THE UNIVERSITY OF IOWA

Institutional Review Board & Human Subjects Office

Food and Drug Administration (FDA) Site Inspection Guide

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The Human Subjects Office created this document to assist Principal Investigators (PI) and research staff throughout the course of a Food and Drug Administration (FDA) inspection.

I. Upon notification that a FDA inspection will occur

a. Complete the Initial Intake Form (see Appendix 1 on pages 11-12) and collect the specific documents requested in the Form.
   1. Ensure all requested documents are available for inspection when the inspector arrives.
   2. Do not volunteer additional information or documentation.
   3. If some of the documents are not immediately available (i.e., offsite storage), obtain them as soon as possible, preferably at least 2-3 days before the scheduled inspection.
   4. Maintain an itemized list with the status of any missing documents.

b. Review guidance documents on the FDA website, including the:
   1. FDA Compliance Program Guidance Manual and Guidance for the FDA Staff
   2. FDA Inspections of Clinical Investigators: Information Sheet Guidance
   3. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance
   4. Electronic Source Data in Clinical Investigations

c. Reserve a meeting room(s) for the duration of the inspection – keeping in mind the following recommendations.
   1. The room should have a phone, and allow convenient access to study staff.
   2. The room should be located away from the clinical/research area to avoid such activities from being conducted near the inspector.
   3. The room should **NOT** contain any other study or medical records, other than the study records that the inspector has requested.

4. The room should be able to be locked when the inspector leaves.
5. The requested staff should be readily available to the inspector at all times. (The inspector generally will not want the study staff coordinating the investigation in the room while s/he works.)

II. Prior to the FDA inspection

a. Immediately notify the following individuals of the upcoming inspection:
   1. Study team members – PI, sub-investigators, study coordinators, data managers, Department Chair or head, and directors of clinics or centers
   2. Study Sponsor or Contact Research Organization (CRO). If your sponsor is an Industry Sponsor, they may send representatives to assist you in preparing for the inspection. Notify the FDA inspector if the sponsor representative requests to be present during the inspection. If the FDA inspector approves the request, explain that the sponsor may observe and take notes but s/he is not to communicate with the inspector unless asked specific question(s).
   3. Institutional Review Board (IRB) - E-mail the Human Subjects Office at irb-monitors@uiowa.edu.
      a) Attach to that e-mail a copy of your completed Initial Intake Form (see Appendix 1 on pages 11-12)
      b) The HSO will contact the Office of the General Counsel on the Principal Investigator's behalf (if, for example, the inspection is for cause, or if it is a follow-up inspection and you worked with the Office during the initial inspection)

      *****IRB Compliance Staff are required to attend the Opening and Exit Interviews.*****
   4. UI Privacy Officer - E-mail deborah-thoman@uiowa.edu or call the UIHC Compliance Office at 384-5897.
   5. Pharmacy - Mike Brownlee - Email michael-brownlee@uiowa.edu or call Pharmacy Administration at 356-2577.
   6. Medical Records - Contact your Human Resources (HR) representative (or your 'trusted requestor' for research). S/he will contact Health Care Information Systems (HCIS) - Identity Management to arrange access to the electronic medical record (EMR).

   In addition, as appropriate, notify other groups or entities who may be involved, including but not limited to:
   7. Investigational Drug Service (IDS).
   8. Ancillary departments – labs, radiology (if the inspector requests to tour these areas).

b. The PI should review his/her investigator responsibilities, including:
   1. The FDA Form 1572 or 'Statement of Investigator' that s/he signed at the beginning of the study.
   2. Study team contact list for the purpose of:
      a) Reviewing roles and responsibilities.

b) Ensuring appropriate delegation of study related tasks.

