

Surviving an Audit of Your Clinical Trial

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Why is My Study Being Audited?

- ◆ The purpose of an audit is to determine that a clinical trial has been performed in compliance with:
 - 📄 The protocol and supporting documents
 - 📄 FDA and/or other government regulations
 - Informed Consent
 - Institutional Review Board
 - Responsibilities of Investigators

Who Performs Audits?

- ◆ Sponsors of clinical trials
- ◆ Regulatory agencies, e.g., Food and Drug Administration (FDA)
 - 📄 Audits by FDA are typically referred to as inspections.
- ◆ Today's presentation will primarily focus on surviving an audit (inspection) by FDA

Monitoring vs. Auditing

- ◆ Sponsors of human studies of products regulated by FDA are required to **monitor** ongoing studies.
 - 📄 Check data against source documents and guide completion/correction of CRFs
 - 📄 Inspect/reconcile drug supplies
 - 📄 Determine that all required documents are present and obtain them for the site if needed
- ◆ Monitors are required to be qualified
- ◆ Monitors involved in study initiation, during the study and at close-out.

Monitoring vs. Auditing

- ◆ Audits are typically performed after the study is completed.
- ◆ May be done during the study
 - 📄 if monitoring reveals a compliance problem.
 - 📄 If monitor requires additional training
 - 📄 If an inspection by the regulatory agency is scheduled.
- ◆ Auditors
 - 📄 Check data against source documents
 - 📄 Review drug accountability
 - 📄 Determine if all required documents are present

Monitoring vs. Auditing

- ◆ Monitoring is generally a reasonably cooperative activity with site personnel
- ◆ Auditing typically more regulatory in nature – review and evaluate, then report status
- ◆ Auditing done to ensure compliance with protocol and regulations, often prior to submission to FDA or to prepare site for FDA inspection

What May FDA Inspect?

- ◆ Any Product or Activity that is Required to Meet Specific FDA Regulations
 - 📄 Manufacturing facilities
 - 📄 Nonclinical toxicology studies
 - 📄 **Clinical trials and clinical records**
 - 📄 Adverse event reporting
 - 📄 Monitoring of patient &/or physician compliance with restricted distribution
 - 📄 etc.

Who Does FDA Inspections?

- ◆ **Inspectors from FDA District Office**
 - 📄 Local District Office in in Stoneham, MA
- ◆ **Inspectors from Office of Bioresearch Monitoring Program - located at FDA headquarters**
 - 📄 Perform GLP and GCP inspections
- ◆ **Reviewers of clinical trial or marketing application at FDA**
 - 📄 More likely with biologic products
- ◆ **FDA Specialists**
 - 📄 e.g., Computer validation or sterile products experts

How Do FDA Inspections Start?

- ◆ **FDA Inspections May Be Scheduled or Unscheduled**
 - 📄 Unscheduled typically occur because the inspection is “for cause” -- FDA believes there is a failure to meet regulatory requirements, and illegal activity may be occurring.
- ◆ **FDA Inspector May Arrive During or Outside of Normal Working Hours**
 - 📄 If outside of normal working hours, you can request that inspector return during normal working hours
 - 📄 inspector does **not** have to comply with this request.

What To Do Before The FDA Inspector Arrives

- ◆ **Identify individual who will serve as the “primary contact” with FDA**
 - 📄 This person will be spending all day, every day with the FDA inspector(s) while they are at your facility
- ◆ **Make sure your staff is well-versed in:**
 - 📄 All study protocols for products regulated by FDA
 - 📄 All FDA regulations governing how clinical trials are to be performed.
 - 📄 All standard operating procedures, policies, etc. of your facility and institution.
- ◆ **Make sure your staff is following all of the above!**

What To Do Before The FDA Inspector Arrives

- ◆ If you know which studies FDA will be inspecting:
 - 📄 Notify the sponsor of the studies so they can help you to prepare for the inspection
 - 📄 Make certain all study files, documentation are available
 - 📄 Review files/documentation
 - 📄 If a deviation occurred or files are incomplete, be prepared to explain why. Perhaps write a “note to file”
 - 📄 Make files organized and neat, easy to find documents

What To Do When The FDA Inspector Arrives

- ◆ **Notify Your Primary Contact for FDA Inspections**
- ◆ **Primary Contact Reviews Inspector's Credentials**
 - 📄 **Badge, Individual's Identification, Notice of Inspection (Form FDA 482)**
- ◆ **Notify All Site/Area Personnel that FDA is in the Building**
- ◆ **Escort Inspector to a Conference Room**
 - 📄 **Keep him/her there at least until others who will be involved in the inspection are assembled.**

What to Do When the FDA Inspector Arrives (continued)

- ◆ **Ask Inspector for Scope of Inspection**
- ◆ **Assemble your Audit Team**
 - 📄 **Principal Investigator**
 - 📄 **Study Coordinator**
 - 📄 **Pharmacist**
 - 📄 **Other Study Personnel**
 - 📄 **Person to take detailed notes**
- ◆ **Accompany Inspector During Inspection**
 - 📄 **Do not ever leave the inspector alone**
 - 📄 **Accompany him/her everywhere**

Handling the Inspection

- ◆ **Ask Inspector to Direct All Questions to the Primary Contact**
 - 📄 **Primary Contact Determines Who Should Answer Each Question**
- ◆ **Be Polite, Honest and Direct in Your Answers**
- ◆ **Do Not Be Evasive**
- ◆ **Provide Only Requested Information**
- ◆ **Do Not Give Incorrect Information**
- ◆ **If You Don't Know the Answer, Say So, Then Get the Answer and Provide it to the Primary Contact**

