INTRODUCTION
This document will outline the actions that are to be taken by Temple University researchers during an FDA or OHRP inspection or audit – from the time the an inspector is greeted until the time the exit interview is conducted and a response to the agency's observations is made. This process for the inspection and the activities that should be done to facilitate the inspection applies to all Temple University and Temple Health System, Inc. faculty, students, and staff involved in the implementation and coordination of any FDA-regulated clinical trials. Please note that although much of the information presented in this document refers directly to FDA inspections and regulations, it is also useful for OHRP-regulated research and much of the same guidance will apply.

FDA inspections of clinical sites are typically conducted to determine compliance with federal regulations and adherence to guidelines, to verify the validity and integrity of clinical data submitted in applications for FDA approval, and to ensure that the rights and welfare of human research subjects have been protected.

The Principal Investigator (PI) is ultimately responsible for the performance and supervision of a clinical trial. The PI may delegate some tasks to sub-investigators or staff, but remains responsible at all times for the conduct of all individuals involved in the research. PIs with investigational new drug (IND) research approved by the FDA have additional responsibilities as Sponsor.

SECTION 1: RECEIVING NOTIFICATION FROM THE FDA
Notify Temple:
If you receive a call or letter for the FDA to schedule an inspection, please immediately notify the individuals listed below at Temple University/Temple University Health System. They will provide you with support and guidance during your inspection.

Chad Pettengill, IRB Director, Temple University
Emily Weber, Associate Counsel, Temple University Health System, Inc.
Chair of the Department in which the audit will be conducted

If your research is an industry sponsored clinical trial, you will also need to notify:
Arleen Wallen, Financial Administrator, Office of Clinical Research Administration

SECTION 2: BEFORE THE SITE INSPECTION
PI Involvement in the Audit:
The PI must be available in person during the FDA inspection. If this PI is unavailable during the day proposed by the FDA inspector, contact the FDA and request to reschedule for a mutually convenient day/time. This request must be made in a timely fashion and be documented along with all FDA/Temple communications. If a new date is agreed upon, it should be communicated to all parties involved. All study personnel must be available to answer questions for which they have direct knowledge.

It is important to note that the FDA can and will perform an inspection without the PI present during a portion or all of the inspection. This can be problematic for Temple because the PI can often provide accurate information more efficiently and effectively than staff, which can help to avoid unnecessary FDA citations. The FDA has also been known to cite for supervision deficiencies when PIs are unavailable during inspections. Minimally, the PI should make every effort to be physically available during the entrance and exit interviews.
Designate a Liaison:
In preparation for the inspection, designate a primary staff person to serve as a liaison to the FDA and to oversee the inspection (usually the PI or research coordinator for the study). The liaison will serve as an institutional monitor and escort, as well as a guide and general study contact person.

Prepare Documents and Records:
Immediately following notification by the FDA and notification of the proper contacts at Temple, the PI and their staff must begin retrieving and assembling the requested study-related records. Several steps should be taken to prepare your records and documents in advance of the FDA inspection:

- Identify all subjects, enrollment/screening log, and all Informed Consent and HIPAA Authorization documentation.
- Identify selected Case Report Forms and all supportive source documentation.
- Complete the FDA Pre-Inspection Checklist and identify the records the FDA is likely to audit during their visit. These are likely to include:
  - SOPs
  - Regulatory records – IRB approvals and communications, enrollment logs, signed and dated consent forms (including screen failures), protocols, investigator brochure, and study correspondence.
  - Monitoring reports
  - Source records – clinical charts, hospital records, x-rays, lab reports, subjects’ data diaries, referrals
  - Test article accountability records

Sequester the records listed above and your reviews in readiness for easy access, but do not volunteer them to the FDA inspector. Always wait for a specific request before providing any information to the FDA inspector. The PI may wish to designate a “documents” person to assist and support the PI or the liaison in obtaining any requested items for the FDA inspector.

Make Space Arrangements:
Make arrangements to provide the FDA inspector(s) with a comfortable work area for the duration of their inspection. You may need to reserve a conference room or other meeting space within your department. The room must contain no confidential records, including any clinical or research-related records. Secure a room that can be locked if the inspection lasts more than one day.

Special Note:
The FDA Compliance Program Guidance Manual 7348.811 provides a list of information that will be requested during every inspection. This reference is very helpful in preparing for the inspection.

