The aim of this guidance is to assist investigators and their staff to prepare for an upcoming Food and Drug Administration (FDA) audit of a clinical investigation regulated by the FDA.

WHAT IS THE PURPOSE OF AN FDA AUDIT?

The purpose of the Biomedical Monitoring Program (BIMO) within the FDA, is to ensure the protection of the rights, safety, and welfare of human subjects involved in FDA-regulated clinical trials, to verify the accuracy and reliability of the clinical 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.

While this program involves site visits to one or more entities including institutional review boards (IRBs), sponsors, Contract Research Organizations (CRO's), animal labs and bioequivalence analytical labs, this guidance will focus on the most common site visits, which are visits to clinical investigators who conduct clinical investigations regulated by the FDA.

These inspections most often occur randomly. This ensures the safety of human research participants. It does not mean that you are doing anything wrong. However, there are certain items that make a site visit more likely. For example, if you are a very high enroller or if the sponsor is filing an NDA, you are more likely to be selected for an inspection.

Remember that a notification of the inspection is a courtesy, not a necessity. If the FDA has been provided with information that raises concern, such as subject protection, data integrity, or a history of problems, they are more likely to show up at your site unannounced.

WHAT TYPES OF AUDITS DOES THE FDA CONDUCT?

There are **four** types of FDA establishment inspections:

- **Pre-approval inspections** are conducted when an organization makes a submission to the FDA requesting to market a new product. The purpose of a pre-approval inspection is to verify the data included on the application and to confirm the facility is suitable for manufacturing the product.
- **Routine inspections** are mandated by law and use a risk-based approach to determine inspection frequency. Organizations should conduct operations as though an inspection might be initiated on any given day, thus always are prepared and ready for an inspection.
- **Compliance follow-up inspections** are used if the organization was issued significant 483 observations or other enforcement actions including warning letters or injunctions during a previous inspection. The FDA will inspect and verify the actions taken in response to those observations. The FDA is confirming the organization has responded adequately and corrected any previous violations. If the follow-up inspection reveals that the organization has not responded appropriately, the FDA will document current violations and may use the additional violations as evidence to support future regulatory actions.
- **For-cause inspections** occur when consumers or employees report an issue to the FDA. Additionally, for-cause inspections can be triggered by reportable events that may have caused significant harm, death, or a product recall.

Inspection procedures vary slightly depending upon the product type (e.g., drug, biologic, medical device) and the type of inspection; however, the FDA conducts both announced and unannounced inspections of clinical investigator sites, typically for the following purposes:

- to verify the accuracy and reliability of data that has been submitted to the agency;
- as a result of a complaint to the agency about the conduct of the study at a particular investigational 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 that FDA has identified as products of special interest in its current work plan (i.e., targeted inspections based on current public health concerns).

HOW WILL THE FDA NOTIFY ME OF AN INSPECTION?

The FDA will usually, but not always, contact the Principal Investigator to schedule the audit. If the PI is not available, they will schedule this with a study team member. When the FDA officer calls, it is necessary to ask for at least the following information:

- The name and contact information of the Auditor/Inspector;
- The number of auditors expected;
- The dates the inspector(s) expects to be on site;
- Why the inspection is being done;
- The study to be audited, if a particular study;
- The subjects to be reviewed, if known; and,
- Whether they plan to tour the facility.

N.B. Please refer to the LSUHSC Audit/Inspection Intake Form as a checklist for what information should be requested from the FDA.

The FDA Inspector typically schedules a bioresearch monitoring (BIMO) audit, with the sites receiving notification at most 5 days prior to the inspector arriving on site. The inspection is a fluid process so the number of days the inspector is on site can sometimes be extended or decreased beyond the estimated time depending on the findings.

WHAT SHALL I DO ONCE NOTIFIED OF AN IMPENDING AUDIT?

Immediately after receiving notice of an FDA audit, the person who took the call should contact the following people, departments, and organizations:

- Principal Investigator (if he/she is not the person who took the call);
- PI's Department Head;
- The entire study team;
- The local Human Research Protection Program/Office of Research/IRB;
- IRB of Record, if applicable;
- Study Sponsor;
- Investigational Pharmacy, if involved; and,
- Institutional administrative official(s) if the research is being conducted at any external collaborative site.

The HRPP office will in turn notify the IRB/QA specialist(s), the IRB Chair, the Vice Chancellor for Academic Affairs (IO), and any other officials that are deemed appropriate.