3. List of current active protocols.

c. Time-permitting, the PI and members of the study team should review the following:
    1. Current IRB-approved version of the protocol.
    2. Current IRB-approved Informed Consent Document(s).
    3. Current Investigator Brochure.
    4. Sponsored Agreement
    5. Correspondence and documentation with sponsor/IRB.
    6. Tracking methods for optional agreements (if applicable).
    7. Test article accountability records, including:
        a) Shipping receipts and accountability logs.
        b) Return to sponsor.
    8. Study Logs.
        a) Screening/enrollment, inclusion/exclusion, specimen tracking
        b) Monitoring activities
    9. Study reports – timeliness of Adverse Event (AE) reporting, sequence of reports, additional treatments.

d. Review each individual subject's study records, eligibility criteria, and signed Informed Consent Documents (ICDs).
    1. If the signed ICDs are kept in individual subject binders, remove them and compile them into a single binder for all enrolled subjects.

e. Identify and locate the following records that the FDA is most likely to inspect, including:
    1. Regulatory documents
        a) Delegation of Authority logs
        b) All IRB-approved versions of the protocol and Investigator Brochures
        c) All IRB-approved versions of Informed Consent Documents
        d) All IRB correspondence (e.g., approvals, continuing reviews, current consent documents, enrollment/screening logs, etc.)
        e) Regulatory agency correspondence – both to/from agencies
            i. Annual report(s)
            ii. FDA Forms 1572 and FDA 1571
    2. Subject Related Documents
        a) Case Report Forms (print copies of any electronic case report forms)
        b) All supporting source documents
            i. Clinical or hospital records (related to the subject's diagnosis/condition, records to support subject eligibility, etc.)
            ii. Laboratory, radiology reports, EKGs, etc.
            iii. Device/Drug Accountability Records
            iv. Adverse Event Logs and Serious Adverse Event Reports
            v. Subject diaries
            vi. Documentation of protocol deviations (missed procedures, missed visits, etc.)

c) The inspector often reviews the first and last subjects' records and then randomly selects other records to review.

f. Review all of the identified records to:
   1. Identify any weaknesses or gaps (i.e., source documents not included in the research record, incomplete or out of date delegation log, etc.).
      a) Pay close attention to protocol variances, as these could be explained through the use of a Note to File (NTF).
      b) Assure that the PI has signed all NTF's, and retrospectively add them (with current date) if they are missing.
   2. Correct items that can be corrected using appropriate correction methods.
      a) Line through date to be corrected/changed, initial and date (with the current date) any changes or corrections.
      b) Retain originals and never use white-out.
   3. Identify any items noted during prior inspections or monitoring visits and ensure that those items have been appropriately addressed.
   4. Develop and implement a written corrective and preventive action (CAPA) plan with appropriate approvals (IRB, FDA, or sponsor) to address identified problems.

g. Designate a person to oversee the inspection.
   1. This person, usually the research coordinator, should be knowledgeable about the study activities and records.
   2. This individual should also be able to coordinate with the study PI and other study personnel both prior to and during the course of the inspection.

III. During the FDA Inspection

a. Basic guidelines
   1. Ensure that ALL members of the research team know that the FDA is in the facility. Inform other staff when you will be giving the inspector a tour of the facility.

      ****Limit idle business conversation by ALL staff.****

   2. During the inspection, the staff coordinating the inspection should oversee all inspector requests and take notes that will be written up at the conclusion of the inspection.
   3. Investigators are required to permit the FDA to inspect and copy any records pertaining to the investigation, including Protected Health Information (PHI).
      a. The UI prefers that research team members make the copies
      b. If the FDA does not require identifiers on the records, the research staff should redact the identifiers with black permanent marker
      c. If the FDA requests that identifiers remain on the records, the HIPAA Privacy Rule at 45 CFR 164.512(b)(1)(iii) permits this.
   4. If the FDA inspector insists on taking photographs or other video or audio recordings, take and retain duplicates at the same time.

5. If the FDA inspector requests to take samples, ask for a receipt for the samples, and pull and retain identical samples at the same time.

b. Procedural steps
    1. Inspector arrival
        a) When the inspector arrives, s/he should check in at a specified location.
        b) Escort the inspector to the appropriate meeting room. The PI should be available when the inspector arrives or shortly thereafter.
        c) The inspector may ask for a tour of the facility.

