Title: Core Standard Operating Procedure for FDA Inspections

I. Procedure Statement
To describe the preparation, reporting, and procedures to follow prior to, during, and following an inspection by the U.S. Food and Drug Administration (FDA).

II. Definitions
1. Investigational Device Exemption: Allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data (FDA, 9/4/15).
2. Investigational New Drug: A request for Food and Drug Administration (FDA) authorization to administer an investigational drug to humans (FDA, 8/31/15).
3. Notice of Inspection (FDA Form 482): Document giving notice of the FDA inspection and giving the FDA authority to inspect a facility.
4. Inspection Observation (FDA form 483): Document issued at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgement may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts (FDA, 4/23/15).
5. Investigator Initiated Research: Research that is both initiated and conducted by an individual. The investigational drug/device/intervention is administered or dispensed under the investigator’s immediate direction. The investigator assumes the responsibilities of, and must comply with, FDA regulations applicable to both a sponsor and an investigator (FDA, May 2015).
6. Case Report Forms (CRFs): Printed or electronic documents designed to record all protocol-required information that is collected on each participant in a research study.
7. For Cause Inspection: may be conducted when the FDA suspects problems with regard to the scientific integrity or protection of patient welfare. Some triggers initiating “for-cause” FDA inspections include suspiciously high volume of clinical research by the investigator, atypically large study population, results grossly inconsistent with data from other sites investigating the same drug or device, unusual publicity, or research subject/staff complaints.
8. Routine Inspections: are conducted on randomly selected sites as part of the general program to ensure that the research findings on which the FDA bases its product approvals are scientifically valid, and that the rights and safety of research subjects are being safeguarded.
III. Procedure/Content/Scope

This applies to all clinical trials research within MU Health including the School of Medicine, School of Health Professions, School of Nursing, and MU Healthcare. This SOP outlines the process of an inspection by the U.S. Food and Drug Administration (FDA) and describes the activities required to facilitate the inspection.

The FDA typically inspects sites to determine compliance with federal regulations and adherence to guidelines; to verify the validity and integrity of clinical data submitted in applications for market clearance of medical devices, drugs, or biologics; and to assure that the rights and welfare of subjects in research are protected.

1. When the FDA contacts the investigational site to schedule an inspection, the following information should be obtained and retained in a file specific to the inspection:
   a. FDA inspector’s name and contact information
   b. Additional inspector’s information, if applicable
   c. The purpose of the FDA inspection:
      i. Routine
      ii. For Cause
   d. The name of the PI being inspected
   e. The study or studies to be inspected
   f. The specific personnel to be made available
   g. The specific documents to be made available
   h. Duration of the inspection
   i. Requested date and time of the inspection: The FDA inspector will usually request that the inspection take place within 10 days.

   Once the above information is obtained, the following individuals or areas must be immediately notified:
   a. Principal Investigator(s) (PI)
   b. Research manager or coordinator
   c. Dean of the appropriate School, or CEO of MU Healthcare
   d. IRB
   e. Office of Compliance
   f. Investigational Pharmacy, if applicable
   g. Department Administrator
   h. Sponsor, if applicable
   i. Medical Records/Health Information Services
   j. Office of Sponsored Programs (OSPA) and Grants & Contracts Office

2. Document any additional telephone conversation(s) that occur between the FDA inspector and the study staff.

3. Reserve and secure an empty workroom or conference room for the inspection to take place. This room should contain no other research records, charts, correspondence, etc.
The research team and PI(s) will immediately begin collecting and assembling the requested study records. Review agreements or contracts for any specific details regarding FDA inspections. Review FDA Compliance Program Guidance Manual 7348.811 which provides a list of information that will be requested during every inspection. This reference is very helpful in preparing for the inspection.

4. All relevant research documentation should be complete and readily available including, but not limited to:
   a. SOPs
   b. Informed Consents/Subject Binders
   c. Regulatory Binder
   d. Monitoring Visit Log
   e. Device or drug approvals and logs
   f. Billing compliance documents
   g. Source documents
   h. IRB approval letters
   i. Approved protocols and consent documents

5. Review study documentation for:
   a. Comprehensiveness, accuracy, and compliance.
   b. Weakness or gaps, and correct if possible (e.g. file violations, draft notes-to-file, missing documents, etc.).
   c. Unresolved or outstanding issues; develop a corrective plan for any unresolved/outstanding issues.

6. The inspection team will need access to research data, medical records, and electronic medical records. They will need a dedicated and reserved room that ensures privacy and does not contain files that do not pertain to the inspection.

