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How to Survive an FDA Inspection

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How to Survive an FDA Inspection

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How to Survive an FDA Inspection




- Background
- Constant readiness
- The phone call
- The inspection
- The follow-up



Background - FDA Inspection Process



- Inspections are Issued by FDA Centers (CDER, CBER, CDRH, and CVM)
- Two types of Inspections:
 - Routine
 - Directed or "For Cause"




Purpose of FDA Inspections



- Verify the quality and integrity of data
- Verify compliance with the protocol, IRB, and regulations
- Ensure human subject protection




Constant readiness





Constant preparation will help result in a good inspection outcome.


- Identify problems soon after they occur
- Correct the problem
- Prevent the problem from reoccurring




Don't let this be you....



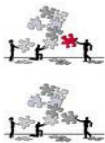
Constant readiness means PI compliance & supervision



- Comply with protocol, regulations and IRB requirements
- Supervise the conduct of the trial
 - Delegate only to adequately credentialed and trained personnel
 - Document delegation (name, delegated tasks, training received)
 - Document review of source documentation
 - Routine meetings with staff to review progress, AEs, changes
 - Routine meetings with sponsor's monitors to review outcome of monitoring visits




Constant readiness includes CAPA




Corrective Actions Preventive Action (CAPA) plans should document:


- Definition of the problem
- Analysis of the problem (root cause)
- Corrective actions taken
- Evaluation of effectiveness of action plan




The phone call....




- Don't panic
- Obtain the following information:
 - Nature and scope of the visit
 - Time of arrival
 - How many FDA investigators are coming
 - How long do they expect to stay
 - List of studies/subjects they would like to review



Start preparation...




- Notify sponsor
- Notify appropriate staff
- Make assignments
 - Person to escort FDA investigator
 - Person to make copies
- Set up introductory meeting space and invite attendees
- Arrange for a work space for the FDA investigator
 - Comfortable
 - Quiet
 - Empty of records



Prepare Documentation


Documents you may need

- Regulatory Binders
- Study files
- List of all PI's studies
 - Protocol number
 - Protocol title and the IND/IDE number
 - Name of sponsor
 - Study dates
- Investigator agreements
- Training Records
- Delegation logs
- Correspondence
- Drug/Device Accountability Records
- SOPs




Prepare Documentation

- Request medical charts (if applicable)
- Organize documentation: CRFs, documentation of AEs, supporting documentation used to capture source documentation, required reports
- Ensure you have every original consent form for all subjects
- If electronic data capture used – assure that personnel can access the eCRFs
- Check regulatory binder – is everything in order?
 - Protocol
 - Amendments
 - IRB approvals
 - SAE reports
 - Correspondence
 - 1572s
 - CVs
 - Delegation logs
 - Monitoring visit log




Be prepared for questions....




- Prepare all study staff for interviews
- Determine what questions might be asked
- Be prepared to answer


The following slides will discuss the areas the FDA Investigator will inspect and the objectives.




Delegated tasks




- Is there an accurate delegation log?
- Is the delegation log signed?
- Is there information about the qualifications of the delegated individuals to demonstrate competence (CV, medical or other license, evidence of other training)?
- Did anyone perform a delegated procedure without evidence of delegation?
- Did anyone perform a delegated procedure without adequate credentials or training (e.g. protocol requires a physician but ARNP performed task)?




Was IRB approval obtained?




- Did the PI obtain IRB approval of the items listed below before initiation of applicable study-specific procedures on subjects?
 - Protocol and any amendments
 - Informed consent document and any revisions
 - Advertisements and other information provided to subjects
- Did the PI submit information promptly to the IRB in compliance with the protocol and regulations?
- Was the correct IRB-approved consent document used?
- Did the PI adhere to the requirements of the IRB?




Was consent obtained and documented appropriately?




- Was consent obtained before any study procedures were done?
- Was the subject (or LAR) given a copy of the consent form?
- Was the correct IRB-approved version of the consent form used?
- Did the IRB stipulate any conditions for consent, and if so, did the PI adhere to the conditions?
- If the consent form was revised, was IRB approval obtained?
- Did the PI follow the IRB's instructions with respect to obtaining signatures on revised consent forms?
- How did the PI determine the authority of the LAR?
- Does the consent form include the eight required elements?
- For studies involving children, was assent obtained from the subject when appropriate?




Source Documents




- Are source documents organized, complete and legible?
- Is there adequate documentation to ensure that all subjects are alive and available for study duration?
- Is there adequate documentation of subject's condition upon study entry?
- Is there documentation of subject exposure to the test article as required by protocol?
- Is there adequate documentation of observations throughout the investigation, including results of lab tests, observations of subject condition, etc.?
- Are key personnel involved in collecting and analyzing data identified and qualified?
- Do study records agree with the source documents and the summary data submitted to the FDA?



Case Report Forms



- Who obtained and recorded the information on the form?
- If corrections were made, who made them, why were they made and was the PI aware?
- Did study subjects meet eligibility criteria?
- Was protocol required testing done?
- Were all AEs documented and reported as required?
- Did the PI assess the severity of the AE and relation of the AE to the test article?
- Are all concomitant medications documented and reported as required?
- Are all subject illnesses documented and reported as required?
- Were subject withdrawals reported to the sponsor?