        ****The designated escort should stay with the inspector at all times.****

    2. Opening Meeting
        a) The inspector should present his/her credentials to the PI to verify that they are in order.
            i. Ask the inspector to see his/her credentials if s/he does not present them.
            ii. Document all information from the inspector's identification as no copies of the identification badges can be made.
        b) The inspector will present a Notice of Inspection (Form FDA 482) to the PI authorizing the inspection.
            i. This presentation officially begins the inspection.
            ii. The inspector will explain the intended purpose and scope of the inspection. **If the team does not ask for the inspector's credentials and/or the Form 482, the inspector may note this as a deficiency in his/her report.**
        c) The inspector will ask the PI to summarize and discuss the study identified for inspection and his/her responsibilities with respect to the study.
            i. The inspector may ask the PI for the list of his/her studies.
    3. Document inspection
        a) Standard procedure is for the inspector to request files for review, starting with the "general" study materials including:
            i. Regulatory documents binders.
            ii. Signed informed consent forms.
            iii. Sampling of specific patient records.
            iv. 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.

    4. Document photocopying
        a) ****Provide only documents specifically requested by the inspector****
        b) Keep a "shadow binder" with a copy of every record/document that is provided to the inspector during the inspection.
        c) When making copies for inspectors:

i. Remove subject identifiers from the copies given to the inspector, unless the FDA requests that identifiers remain (see III.a.3.c above)
ii. Mark/stamp the copies that are given to the inspector "Confidential".
iii. Mark/stamp the copies that are for the site's FDA inspection file (shadow binder) "Copy".
iv. Patient records may need to be obtained from the hospital or clinic to supplement or corroborate the research records.

d) Copies are provided without charge to the FDA.
e) Except for training/qualification records, the FDA inspectors ordinarily will not request to see personnel records, financial records, and records of internal inspections (Section 704(a) FDC Act).

5. Principal Investigator availability during the inspection
   a) The PI should plan on being available each day to talk with the inspector, either in person or by phone, in order to answer any questions that may arise.
   b) These arrangements are usually discussed during the opening meeting.

6. Study staff response to inspector's questions
   a) During the inspection, the person coordinating the inspection should keep an exhibit log that includes a list of ALL questions asked by the inspector.
   b) The inspector will ask the PI, study coordinator and members of the study team questions in order to:
      i. Assess consistency and accuracy in response.
      ii. Compare knowledge and practice of study procedures.
      iii. Assess for PI oversight, involvement, and knowledge of day-to-day, routine activities.
      iv. For questions frequently asked by the FDA inspectors, see Appendix 2 on pages 13-14.
   c) The inspector may ask to review the research team's standard operating procedures (SOPs) or documentation of team training. If applicable:
      i. Provide documentation of research team's meeting minutes.
      ii. Provide copies of power point presentations/other training or certificates that are available.
   d) Answer questions with the following tips in mind:
      i. Listen to the question carefully. If you do not understand the question, ask the inspector to explain. Do not attempt to interpret the meaning of unclear questions being asked.
      ii. Be truthful – answer the question that was asked in an honest manner.
      iii. Be concise –use "yes" or "no" when sufficient, and stop when the question is fully answered and wait for the next question.
      iv. Answer only the question that is asked.

v. DO NOT speculate or guess – if you do not know the answer to a question, do not be afraid to tell the inspector you don't know. If a question is outside your area of responsibility, say so and write down the question and refer it to the correct person.
vi. Do not bring documents to an interview unless requested to do so.
vii. **DO NOT argue.**

7. Signatures on Affidavits
    a) **DO NOT** sign any affidavits provided to you by the inspector.
    b) 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.

8. Exit Interview
    a) Prior to the exit interview, study staff should notify the Privacy Officer and Pharmacy Administrator in case these individuals want to attend the visit.
    b) The inspector will usually hold a "close-out" visit at the conclusion of the inspection.
    c) The inspector will discuss findings and notify the PI if deficiencies were found. This is an opportunity for the PI to provide information and clarify any questions or concerns raised during the inspection.
    d) If serious deficiencies have been found during the inspection, a written Inspectional Observations (Form FDA 483) will be issued, which lists the deficiencies.
    e) If no deficiencies are found, or the inspector has comments that s/he believes are not serious enough to warrant a Form FDA 483, no form will be issued.
    f) Study staff should:
        i. Document the interview, specifically noting observations, comments, and any commitments discussed.
        ii. Seek to correct any errors in the findings.
        iii. Email the IRB Compliance Specialist a copy of the Exit Interview summary at irb-monitors@uiowa.edu.