SECTION 3: FDA INSPECTOR ARRIVAL

The designated liaison will greet the FDA investigator and verify their identification or credentials. Do not expect the investigator to permit a copy to be made of their badge or credentials. When a sign-in log is used, and the inspector will likely not sign in, in which case make a note in the sign-in log of the name, date/time, purpose, and liaison name. The liaison should walk the FDA inspector to the appropriate meeting room. The FDA inspector will present a Notice of Inspection (Form 482) to the PI or the most responsible individual. This notice authorizes the inspection and its presentational officially begins the inspection. If the FDA does not provide a Form 182, you must immediately notify Temple University Health System Legal Counsel. The FDA inspector will then explain the intended purpose and scope of the inspection, and ask the PI to summarize the study.

Provide a tour of the facility. The FDA inspector may request a tour of the facility where the research took place. Staff should be notified in advance and be prepared to answer questions.
SECTION 4: DURING THE FDA INSPECTION

The liaison or PI should take notes concerning the progress of the inspection. You may wish to develop a form for use in this process, with space for the FDA inspector’s name, documents requested, date and time of request, and date and time delivered.

The FDA inspector should be accompanied by the liaison or designee at all times while in the presence of study related documents, samples, or other confidential information, including when they are in the designated conference room. FDA inspectors should not be allowed to enter patient care areas or research staff workspaces areas unescorted at any point during the inspection. If the FDA inspector needs to make a phone call or requires privacy, they should be first escorted to a “sterile room” (where no study related information is present) or a public area. In general, when an FDA inspector is here in an official capacity, they should not be left alone.

The FDA inspector must never have access to any site records not specifically provided by the liaison or PI. Standard procedure is for the inspector to request files for review, starting with “general” study materials, including the regulatory documents binders, then all signed informed consent documents, followed by a sampling of specific patient records. The liaison or PI will provide the requested records and make photocopies for the FDA and in duplicate for retention at the site. Study finances and personnel records are not included in the standard inspection. If they are not also serving at the primary liaison to the FDA inspector, the PI should be available to answer any questions that may arise, and should set aside time each day to talk with the FDA inspector.

The role of the liaison is to coordinate all FDA requests and ensure that the inspector’s questions are answered honestly and completely. The liaison should arrange any interviews requested by the FDA inspector and accompany them on any visits. Document the name and title of all persons interviewed by the FDA, and the date and time of the interview. The liaison should document any line of questioning, including issues that could not be resolved and steps taken at the inspection to resolve them. Each question should be answered by person(s) most knowledgeable of the issue. Listen to the question in its entirety, and answer the question that was asked. Defer to others if you do not know an answer. When possible, use documents already provided in support of your answers. Stop talking when the question is fully answered. There is nothing wrong with being silent. When you have answered a question, you may be silent and wait for the next question.

How to Answer FDA Questions:

- Ensure that each question is answered by the person(s) most knowledgeable of the issue.
- Concisely answer only the question asked.
- Provide clear answers.
- Be positive and confident.
- If possible, take corrective actions. Only commit to what you can deliver.
- Do not volunteer information.
- Do not guess or speculate.
- Do not lie.
- Do not argue.
- Do not panic.
- Do not sign affidavits.
- The liaison or PI should arrange for follow-up as required for any unanswered questions.

Inspection of Documents:

- Escort the FDA inspector to an information sterile room away from sources of casual conversation to review requested documents.
- Ensure that the FDA investigator is not permitted free access to areas where files are kept.
- Always sequester the FDA inspector in an isolated room and bring the documents to them.
• Temple researchers are required to permit the FDA to inspect and copy and records pertaining to the investigation including, in certain situations, those which identify subjects.
• Only documents specifically requested by the FDA shall be provided for review. The liaison may need to obtain patient or clinical records to supplement or corroborate the research records.
• Gather the documents requested for review. When documents are copied for FDA inspectors, make two copies – one for the FDA and one to retain on site following the inspection. All copies provided should be stamped “Confidential”. Usually copies are provided without charge to the FDA; however, if the FDA inspector requests an inordinate number of copies, notify the inspector that an invoice will be provided.
• FDA inspectors are not entitled to review or copy financial documents, personnel documents (except for training/qualification records), and internal audits.
• The escort should arrange for follow-up as required for any outstanding document reports.

Photographs:
If the FDA inspector insists on taking photographs, take duplicates simultaneously.