HOW SHOULD I PREPARE FOR THE AUDIT?

If your research is industry sponsored, the sponsor may send representatives to assist you in preparing for the audit. The study sponsor will frequently offer assistance in organizing the study records if time permits, as they are sometimes aware of a possible upcoming audit prior to actual contact by the FDA inspector.

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 questions

Study files and subject records should be audit-ready at all times throughout the life of the trial. The following preparations should be made prior to the audit:

- Clinical investigators who conduct FDA-regulated clinical investigations are required to permit the FDA investigators to access, copy, and verify any records or reports made by the clinical investigator with regard to, among other records, the disposition of the investigational product and research subjects
- Review the regulatory files/binders for completeness;
- 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. It is also recommended to select a room that is located away from the research area to avoid other research activities and related conversations. Support required would include a desk, phone, nearby printer, computer, and an inspection request log. A sign should be placed on the door to alert others of an ongoing FDA audit; there should be no confidential records in the workspace designated for the FDA Inspector.
- 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. They will also schedule any meetings with key personnel requested by the auditor.
- 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.
- Designate a person as a “scribe” who will take minutes of all that occurs during the inspection, and records all the requests for documents and records by the Inspector(s). The scribe should record what is being reviewed and the individuals being interviewed during the inspection.
- A designated “audit support room or office” should also be allocated and not be located close to the FDA representative's conference room, as it sometimes becomes busy and inadvertently loud. This room is where document and record requests are compiled and reviewed prior to submission to the Inspector.
- The Principal Investigator (PI) and all members of the study team should review the current protocol.
- Identify and locate 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, amendments, 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.)
  - Review case report forms and medical charts of enrolled subjects, and screen failures
- Review study records
  - The FDA INSPECTION CHECKLIST and the LSUHSC-NO POST APPROVAL MONITORING AND EDUCATION SELF-EVALUATION REVIEW TEMPLATE 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 with a Note to File (NTF). Assure that PI has signed all NTFs, 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 whiteout.
  - Develop and implement 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 you are proactively addressing potential concerns.
- Review training records and make copies for the auditors/Inspector;
- Make certain that all documents are organized and easily accessible for the Inspector's requests.

WHAT HAPPENS DURING THE FDA INSPECTION?

The FDA Inspector typically verifies compliance with the regulations governing the use of investigational products and human subject protections by inspecting records and talking to individuals involved in the conduct of the study. The inspector audits the study data by comparing the data filed with the FDA or the sponsor with the site records (SOURCE DATA). This would include case report forms and supporting source documentation of informed consents, progress notes, hospital charts and nurses' notes. These records may be in hard copy and/or electronic format. For electronic records and/or electronic signatures, the inspector may also gather information to determine whether 21 CFR 11 requirements have been met.

How our organization initially presents itself when the FDA arrives will generally set the tone for the inspection. Organization and confidence will project a favorable impression with the inspector(s).

Inspector Arrival -

- Once the Inspector arrives, ensure that an escort walks the inspector to the predetermined "inspection room" that is allocated for the inspector. The P.I. should be available when the inspector arrives.
- The Inspector will present his/her credentials to all individuals present at the opening interview. 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.

- The FDA Inspector will present his/her FDA credentials/badge to all individuals present at the opening interview. Record the name, date/time and purpose of the inspection. The FDA Inspector will issue a completed Form FDA 482 (Notice of Inspection) to the Principal Investigator or appropriate study staff. The Notice of Inspection is usually read by the inspector and the focus of the inspection stated, i.e., "for cause" or "routine" inspection. Generally, the inspector does this with the P.I. present in order to obtain his/her signature on the 482.
- 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.
- Ensure that ALL members of the research team know that the FDA is in your facility. Limit idle business conversation by ALL staff.
- It is suggested that the FDA inspector be accompanied at all times and should have someone to make any requested copies;
- A brief introductory presentation showing the organizational chart, headcount, hours of operation and facility layout may be made on the first day. In addition, the inspection probably will include a facility tour, generally on the first day. If so, provide the inspector a copy of the facility diagram plainly depicting the equipment flow and the personnel. If the inspector requests to take photographs ensure management representative or scribe, take similar photographs.

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.
- The Inspector may ask for a tour of the facility. The designated escort should stay with the inspector at all times.
- 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. 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". 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.
    - 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 should contact the site (hospital or clinic) to identify how the site wants to give access to their 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)

- 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
- 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.