IV. Post FDA inspection

a. Inspection Summary Report
    1. Immediately after the visit, a detailed report summarizing the inspection should be written (by the PI or the person designated to coordinate the inspection) based on the inspection notes. The report should be kept with essential study documents and include:
        a) A summary of questions and discussions between inspector and each employee.
        b) List of all studies or facilities/departments viewed.
        c) List of all records reviewed.
        d) Copies of all documents duplicated for the inspector.

e) Note of all samples taken, and receipt for samples.
f) Note of all commitments made (include completion dates if set with FDA).
g) Comments of inspector related to inspection.

b. Response to FDA report
   1. Upon receipt of a report from the FDA, the PI/research team should email an electronic version of this document to the Compliance and Education Specialist. The following steps describe how to proceed whether the findings are significant (Form 483) or non-significant.
   2. If the outcome of the report is significant and results in the receipt of a Form FDA 483, the appropriate individual(s) shall draft a response. See Section IV(c)(1) below for examples of when the University's HSO/IRB and/or Office of the General Counsel may assist the PI in drafting a response.
   3. The PI is responsible for the response content and for sending the written response within 15 working days.
      a) If you are unaccustomed to responding to a Form 483, having someone with prior experience provide assistance is beneficial, so either consult with your administrator and/or,
      b) Consult with Privacy Officer if the response involves PHI
      c) Consult with Pharmacy Administrator if the response is related to study drugs
   4. The written response should:
      a) Address each particular observation or finding, point by point.
      b) Determine if a finding was an oversight/one-time occurrence or systemic, where a change of procedure is indicated.
      c) If the PI disagrees with an observation, respond factually and provide clear and verifiable evidence.
      d) Delineate corrective and preventive action (CAPA): include justification of why the proposed response will remediate the issue and a realistic timeline for implementation.
      e) Keep a copy of the final signed response in your records along with all attachments.

c. Reporting to the IRB of Record
   1. If the UI is the IRB of record, and:
      a) If the outcome of the report is significant and impacts the current status of the study, the PI should submit a HawkIRB modification to address the finding(s), at the time the '483' is received. If necessary, the IRB will confer with the University's Office of the General Counsel and seek assistance in formulating the written response to the FDA.
      Significant findings could include items such as the following:
         i. PI did not conduct the research study according to the investigational plan (i.e., protocol and HawkIRB application).
         ii. PI failed to maintain adequate case histories with respect to observations and data pertinent to the investigation.

iii. PI failed to obtain informed consent or maintain all pages of the signed Informed Consent Documents for each enrolled subject.
iv. PI failed to report to the sponsor, per reporting guidelines, adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug.

b) If the outcome of the report is non-significant and does not impact the current status of the study, the PI should report in the next Continuing Review that s/he has been monitored by responding 'Yes' to Section CRIII.12 and attach the FDA Inspection Report in the Continuing Review Attachment section.

2. If UI is not the IRB of record, and:
   a) If the outcome of the report is significant and impacts the current status of the study, the Education and Compliance Specialist will:
      i. Document the outcome information in the FDA Inspection Report
      ii. Present the report findings to the HSO Director (in case the findings warrant additional guidance from the Institutional Official and/or General Counsel).
      iii. Notify the external IRB of Record of the FDA inspection.

   b) If the outcome is non-significant and does not impact the current status of the study, the Education and Compliance Specialist will:
      i. Document the outcome information in the FDA Inspection Report
      ii. Remind the research team that they must adhere to the reporting policies and procedures as outlined in the reliance agreement with the external IRB.
      iii. Notify the external IRB of the FDA inspection.

d. Sponsor Notification
   1. The PI should notify the sponsor of the issuance of a Form FDA 483 and provide the sponsor with a copy of the PI's formal written response to the FDA; moreover, the PI should review his/her other clinical trial agreements and grant documents for any requirements regarding notification to other sponsors whenever inspection of an unrelated study results in issuance of a Form FDA 483.

e. Inspector's EIR (Establishment Inspection Report)
   1. 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 483, Warning Letter, or other actions arising from the inspection.

f. Additional Action

1. The FDA considers all information provided in response to the Form 483 and then determines what further action, if any, is appropriate to protect public health.

