I.PURPOSE AND SCOPE

The purpose of this procedure is 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).

Scope: Applies to all LUC and LUMC faculty and staff involved in the implementation and coordination of clinical investigations (defined to include any FDA-regulated clinical trials).

Personnel responsible: The Principal Investigator (PI) is ultimately accountable for the performance and supervision of a clinical investigation. While the PI may delegate some required tasks to sub-investigators and other research staff, the PI remains at all times accountable for their conduct. If the PI also files an investigational new drug application (IND) which is approved by the FDA, the PI has additional responsibilities as Sponsor.

II.BACKGROUND

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

In order to be well prepared for FDA inspections (alternatively known as surveys or audits) on an ongoing basis, it is very important to maintain well-organized and robust research files for all studies at LUC. In addition, the research file must match all true original source documents for each subject found in paper or EMR patient charts. FDA Inspectors (alternatively known as surveyors, auditors or investigators) will request original source documentation during the FDA inspection.

III.DEFINITIONS and ABBREVIATIONS

IDE- Investigational Device Exemption (IDE): Allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data (FDA, 9/4/15).
IND- Investigational New Drug (IND): A request for Food and Drug Administration (FDA) authorization to administer an investigational drug to humans (FDA, 8/31/15).
Form 482 - Notice of Inspection (FDA Form 482): Document giving notice of the FDA inspection and giving the FDA authority to inspect a facility.
Form 483 -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).
FDA Warning Letter- When FDA finds that a manufacturer has significantly violated FDA regulations, FDA notifies the manufacturer. This notification is often in the form of a Warning Letter. The Warning Letter identifies the violation, such as poor manufacturing practices, problems with claims for what a product can do, or incorrect directions for use. The letter also makes clear that the company must correct the problem and provides directions and a timeframe for the company to inform FDA of its plans for correction.
IST- Investigator Sponsored/ Initiated Trial (IST or IIT): 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).
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, a typically

large study population, results grossly inconsistent with data from other sites investigating the same drug or device, unusual publicity, or research subject/ staff complaints.

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.

IV. PROCEDURES

A. Notification: FDA Inspection

1. The FDA Inspector will contact the Principle Investigator directly if an inspection is planned.

2. The PI should contact the Clinical Research Office or Cancer Clinical Trials Office immediately to assist with preparing for the Inspection. The FDA representative should speak to a study team member as soon as possible to schedule the site visit.

   Collect the following from the FDA inspector:

   a. FDA inspector's name and contact information
   b. Additional inspector's information, if applicable
   c. The purpose of the FDA inspection: Routine or 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.

3. If the PI is unavailable during the proposed date of the audit, and the date must be rescheduled, the PI or designee may contact the FDA investigator to request rescheduling at a mutually convenient time. This request and response should be made in a timely fashion and should be documented together with the agency's response. Document any additional telephone conversation(s) that occur between the FDA inspector and the study staff.
4. The FDA Notification letter should be obtained and retained in a file specific to the inspection,

Note: FDA can and in the past has been known to perform an inspection without the PI present during all or a portion of the inspection. This can be problematic as the PI can often clear up misunderstandings more efficiently and effectively than staff, thus potentially avoiding unnecessary citations. At a minimum, the PI should make every effort to be physically available during the entrance and exit interviews. Note that FDA has cited some sites for supervision deficiencies where a PI has been unavailable in person for any extended period during which a new PI has not been named.

5. Internal Notification
   Upon receipt of notification from the FDA of an inspection or site survey, the Study Team will immediately notify the following within 24 business hours:
   a. LUC Officials (VPR, ORS)

b. Clinical Trial Sponsor:
c. The Research Manager of the CRO or CCTO/ Research Team
d. The Chair or other appropriate representative of Department where inspection will occur;
e. IRB Chair and the Director of the Human Research Protection Program (HRPP
f. LUMC Research Operations
g. Investigational Pharmacy
h. Cell Therapy Lab

Note: The sponsor may offer to assist with pre inspection preparation and conduct a QA review

B. **Preparing for the Inspection**

1. Reserve a dedicated office that ensures privacy and does not contain files that do not pertain to the inspection.

2. The PI will ensure that his/her research staff immediately begin to retrieve and assemble all requested trial-related records.

