Audits and Inspections

Module 7 Topic 5

Why are Inspections Done?

- Protect the rights and welfare of human subjects
- Assure quality and integrity of data
- Ensure compliance with regulatory requirements

When are Inspections Done?

- Clinical Investigator inspections are performed:
  - For most clinical trials that support primary claims of efficacy and safety.
  - For trials supporting important efficacy supplements
  - Studies of any phase if there is data integrity concerns
  - Phase IV studies

Who is inspected?

- Investigator sites are selected for inspection based on multiple factors:
  - Importance of study
  - Statistical importance of the data
  - History of the Clinical Investigator
- Importance- to labeling and size of number of outliers
- History, including previous inspections and findings

How to Prepare for a Successful Inspection

- Accommodate the Inspector. Requests for an inspection are usually less than 2 weeks
- You should speak directly with the FDA Inspector whenever possible to arrange the inspection date.
- Inspectors must report “undue delay” in scheduling which is usually more than 10 days without sufficient justification.
- This is your first opportunity to develop a positive relationship with the Inspector.

Prepare for a Successful Inspection

- Ask the inspector about the nature and scope of the visit
- How many inspectors are coming and how long they planning to be on site
- Could they provide you with a list of subjects they would like to review
- Identify the time they will arrive and set that time for the introductory meeting

Prepare for a Successful Inspection

- Notify your sponsor of the inspection
- Ask in a manner that suggests you are only trying to prepare so their visit will go smoothly
- This helps you to provide the medical records in a timely manner
- They will probably provide assistance in preparation

Prepare for a Successful Inspection

- Approach the Inspection as an opportunity to learn
- Identify Roles during the Inspection
- List staff names and positions
- Assign one person responsible for making copies for the inspector
- Arrange for adequate work space for the inspector

Prepare for a Successful Inspection (Contd)

- Away for busy areas
- Empty of any records
- Comfortable
- Including contact information. Invite them to the planning meeting
- Maintain a log of all copied materials. Make one copy for the inspector, one for the site and the sponsor may request a copy

Prepare for a Successful Inspection

- Anticipate needing:
  - List of all studies performed by the investigator
  - List of all 1572s
  - List of all labs used, certificates, and normals
  - Copies of all protocols, IRB approvals, approval of changes, consents
  - List of all staff, signature list, delegation list
  - IRB name, address, chairperson
  - Monitoring log, telephone contact records
  - Information and contacts for electronic record system

Most of this information is located in the Regulatory Binder/files. All items should be easy to locate and filed chronologically

Prepare for a Successful Inspection

- All Study staff should be prepared to be interviewed
- Principle Investigator should anticipate being asked to:
  - Describe orientation/training on test article, protocol, Investigator obligations
  - Describe delegation of authority and how you retain control and knowledge of the study
  - Describe on-going communications with sponsor
  - Who does subject consenting and how
  - Who dispenses test article

During the Inspection

- The Inspector should present their official credentials and a form 482 Notice of Inspection
- Meet with the Inspector and set an agenda for the visit. Allow time at the end of each day to meet with Inspector to answer questions, or provide clarification. This can help avoid additional exploration or misunderstanding by the Inspector. If the Inspector identifies a problem/issue that you have addressed through process improvement let the Inspector know

During the Inspection

- A staff member should be available to the Inspector to request additional record or copies at all times. Show the Inspector where comfort facilities are located. It is OK to offer snacks to the Inspector that are available for all staff
- The Inspector is required to notify the District Office of any refusal to provide or copy requested records. They do not generally ask for contractual or Quality Assurance records. Review you institutional policies on this matter before the inspection

What Will the Inspector Look For?

- General condition of source documentation

ALCOA- Attributable, Legible, Contemporaneous, Original, Accurate

Adequate documentation that all subjects existed

Compare Source, CRFs and data listings (AE/SAEs)

Subjects meet inclusion criteria

Subject baseline condition and condition throughout trial

Identity of all persons obtaining data

What Will the Inspector Look For?