FDA Warning Letters summarize inspections of clinical investigators and these are posted on the FDA website.

University of Iowa Human Subjects Office and Institutional Review Board FDA Site Inspection Guide		
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Approved by: HSO Director	Michele Countryman	
Approved by: IRB Primary Chair	J.A. Bertolatus	
Approved by: Institutional Official	Heather Gipson	
Annual review		

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Appendix 1

Initial Intake Form

Take good notes during all communication and interaction with the inspector.

Initial Contact Information
Staff member who received FDA communication:
Contact/Notification Date:
Anticipated Start Date:
Expected Duration:

Inspector Contact Information
Name:
Title:
Telephone:
E-mail:
Additional inspector names:

Purpose of Inspection – Who and what are being inspected?
Wait for specific answers. Do not make suggestions.
☐ Clinical trial(s)/study:
☐ Principal Investigator:
☐ Co-Investigator(s):
☐ Routine (i.e. IND)
☐ Directed (for cause)

☐ Follow-up (i.e. 483; warning letter)
☐ Other
Additional Details:
Has the FDA requested that specific personnel be available? ☐ Yes ☐ No

Name	Date

Has the FDA requested that specific documents be available? (List on separate sheet if needed)

Request that the inspector provide in writing the exact documents that s/he wishes to review. S/he may not provide this, but you can request it.

Appendix 2

Questions Frequently Asked during FDA Inspections

Overview of the study

1. Provide an overview of the study including background, objectives, study design, duration of the study, subject population, and number of subjects enrolled.
2. What responsibilities are delegated to other members of study team?
3. How are potential subjects identified?
4. Who screens and recruits subjects?
5. Were all methods and materials used for recruitment IRB approved?
6. Who verifies inclusion and exclusion criteria?
7. Who obtains consent/assent?
8. Was written documentation of consent required?
9. Is the informed consent process documented in the medical record?
10. Was assent required? (Include age of assent)
11. Were there any research participants who were wards of the state?
12. How are screening/enrollment logs used and maintained during the conduct of the study?
13. Where were study procedures conducted? (e.g., inpatient or outpatient)
14. What are the study start and/or completion dates?
15. How do you communicate protocol or study design changes to study staff, pharmacy, and/or ancillary department staff?
16. How do you obtain, record, secure, and retain data?
17. What do you use as source documentation (study specific source documents, separate research chart, shadow chart, CRFs, lab data, imaging or diagnostic data)?
18. Do you use electronic records?
    a. How are records validated?
    b. Do you use electronic signatures?
    c. What are the data security/controls?
    d. Is there an inspection trail?
19. Was data transferred or transmitted outside the institution?
20. What is your record retention policy?
21. Were there any protocol deviations or exemptions?
22. Who is responsible for receipt, distribution, administration and accountability of test articles?
23. Who are the investigational pharmacists?
24. How is the test article stored?
25. Describe procedures for destruction and/or return of the test article.
26. Where and how are specimens stored?
27. Describe your procedure for maintaining and documenting storage of specimens.

Questions Frequently Asked during FDA Inspections continued

28. Describe maintenance of temperature logs and how you deal with temperature excursions, including:
    a. Frequency of temperature monitoring (manual check or electronic monitoring)
    b. Frequency of quality control checks
29. Was the study routinely monitored?
    a. Documentation of monitoring communications and evaluations
    b. Frequency of monitoring
    c. Was the study team satisfied with overall monitoring of the study?
30. Did study team receive study-specific training?
    a. Documentation of training
    b. Study team training, pharmacy
31. Did any unanticipated problems occur (AEs, SAEs or deaths)?
    a. Were events reported to the IRB, Sponsor, IRB, regulatory agency in a timely manner?
    b. Were the event related to the test article?
    c. Did the subject require any intervention/treatment as the result of the event?
    d. What was the intervention/treatment?
32. Are there any study specific standard operating procedures (SOPs) for this study?
33. Is the study registered with Clinicaltrials.gov or equivalent registry?