Samples:
The FDA inspector may request a reasonable quantity of samples. Fill the request, but pull identical samples to retain. Ask the FDA inspector to issue a receipt for the samples using the FDA Form 484. Depending on the nature of the samples provided, advise the FDA inspector that an invoice may be presented.

SECTION 5: FOLLOWING THE FDA INSPECTION

The Exit Interview/End of Day Discussions:
The PI or liaison should request an end of day discussion during each day of the inspection to review any preliminary findings. The liaison should document any questions where answers could not be provided, along with the appropriate follow up to obtain the requested information. At the conclusion of the inspection, the FDA inspector will conduct an exit interview. The FDA inspector will notify the liaison or PI, who must then notify a representative from the Temple IRB, Temple Legal Counsel, the Chair of the department in which the audit is occurring, and other individuals as appropriate of the time and place. All should be expected to attend.

Responding to FDA Findings:
If the FDA inspector found serious deficiencies, an Inspectional Observations Form (FDA Form 483) will follow from the regional office. The form will detail the deficiencies observed. If no deficiencies were found, or if the inspector did not find the deficiencies serious enough to warrant an FDA Form 483, no form will be issued.

If the PI receives an FDA Form 483, they must immediately consult with the Temple contacts listed in “Temple University Institutional Follow Up” below. If the study is sponsored, the sponsor should also be informed (via the Temple Office of Clinical Research Administration) and be provided with the opportunity to assist in the development of our response. As necessary, these parties will meet to discuss the FDA’s findings and Temple’s response.

In consultation with the appropriate Temple contacts, the PI or designated staff is responsible for drafting a response to the FDA Form 483 and submitting it to the FDA within the time specified, typically 15 days. The written response should include the following specific elements:
• Determine if a finding was an oversight or one-time occurrence; or systemic, where a change of procedure is indicated.
• Delineate corrective actions, including justification of why the proposed response will remediate the issue, and a realistic timeline for correction.
• If the PI disagrees with an FDA observation, they must present a factual response and provide clear and verifiable evidence.
• Address each particular observation or finding, point by point.
The PI must ensure that the Temple IRB and all appropriate institutional officials receive copies of the final written report to the FDA. Additionally, if there is a sponsor of the study, the sponsor will either need to be included in the review of the response or will be required to be provided a copy of the response so provided to the FDA. Please check with the Temple Office of Clinical Research Administration to inquire about any sponsor notification requirements. The PI should keep a copy of the final signed response in his or her files.

Establishment Inspection Report:
The FDA inspector will file an Establishment Inspection Report (EIR) within approximately 30 days. At the conclusion of the 483 response, the Temple IRB and Legal Counsel will attempt to obtain a copy of the report through the Freedom of Information Act. The FDA will not typically respond to an EIR request until the matter is formally closed.

Temple University Institutional Follow Up:
The PI is required to confer with the following individuals at Temple University/Temple University Health System on all post-inspection communications with the FDA:

Chad Pettengill, IRB Director, Temple University
Emily Weber, Associate Counsel, Temple University Health System, Inc.
Chair of the Department in which the audit will be conducted

Industry Sponsored Clinical Trials only:
Arleen Wallen, Financial Administrator, Office of Clinical Research Administration

SECTION 6: ONGOING AUDIT READINESS
The average notice of FDA inspection falls between a two day and twenty four hour timeframe, although it may be more or less. This is why it is extremely important to always be prepared for an audit. Researchers should maintain well-organized and robust research files for all studies at Temple. Research files should match all true original source documents for each subject found in paper or EMR patient charts. FDA inspectors will request original source documentation during their inspections.

You can follow several ongoing steps to ensure that your research is always ready for inspection:

Research File Maintenance
1. Keep your files organized at all times.
2. Retain all correspondence from the sponsor, the IRB, study subjects, letters, faxes, emails, memos, and phone contacts.
3. Retain all test article records.
4. Retain shipping receipts, screening and enrollment logs, and dispensing logs.

FDA Inspection Triggers
1. Studies with a high enrollment, where test article approval is pending.
2. Studies with few or no adverse events.
3. PIs who have received an FDA Form 483 in the past.
4. Studies where other sites have had problematic inspections.

SECTION 7: RELATED DOCUMENTS
- FDA Pre-Inspection Checklist
- FDA Compliance Program Guidance Manual 7348.811
- Notice of Inspection – FDA Form 482
- Receipt of Samples – FDA Form 484
- Inspectional Observations Form – FDA Form 483

Acknowledgement:
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