- Number of subjects screened, entered, dropped. Date of first and last entry
- Review of consent obtained for all subjects (correct, approved versions)
- IRB records, reports, and actions maintained. IRB approval received prior to enrolling subjects.
- All deaths, SAEs and safety reports reported to the IRB
- Did the Investigator provide or report to sponsor all required items

What Will the Inspector Look For?

- Did the sponsor adequately monitor the trial
- Test article accountability procedures: receipt, dispensing, Lot #/ID, correct dose calculations, correct administration, appropriate disposition
- Adverse findings in any area are likely to increase overall intensity of inspection. Well organized, easy to review records send a strong, positive message

General Inspection Instructions for All Staff

- Always answer truthfully
- Do not answer a question until you have heard and understood the whole question. If you do not fully understand what the Inspector wants, ask “Would you please restate the question”
- Answer only the question asked
- Answer questions with yes or no whenever possible
- Do not answer questions outside your area of responsibility
- Do not volunteer additional information

General Inspection Instructions for All Staff

- If you do not know the answer to a question, state that you do not know the answer, do not speculate
- Speak clearly, slowly and at a reasonable volume
- Beware of pauses
- Beware of being asked the same question twice

General Inspection Instructions for All Staff (Contd)

- Do not bring documents in to the inspection area that have not been requested
- Dress professionally
- Do not feel that you need to keep talking
- This is done to see if you will answer the same way- don't assume that it is because you did not answer correctly or fully

What Will the Inspector Find?

- Common Clinical Investigator Deficiencies*

  54% failure to follow investigational plan

  16% protocol deviations

  24% issues with Informed Consent documentation

  14% inadequate device/drug accountability

  13% lack of FDA &/or IRB approval

*2004 numbers

What Will the Inspector Find?

- Common Sponsor Deficiencies*
  - **40%** inadequate monitoring
  - **21%** failure to secure investigator compliance
  - **16%** inadequate device accountability
  - **11%** failure to obtain FDA/IRB approval

*2015 numbers

The Final Hour

- At the inspection close out meeting the Inspector will review their general findings with you. If there are no regulatory deficiencies, that will be the end of the inspection. You should receive a letter from the FDA documenting the inspection some time later
- If the Inspector has identified regulatory deficiencies you will receive a 483 Inspectional Observations form outlining the deficiencies

The Final Hour

- If you are presented a 483, review the items with the Inspector. If the deficiency identified has already had a corrective action put in place tell the Inspector. If there was a misunderstanding, provide the information necessary to clarify. Accept the findings with grace and let the Inspector know you will carefully review the findings and forward your response. Thank the Inspector for their time and commitment

483 Response

- You are not required to respond to a 483. The FDA will review all of the information gathered by the Inspector and reserves the opportunity to expand or contract the items listed. You will receive a letter from the FDA outlining the findings and a request to respond
- It is recommended to respond to the 483 prior to receiving a letter. This is especially important if there are items that you can successfully clarify with documentation, or if the 483 is 'significant'

Responding to the 483

- The response should be from the Investigator
- Explain and provide documentation if there were any mistakes or misunderstandings by the Inspector
- For everything else Accept Responsibility

Responding to the 483

- Evaluate the errors and identify what happened to cause the deficiency
- Tell the FDA what you have done/will do to ensure it will not happen again
- Request that your redacted response be included with any release of you 483 through the FOIA

Responding to the 483

- If your response is completed in a timely manner it will be included in the review of the inspectional materials. Usually you will receive a letter outlining the 483 items and noting your response.
- If your response is not acceptable or the findings are serious additional actions may take place.
- Request for additional corrective/improvement plans
- You may have additional inspections
- You may receive a warning letter with additional actions required
- Most serious cases receive NIDPOE or NOOH letters

Responding to the 483

- Notification Of Initiation of Disqualification Proceedings and Opportunity to Explain
- Notification of Opportunity for Hearing.


LOOKS LIKE THE AUDIT UPSTAIRS ISN'T GOING TOO WELL!
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