7. Prior communication with the inspection team should include arrival times, name of the MU Health personnel that will be escorting the inspection team to the appropriate location, and information about the ability of the inspection team to accept meals or food.

8. Assign a designated liaison to perform the following tasks during the inspection:
   a. Take notes concerning the progress of the inspection. A form may be used to assist in this task, with spaces for the FDA Inspector's name, documents requested, date and time of request, date and time delivered.
   b. Provide requested records and make photocopies for the FDA and clinical site. Any copies of case report forms or medical records requested by the FDA Inspectors will be made in duplicate for retention at the site.
   c. Arrange any interviews requested by the FDA Inspector, and escort the FDA Inspector if they request to go to other areas related to the research.
   d. Document any line of questioning pursued by the PI and the FDA Inspector, including issues that could not be resolved and steps taken during the inspection to resolve the issue.
   e. Document the name and title of all persons interviewed by the FDA, and the
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9. Conducting the Investigation:
   a. The PI and liaison will:
      i. Greet the FDA Inspection team and verify identification and credentials. The FDA will provide the PI with the form FDA 482 (Notice of Inspection). FDA regulations generally require the FDA Investigator to give the FDA 482 to the most responsible individual. This may not occur in certain situations, for example, in connection with a criminal investigation. If the FDA does not provide the 482, notify the IRB immediately.
      ii. Provide a tour of the facility. The FDA Inspector may request a tour of the facility where the research took place. Research staff will have been notified in advance, and should be prepared for the visit and possible questions.
      iii. Provide requested records. Do not volunteer a list of documents or records to the inspector; always wait for a specific request to provide information.
      iv. The liaison will make two (2) copies of each record requested by the FDA: one for the FDA, and one for retention on site following the inspection.
      v. Ensure that each question is answered by the person that is most knowledgeable about the issue.
      vi. Accompany the FDA Inspector at all times, other than when they are in the designated conference room. FDA inspectors are not allowed to enter patient care areas or research staff workspace areas unescorted at any point during the inspection.
      vii. Assist the FDA Inspector as needed.
      viii. Arrange for follow-up as required for any unanswered questions or outstanding document reports.

10. Post-Inspection
   a. The PI or designee should request an end-of-day discussion with the FDA Inspector on each day of the inspection to review any preliminary findings.
   b. The PI or designee will document any questions that could not be answered, along with appropriate follow-up to obtain the requested information.
   c. If the PI receives a Form FDA 483 (report of observations) after the audit, he/she should consult with the IRB on how to respond. The sponsor should be provided with an opportunity to assist in the response. A copy of the FDA 483 must be forwarded to the IRB, the sponsor's project manager, and the MU Office of Compliance.
   d. The PI must arrange a meeting to discuss the findings with the IRB and other offices as necessary or determined by the findings.
   e. The PI will prepare a written response with input from the IRB and appropriate persons to any observations noted in the Form FDA 483, and send the response to the FDA within the time specified, typically within 15 days. The written response should:
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i. Address each observation and explain what steps have been implemented or will be implemented to remedy the observation, and prevent future occurrences of similar observations.

ii. Be factual and written in a tone that is respectful, professional and cooperative.

f. The FDA will sometimes extend the deadline for response depending on the circumstances. If such a request is necessary, it should be made as soon as possible. The PI should contact their Department Director to discuss the reason for the delay. The IRB can assist in facilitating such a request.

g. The PI or designee should attempt to obtain a copy of the official FDA investigator's field audit report (Establishment Inspection Report [EIR]) under the Freedom of Information Act (FOIA Request). This request can be made at the conclusion of the FDA 483 response. The FDA will not typically respond to an EIR request until the matter is formally closed.

h. The PI or designee should not contact the FDA Inspector directly without first consulting with IRB, Office of General Counsel, or the Office of Compliance.

IV. REFERENCES:

1. Title 21 CFR part 11 - Electronic Records; Electronic Signatures
2. Title 21 CFR parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards)
3. Title 21 CFR part 312 (Investigational New Drug Application),
   part 312.62 - Investigator Record Keeping and Record Retention for Clinical Drug or Biological Trials
4. Title 21 CFR part 812 (Investigational Device Exemptions),
   part 812.140 - Investigator Record Keeping and Record Retention for Device Trials
5. ICH GCP Consolidated Guideline - Part 4.9 Records and Reports
6. ICH GCP Consolidated Guideline - Part 5.15 Record Access
7. FDA Compliance Program Guidance Manuals 7348.811 – Investigators and 7348.810 – Sponsors/CROs/Monitors
8. FDA Investigations Operations Manual