked.
    - DO NOT speculate or guess – 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.
    - DO NOT argue.

V. Exit Interview

1. The FDA Investigator will usually hold an exit interview, or "close-out," at the conclusion of the inspection. In the event that the Inspector does not initiate such meeting, the PI should request such. The escort should notify the Principal Investigator and FDA program representative(s) of the time and place of the exit meeting for them to attend. It is recommended for Program and Institutional Representatives to be present during the exit interview or close-out meeting with the FDA inspector to answer institutional policy and procedure questions, as well as demonstrate the institutional commitment and support. Email inspection-notification@lists.wisc.edu to coordinate scheduling the exit interview or close-out meeting.
2. During this meeting, if serious deficiencies have been found during the inspection, an Inspectional Observations Form FDA 483 will be issued, which lists the deficiencies. If no

deficiencies are found, or the Inspector has comments that he/she believes are not serious enough to warrant a Form FDA 483, no form will be issued.

3. Document the exit interview, specifically noting observations, recommendations, comments, and any commitments discussed. Clarify and seek to correct any errors in the findings.
4. Consult with the Office of Legal Affairs prior to signing any affidavits provided to you by the Inspector. If the Inspector presents an affidavit for signature, tell the Inspector that you must consult with the University's legal counsel before signing any affidavit and then immediately contact the Office of Administrative Legal Services at: (608) 263-7400.

VI. Actions to be taken after an FDA inspection

1. Inspection Summary Report

   A detailed report, summarizing the inspection should be written (by the PI or the person designated to coordinate the inspection) from the inspection notes immediately. The report should be kept with study critical documents & include:
   - A summary of questions and discussions between Inspector and each employee
   - List of all studies or facilities/departments viewed
   - 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 Inspector related to inspection.

2. Response to Form FDA 483 (if applicable)

   Individuals as appropriate shall draft a response to Form FDA 483. Program and Institutional Representatives request review of follow-up correspondence to the FDA, including a response to a Form FDA 483 if issued, prior to submission the FDA. Email draft(s) of written response to inspection-notification@lists.wisc.edu to facilitate the review and approval process.

   The PI is responsible for response content and sending the written response **within 15 working days.**

   The written response should include the following information:
   - Repeat the observation, followed by a response, point by point.
   - If you disagree 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. Refer to the HRPP Guidance titled "Investigating the Cause of Noncompliance and Implementing Corrective and Preventive Action (CAPA) Plans Guidance" for more information.
   - Delineate corrective and preventive action (CAPA): include justification of why the proposed response will remediate the issue and a realistic timeline for implementation.
   - Keep a copy of the final signed response in your office along with all attachments. The Form FDA 483, PI response and CAPA plan(s) will need to be submitted to the HSIRB.

- The PI/study team is asked to provide Program and Institutional Representatives with copies of any further communication(s) from the regulatory agency regarding the audit/inspection.

3. Notifications to Sponsors

   The Investigator should notify the sponsor of the study of an issuance of a Form FDA 483. The Investigator also should review his/her 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 FDA 483.

4. Inspector's Establishment Inspection Report (EIR):

   The FDA Inspector will file an EIR within approximately 30 days. This report is subsequently available through the Freedom of Information Office (FOI) after the conclusion of any follow-up by the FDA to Form FDA 483, Warning Letter or other actions arising from the inspection.

VII. References

- Information Sheet Guidance For IRBs, Clinical Investigators and Sponsors, FDA Inspections of Clinical Investigators, DHHS, FDA, June 2010
- Bioresearch Monitoring Program (BIMO) Compliance Programs, Program 7348.811, CHAPTER 48 Bioresearch Monitoring, SUBJECT: Clinical Investigators, Implementation Date: December 8, 2008.