Test article control issues



- Who is authorized to administer or dispense the test article (did an unauthorized person receive or dispense the test article?)
- Does the site have accurate records showing receipt of test article (receipt dates, quantity received, condition)?
- Does the site have accurate records of test article disposition (date, quantity, how disposed)?
- Does the site store the test article appropriately (limited access, correct temperature, security)
- Is test article appropriately labeled?



Did the PI follow the protocol?



- Inclusion and exclusion criteria
- Number of subjects and source of study subjects
- Randomization
- Required procedures
- Required evaluations
- Administration of investigational product
- Frequency of observations



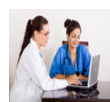
Records custody and retention issues



- Are case histories attributable, legible, contemporaneous, original and accurate (ALCOA)?
- Were required reports submitted as outlined in protocol and regulations? (progress reports, SAEs, final reports, financial disclosure reports, etc.)
- Were study records retained according to the requirements of the protocol and regulations?
- Did the sponsor monitor the study as outlined in the protocol and regulations? (pre-study contacts, frequency and nature of monitoring)
- Did the PI conduct appropriate follow-up activities when deficiencies were noted?



Part 11 Compliance



- Does the site have records subject to 21 CFR Part 11 (Electronic records used in place of paper records that are required by regulations - or that are relied upon to perform regulated activities)?
- Does site have documentation to show compliance with 21 CFR Part 11, including:

- SOPs
- Training
- Security
- Accessibility
- Validation
- Audit trails
- Backup files
- Disaster recovery plan
- Adequate error messaging



Additional issues



- Has the sponsor provided information to the PI about the test article, protocol, and the obligations of a PI? (evidenced by memo, meeting, etc)
- If any testing done at PI's site, is the site adequately equipped and are personnel properly trained.
- Did the PI use recruitment material that was coercive or that represented the test article as safe and effective for purpose under investigation?




The Inspection


- The FDA Investigator will present official credentials and Form 482 Notice of Inspection
- Discuss agenda for visit during introductory meeting
- Show FDA Investigator the work area, bathroom, etc.
- PI must allow time each day for questions and answers
- Escort should stay with FDA investigator, coordinate requests and answers questions – or refer the question to the appropriate individual
- Exit meeting each day should be held to discuss findings, provide clarification and provide information on previous corrective action or ongoing corrective actions




The FDA Investigator asks questions




- Listen carefully to the question
- Ask for clarification if you do not understand the question
- Take your time – a moment of silence is okay
- Answer only what is asked
- Do not volunteer information
- Answer truthfully
- Do not argue
- Be positive and confident
- If you don't know the answer, tell the investigator you do not know – don't try to guess
- Do not bring any documents in to the inspection area that have not been requested
- After the interview, take notes on what was asked and how you answered




The FDA Investigator inspects documents




- Sequester the FDA Investigators in an isolated room and bring the requested documents to them
- Bring only documents specifically requested
- Make two copies of each document – one for the FDA and one for your record of the inspection
- Follow your SOPs with regards to stamping documents "confidential"
- FDA Investigator is not entitled to review or copy financial records, personnel records (except for training records) and internal audit records



The Inspection is done




- A close out meeting will be held – FDA Investigator will discuss findings
- An FDA Form 483 will be issued if the Investigator believes any observations represent deviations from applicable statutes and regulations
- Discuss the 483 with the investigator
- If you have already corrected identified observations – let the investigator know
- If the 483 seems incorrect – provide information to correct it
- Don't argue with the FDA Investigator
- Thank the investigator for the time he/she took to inspect your site




If you received a 483...

"As a general rule, a Warning Letter should not be issued if the agency concludes that a firm's corrective actions are adequate and that the violations that would have supported the letter have been corrected." FDA Regulatory Procedures Manual


- Respond to the 483 within 15 business days
- Respond to each observation
 - If you disagree with an observation – provide clear, verifiable facts
 - If you agree with an observation - outline corrective actions
 - Identify and focus on the root cause of the observation
 - Develop achievable plan for short & long-term compliance – objective: no recurrence
 - Specific
 - Complete
 - Realistic
 - Verifiable
 - Provide a timeline for completion and supporting documentation
- Include a statement indicating a commitment to maintain compliance




FDA Actions following inspection



- One of the following letters from FDA:
 - FDA observed no significant deviations from regulations
 - Identifies deviations and corrective actions are sufficient (information or untitled letter)
 - Identifies serious deviations, corrective actions not sufficient – requires prompt correction (Warning Letter)
- Establishment Inspection Report (EIR)
- FDA can take the following actions if significant noncompliance is found or if the PI is willfully noncompliant:
 - Rejection of data from site
 - Initiation of Disqualification Proceedings
 - Civil/Criminal actions



Frequent findings



- Failure to follow protocol
 - Ineligible subjects
 - Procedures not done
 - Out of window procedures
- Inadequate recordkeeping – inadequate case histories
- Inadequate accountability of investigational product
- Inadequate subject protection
- Inadequate informed consent process
 - Procedures done before consent obtained
 - Incorrect consent form
 - Missing signatures, initials, dates
 - Dates do not match
- Inappropriate delegation