Handling the Inspection (continued)

- ◆ Minimize Background Conversations in the Inspection Area and in the Building
- ◆ **Follow** your SOPs/Policies
- ◆ Some Typical Policies
 - 📄 Do not sign affidavits -- it is NOT required by law.
 - 📄 Do not allow the use of cameras or audio/video recording equipment - No photographs, tape recording
 - 📄 Employees are not required to respond to questions outside of the workplace.
 - 📄 Samples are not given to FDA without the owner's permission (e.g., if inspection is at a contract manufacturing facility)

Handling the Inspection (continued)

◆ Photographs

- 📄 BU and/or your office may have a policy that does not allow photographs to be taken during inspections.
- 📄 However, the courts have allowed photos to be taken.
- 📄 If FDA insists on taking photos:
 - Get film developed for FDA and have two sets of prints made, so you have an exact copy
 - OR
 - Take a duplicate photo, at the same time and location as FDA's photograph.

Handling the Inspection (continued)

- ◆ What is the FDA Inspector Authorized to Inspect?
 - 📄 Standard Operating Procedures
 - 📄 Records of the Clinical Study, Adverse Events, etc.
 - 📄 Training Records and other Personnel Information Related to Job Qualifications
 - 📄 Drug Product used in a clinical trial of an FDA-regulated Product.
 - 📄 Procedures Underway with Patients that are Relevant to a Regulated Product Covered in this Inspection.
 - 📄 Submissions to FDA, if any
 - 📄 Submissions to your IRB
 - 📄 Adverse events, other data submitted to the sponsor

Handling the Inspection (continued)

- ◆ What is the FDA Inspector **NOT** Authorized to Inspect?
 - 📄 Financial Records (except those related to Financial Disclosure for Investigators who are participating in or have participated in an FDA-regulated clinical trial)
 - 📄 Other personnel information, e.g., salary information
 - 📄 Information on business activities not regulated by FDA
 - 📄 Quality Assurance or sponsor audit reports

Handling the Inspection (continued)

- ◆ **Provide Documentation as Requested by Inspector**
 - 📄 If request is broad, ask for clarification so you know exactly what documentation to provide.
 - 📄 Review each piece of documentation before providing it to the Inspector.
 - 📄 Record documents reviewed by the Inspector.

Handling the Inspection (continued)

- ◆ If the Inspector Requests Copies of Documentation to Take Off-Site
 - 📄 Review documentation prior to making copies
 - 📄 Make an exact copy for your files
 - 📄 Mark each page of each copy “Confidential.”
 - 📄 Number, initial and date the back of each copied page provided (as well as your own exact copy).

Handling the Inspection (continued)

- ◆ **At the End of Each Inspection Day, the Inspector May Have an End-of-Day Briefing**
 - 📄 If so, assemble relevant staff and principal investigator for each briefing.
- ◆ **After the Inspector Leaves Each Day**
 - 📄 Relevant staff and investigator meet to discuss status of inspection, correction of observations that can be corrected immediately, items anticipated for discussion on following days, etc.

Handling the Inspection (continued)

- ◆ **At the End of the Inspection, the Inspector Will Hold an Exit Interview**
 - 📄 All relevant site personnel and the principal investigator should attend.
- ◆ **The Inspector will Review Observations**
 - 📄 If you are unclear on an observation, request clarification.
 - 📄 Note that comments made by site study staff are not confidential and may be included in the Establishment Inspection Report (EIR), which becomes a public document

Handling the Inspection (continued)

- ◆ If the Inspector Has Observations and Issues a Form FDA 483
 - 📄 Work with your study sponsor to determine how to address these observations, and provide a written response to FDA
 - 📄 This response should be submitted to FDA within 20 working days if possible
- ◆ Changes to be made in order to respond to these observations must be implemented as soon as reasonably possible, and within the timeframes established in the response to the FDA 483

Inspection Files

◆ Maintain a File for each Inspection

- 📄 Form FDA 482, Notice of Inspection
- 📄 Duplicates of copies provided to Inspector to take off-site
- 📄 Form FDA 484, Receipt for Sample
- 📄 Form FDA 483, Inspectional Findings
- 📄 Your own report of the inspection
- 📄 Internal notes on the inspection
- 📄 FDA Establishment Inspection Report (EIR)
- 📄 Response to Form FDA 483
- 📄 Subsequent documentation, e.g. Warning Letter and your response.

FDA Enforcement Actions

- ◆ What Can FDA Do If a Regulated Individual/Company/Facility Does Not Comply with FDA Regulations?
 - 📄 Issue Form FDA 483
 - 📄 Issue Warning Letter
 - 📄 Refuse to consider your data when reviewing the marketing application for this product
 - 📄 Debar an individual from working on FDA-regulated products.
 - 📄 Suspend product approval (remove product from the market)
 - 📄 Impose civil money penalties = Fines
 - 📄 Initiate criminal prosecution
 - 📄 Etc.

Conclusions

♦ Audits/inspections are:

- 📄 Necessary to determine that studies meet regulatory requirements
- 📄 Useful in helping clinical sites to improve
- 📄 Nerve-wracking – although with preparation, they don't need to be!