**FACILITATING FDA INSPECTIONS**

**PURPOSE**

To outline the process for FDA sponsor or clinical investigator inspection, and describe activities that should be done to facilitate the inspection.

**SCOPE**

Applies to all UF 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) or investigational device exemption (IDE) which is approved by the FDA, the PI has additional responsibilities as Sponsor.

**BACKGROUND**

FDA inspections are typically conducted at clinical sits to determine compliance with federal regulations and adherence to guideline, to verify the validity and integrity of clinical data submitted in applications for approval, and to assure that the rights and welfare of subjects participating in clinical studies have been protected.

**REFERENCES**

Title 21 CFR part 11 Electronic Records; Electronic Signatures

Title 21 CFR parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards)

Title 21 CFR part 312 (Investigational New Drug Application), part 312.62 – Investigator Record Keeping and Record Retention for Clinical Drug or Biological Trials

Title 21 CFR part 812 Investigational Device Exemptions, part 812.140 – Investigator Record Keeping and Record Retention for Device Trials

ICH GCP Consolidated Guideline Part 4.9 Records and Reports

ICH GCP Consolidated Guideline Part 5.15 Record Access

FDA Compliance Program Guidance Manuals 7348.811 Investigators, and 7348.810 Sponsors/CROs/Monitors

FDA Investigations Operations Manual

**PROCEDURES**

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 UF. 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.

**A. NOTIFICATION**

1. Upon receipt of notification from the FDA of an inspection or site survey, the PI will immediately notify the following UF Officials, Offices, and Sponsors:
2. The Chair or other appropriate representative of Department where inspection will occur;
3. The UF IRB;
4. The UF Office of General Counsel;
5. The UF Office of Clinical Research (OCR);
6. The sponsor will be notified by the Office of Clinical Research per the terms of the agreement prior to the site inspection, and

A copy of any inspection letter will be forwarded to the Chair or other appropriate representative of Department where inspection will occur. The PI is advised to review the following FDA information as applicable:

[FDA Compliance Program Guidance Manual and Guidance for the FDA Staff](http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm)

[FDA Compliance Program Bioresearch Monitoring Sponsors, CROs and Monitors](https://www.fda.gov/iceci/enforcementactions/bioresearchmonitoring/ucm133777.htm)

[FDA Inspections of Clinical Investigators: Information Sheet Guidance](http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126553.pdf)

[Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM464506.pdf)

[Electronic Source Data in Clinical Investigations](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf)

1. The PI will ensure that his/her research staff immediately begin to retrieve and assembly any requested trial-related records
2. The Lead Study Coordinator will immediately forward the list of study participants to be included in the inspection to the PI or PI designated individual who will then request each study participant’s complete medical record, including original hospital and clinic charts and/or access to EPIC.
3. The Lead Study Coordinator will immediately communicate any difficulty in obtaining charts to the PI so that issues are resolved immediately and collection of required materials is completed in the desired timeframe.
4. The Lead Study Coordinator will immediately send an email notification to the following study-delegated personnel about the date/time and occurrence of the FDA inspection:

* Principal Investigator
* Office of Clinical Research
* Protocol Project Manager for the research unit
* Director of the IRB
* Investigational Pharmacist

The PI must be available in person during the FDA inspection. 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.

If a new date is agreed upon, the reschedule inspection must be communicated to all involved, as noted above including but not limited to the Chair or other appropriate representative of Department where inspection will occur; the UF IRB; the UF Office of General Counsel; the UF Office of Clinical Research; the sponsor, if deemed applicable by OCR.

*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.*

**B. PREPARING FOR THE INSPECTION**

1. UF faculty and staff must cooperate with any FDA inspection. All study personnel will be available to answer questions for which they have direct knowledge.
2. The PI, Lead Study Coordinator or Protocol Project Manager will be responsible for securing a room for the entire inspection process that can be locked if the inspection is expected to be longer than one day.

* the room should have a telephone and allow convenient access to study staff
* the room should be located away from the clinical/research area to avoid such activities from being conducted near the inspector
* the room should NOT contain any other study or medical records, other than the study records that the inspector has requested
* the room should be able to be locked when the inspector leaves

1. The PI or Lead Study Coordinator will designate a ‘documents’ person to assist and support his/her to obtain any requested items for the FDA inspector. This person should be readily available to the inspector at all times, but not in the room with the FDA inspector.
2. In preparation of the audit, the Lead Study Coordinator, designee or Protocol Project Manager will review the FDA form 1572, retrieve and assemble all study-related records including:
3. SOPs
4. Regulatory records – CHR approvals, enrollment logs, signed and dated consent (including screen failures), protocols, delegation of authority logs, investigator brochure, and correspondence
5. CRFs, monitoring reports
6. Source records – clinic charts, hospital records, x-rays, lab reports, subject’s diaries, referrals
7. Test article accountability records
8. The Lead Study Coordinator will organize all study-related files, arrange logistics and prepare for the audit according to the FDA Inspector’s request.
9. The PI along with designated department representative will function as the liaison/escort for the FDA Inspector and will facilitate all document requests or requests for personnel interviews with the Lead Study Coordinator.