3. All relevant research documentation should be complete and readily available including, but not limited to:
    a. Institutional Standard Operating Procedures
    b. Regulatory records – IRB approvals, enrollment logs, signed and dated consents (including screen failures), protocols, investigator brochure, and correspondence. Delegation of Authority and Training logs CRFs, monitoring reports.
    c. Source records – clinic charts, hospital records, x-rays, lab reports, subject's diaries, referrals. Electronic medical records
    d. Test article accountability records

Refer to FDA audit preparation checklist.

4. 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.
    b. Review agreements or contracts for any specific details regarding FDA inspections
    c. 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.
    d. Documents that the inspector is not entitled to review or copy: financial, personnel (except for training/qualification records), and internal audits (section 704(a) FDC Act).

C. Conducting the Investigation:

1. The LUC liaison (Designated department representative or Study Team Member) and the PI will:
    a. 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 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 LUC Officials immediately.

b. Provide an initial tour of the facility. The FDA Inspector may request a tour of the facility where the research took place. Arrange any interviews requested by the FDA Inspector and escort the FDA Inspector if they request to go to the pharmacy or IRB. Document the name and title of all persons interviewed by the FDA and the date (and time if possible) of the interview.
c. Provide requested records. Do not volunteer a list of documents or records to the inspector; always wait for a specific request to provide information.
d. The LUC 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. Ensure that each question is answered by the person that is most knowledgeable about the issue.
e. 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.
f. Arrange for follow-up as required for any unanswered questions or outstanding document reports
g. 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.

D. **Post-Inspection**

1. If the PI receives a Form FDA 483 (report of observations) after the audit, he/she should consult with LUC Officials. 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.

2. 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:
    a. The written response should include specifics:
        i. Determine if a finding was an oversight/one-time occurrence; or systemic, where a change of procedure is indicated.
        ii. Delineate corrective actions: including justification of why the proposed response will remediate the issue; and a realistic timeline for correction.
        iii. If the PI disagrees with an observation: respond factually, providing clear and verifiable evidence.
        iv. Address each particular observation or finding and what steps have been implemented or will be implemented to remedy the observation, and prevent future occurrences of similar observations.
        v. The reply should be sent within two weeks. Keep a copy of the final signed response.
    b. 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.
    c. 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).
    d. The PI or designee should not contact the FDA Inspector directly without first consulting with LUC Officials.
    e. Please provide a copy of the final establishment inspection report (EIR) and/or the Inspectional Observation Form 483 upon receipt to the local IRB in addition to the IRB of record.

E. On- GOING READINESS

1. Research Study File Maintenance
   a. Keep files organized at all times.
   b. Retain all correspondence from – sponsor, IRB, monitors, study subjects, letters, faxes, e-mails, memos, And phone contacts.
   c. Retain all test article accountability records.
   d. Retain Shipping receipts, screening and enrollment logs, dispensing logs.

2. FDA Inspection Triggers which may increase the chance of an FDA audit:
   a. Studies with a high enrollment, where test article approval is pending.
   b. Studies with few or no adverse events.
   c. PIs who have received an FDA Form 483 in the past.
   d. Studies where other sites have had problematic inspections.

3. Common Audit Findings at Clinical Sites:
   a. Protocol non-adherence- Study processes inadequately followed
   b. Failure to report concomitant therapy
   c. Inadequate and inaccurate records
   d. Failure to report adverse events- Safety reporting violation
   e. Inadequate drug accountability
   f. IRB problems
   g. Informed consent- Improper informed consent process
   h. Documentation issues- Source document and CRF mismatch
   I. Inadequate training records
   j. Protocol violations
   k. Procedural violation
   l. Source document and CRF mismatch

V. 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. ASCO FDA Audit Toolkit v 2019
9. LUC SOP QA-001

VI. APPROVALS

Jessica Shore

Digitally signed by Jessica Shore
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Date: 2020.11.10 12:28:04 -06'00'

LUC Senior Director, Clinical Research Office (or designee) Date

11-10-2020

Manager, Cancer Clinical Trials Office (or designee) Date