The inspector will always attempt to ascertain and/or review the following items during the inspection:

- Investigational Review Board (IRB) correspondence, 1572, Principal Investigator's CV and license, Staff Log, Site Visit Log, Subject Screening and Enrollment Log, Protocol Deviation Overview, Informed Consent versions, Serious Adverse Events (SAE) reporting to Sponsor and Institutional Review Boards (IRB);
- Who performed various aspects of the protocol for the study (i.e. who verified inclusion and exclusion criteria, who obtained informed consent, who collected adverse event data);
- Whether the IRB approved the protocol, informed consent form, and any amendments to the protocol prior to implementation;
- Whether the condition under study was in fact diagnosed;
- Whether the clinical investigator and study staff adhered to the sponsor's protocol and investigational plan and whether protocol deviations were documented and reported appropriately;
- Whether the subject, or the subjects' legally authorized representative, signed informed consent documents prior to entry into the study;
- Whether study eligibility criteria were met;
- Whether the subject received any potentially interfering medication prohibited by the protocol;
- Whether authority to conduct aspects of the study was delegated, and if so, how the conduct of the study was supervised by the clinical investigator;
- Where specific aspects of the investigation were performed;
- How the study data were obtained and where the study data were recorded;

- Accountability for the investigational product, including shipping records and disposition of unused investigational product;
- Whether the clinical investigator submitted all reportable adverse events;
- Whether the subject received proper follow-up, as outlined in the protocol, after completion of the study-related activities;
- The monitor's communications with the clinical investigator/study team;
- The monitor's evaluations of the progress of the investigation; and,
- Corrective actions in response to previous FDA inspections, if any, and regulatory correspondence or sponsor and/or monitor correspondence.

WHAT HAPPENS DURING THE EXIT INTERVIEW

- The FDA Inspector 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. A representative from the LSUHSC Office of Research Services and/or Institutional Representatives should be present during the exit interview or closeout meeting with the FDA inspector to answer institutional policy and procedure questions, as well as demonstrate the institutional commitment and support.
- During this meeting with the PI the Inspector will review audit findings and clarify any issues found during the inspection. If serious deficiencies have been found, 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.
- Document the exit interview, specifically noting observations, recommendations, comments, and any commitments discussed. Clarify and seek to correct any errors in the findings.

WHAT HAPPENS AFTER THE FDA INSPECTION?

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.

After the inspection has been completed, the FDA investigator submits a written report of findings to FDA headquarters. Upon review and consideration of the report provided, FDA Headquarters will send the investigator one of the following types of communication:

- **No significant deviations**: The FDA investigator observed basic compliance with pertinent regulations. Note that a letter is not always sent when there are no significant deviations. A response from the PI is not required. You may and should request a letter for your records.
- **Informational or Untitled letter**: The informational letter identifies deviations from the statutes and regulations that do not meet the threshold of regulatory significance for a Warning Letter. Such letters may or may not require a response from the PI.
- **Warning letter (also known as FDA Form 483)**: This warning letter identifies serious deviations from statutes and regulations and is issued for violations of regulatory significance. These violations may lead to enforcement action if not promptly and adequately corrected. A response from the PI is required within 15 calendar days and requires careful preparation. Sanctions may be taken against the sponsor and/or the PI in addition to receiving this letter.
- **A Notice of Disqualification Proceeding and Opportunity to Explain (NIDPOE) Letter**: The FDA may initiate a process to disqualify the PI from receiving investigational product (drug or device) if the investigator:
    - has repeatedly or deliberately failed to comply with applicable regulatory requirements, or
    - has deliberately or repeatedly submitted false information to the sponsor or FDA in any required report, as described under 21 CFR 312.70 and 812.119 .

  See FDA Guidance, Clinical Investigator Administrative Actions—Disqualification , for more information.

WHAT HAPPENS IF I RECEIVE A 483 OR NIDPOE?

These findings must be taken seriously, and the FDA will expect responses usually within 15 calendar days. The Sponsor, LSUHSC HRPP and/or the Clinical Trials Office, and possibly Legal should work with the PI in preparing responses to FDA warning letters and NIDPOE, however the P.I. is ultimately responsible. To expedite corrective action, and to ensure protection of research subjects, copies of the warning letters and NIDPOEs are sent to the study sponsor and the reviewing IRB.

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.

Please refer to HSC CTO SOP 2.15_Clinical Research Audit document for additional guidance.