**C. CONDUCTING THE INSPECTION**

1. The liaison (Designated department representative) and the PI will:
2. Greet the FDA Inspector(s) and verify identification credentials. The FDA will provide

the PI with the FDA 482 (Notice of Inspection). FDA regulations general 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 FDA does not provide the 482, notify the UF Office of General Counsel immediately.**

1. Provide a tour of the facility. The FDA Inspector may request a tour of the facility where the research took place. Staff will have been notified in advance and be prepared for the visit and possible questions.
2. Provide requested records. The liaison or designee 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.
3. Assist in ensuring that each question is answered by the person(s) most knowledgeable of the issue.
4. Accompany FDA Inspector(s) at all times when they are in the designated conference room reviewing documents. FDA inspectors should not be allowed to enter patient care areas or research staff workspace areas unescorted at any point during inspection.
5. Assist the FDA Inspector as needed.
6. Arrange for follow-up as required for any unanswered questions or outstanding document reports.

*Note: The publications ‘FDA Compliance Program Guidance Manual and Guidance for the FDA Staff’ and ‘FDA Compliance Program Bioresearch Monitoring Sponsors, CROs and Monitors’ provides a list of information that will be requested during every inspection. This reference is very helpful in preparing for the inspection. (See links in ‘A. Notification’ above).*

1. The designated liaison will:
2. 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 (if a team inspection), documents requested, date and time of request, date and time delivered.
3. Provide requested records and make photocopies for the FDA and clinical site. Any copies of CRFs or medical records requested by the FDA Inspectors will be made in duplicate for retention at the site.

* If the FDA does not require identifiers on the records, the research staff should redact the identifiers with black permanent marker.
* If the FDA requests that identifiers remain on the records, the HIPAA Privacy Rule at 45 CFR 164.512(b)(1)(iii) permits this.
* If the FDA inspector insists on taking photographs or other video or audio recordings, take and retain duplicates at the same time

1. Arrange any interviews requested by the FDA Inspector, and escort the FDA Inspector if they request to go to the pharmacy, IRB, etc…
2. 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
3. Document the name and title of all persons interviewed by the FDA, and the date (and time if possible) of the interview.
4. Expectations for the Conduct of Research Team during the Inspection:
5. Ensure that ALL members of the research team know that the FDA is in the facility
6. Inform other staff when you will be giving the Inspector a tour of the facility
7. Limit idle business conversation by ALL staff

**D. POST INSPECTION**

1. The PI or liaison should request an end of day discussion during each day of the inspection with the FDA Inspector to review any preliminary findings
2. The liaison will document any questions whose answer could not be provided, along with appropriate follow-up to obtain the requested information
3. DO NOT sign any affidavits provided to you by the inspector
4. If the inspector presents an affidavit for signature, politely decline to sign and tell the inspector that you must first consult with the University’s Office of the General Counsel
5. If the PI receives a Form FDA 483 (report of observations) after the audit, he/she should consult the UF Office of General Counsel on how to respond and provide the sponsor with the opportunity to assist in the response. A copy of the 483 must be forwarded to the UF Office of General Counsel
6. The PI or designee must send a copy of the Form FDA 483 to the Study Sponsor’s project manager, the IRB, and the UF Office of Clinical Research
7. The PI must arrange a meeting to discuss the finding with the UF Office of General Counsel, the IRB, and other offices as necessary or determined by the findings
8. The PI will prepare a written response with input from the UF Office of General Counsel, 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 by the FDA, typically within 15 days. The written response should:

* Address each observation and explain what steps have been implemented or will be implemented to remedy the observation, and prevent future occurrence of similar observations
* The response should be factual and the tone should be respectful, professional and cooperative

*Note: FDA sometimes will extend the deadline for response depending on the circumstances. Such a request should be made, if at all, as soon as possible. The PI should contact their Department Director to discuss reason for delay and the UF Office of General Counsel can assist in facilitating such a request.*

1. 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 483 response; alternatively, the UF Office of General Counsel can assist with a separate request. FDA typically will not respond to an EIR request until the matter is formally closed.

*Note: The PI or designee should not contact the FDA Inspector directly without first consulting with the IRB and the UF Office of General Counsel.*

**E. ON-GOING READINESS**

Note: While the average notice of inspection fall within a two-day to twenty-four-day timeframe, it may be more or less than this timeframe. The rule is to always be audit ready!

1. Research Study File Maintenance
2. Keep files organized at all times
3. Retain all correspondence from sponsor, CRO, monitors, study subjects, letters, faxes, e-mails, memos, and phone contacts
4. Retain all test article accountability records
5. Retain shipping receipts, screening and enrollment logs, dispensing logs
6. FDA Inspection Triggers (increase the chance of an FDA audit):
7. Studies with a high enrollment, where test article is pending
8. Studies with few or no adverse events
9. PIs who have received a FDA form 483 in the past
10. Studies where other sites have had problematic inspections
11. If any of the above triggers apply to your study, contact the IRB Quality Program once the study is closed to enrollment. Advanced preparation is recommended in case your study is selected for an inspection