Clinical Monitoring Visits and FDA Audits: How Do You Prepare

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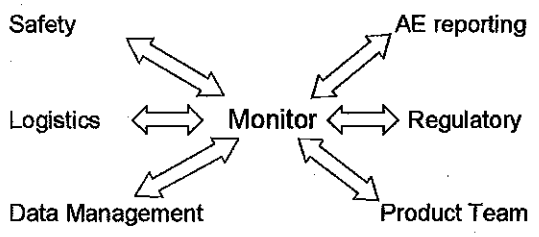
Objectives

- By the end of the presentation, the participant will understand the purpose of clinical monitoring and how to prepare for a monitoring visit.
- By the end of the presentation, the participant will understand the purpose of an FDA audit and know how to prepare for one.

Take-Home Message

Working with the Clinical Monitor
is one of the best ways
to prepare your site for an FDA Audit.

The Central Role of the Monitor



Common Audit Findings
(FDA 2004 Annual Report)

1) Failure to follow the protocol.
2) Failure to keep adequate and accurate records.
3) Failure to account for the disposition of study drugs.
4) Failure to report adverse events.
5) Problems with the informed consent form.

Key Monitor Responsibilities
(From ICH E6, Section 5.18.4)

Before the Study Begins

- To act as the main line of communication between sponsor and investigator (throughout the study).
- To verify that the investigator has adequate qualification and resources to conduct the study (ICH E6, Section 4.1, 4.2 & Section 5.3).
- If an investigational product is used, ensuring that it will be stored in safe, acceptable conditions throughout the trial (Section 4.6 and Section 5.14).
- The Site Assessment Visit

Key Monitor Responsibilities

(From ICH E6, Section 5.18.4)

During the Study

- The monitor verifies that the investigator is following the approved protocol and any amendments.
- Verifies that written informed consent was obtained before subject begins participation.
- Verifies that source documents and other records are accurate and complete.
- Determines whether all adverse events are appropriately reported as required.
- Verifies the receipt, use, and return of investigational product.

Key Monitor Responsibilities

(From ICH E6, Section 5.18.4)

During the Study (Continued)

- Ensures that the investigator receives all necessary documents (i.e., Investigator's Brochure) and all study supplies needed to carry out the study.
- Keeps the investigator and study staff informed about the progress of the trial.
- Verifies that the investigator is only enrolling eligible subjects.
- Reports on the subject recruitment rate.

Preparing for the MV

- Have all Regulatory documents for the study complete and ready for review (updated).
- Have subject source documents and CRFs ready for review (including Informed Consent, lab forms, etc).
- If there have been Serious Adverse Events, make sure to have supporting documentation available as much as possible.
- If CRA has identified items requiring correction during a previous visit, try to have these addressed.
- Be prepared to show IP storage and accountability.

Preparing for an FDA Audit

Why does the FDA audit?

- Routine audit to verify data submitted to FDA
- As a result of a complaint
- In response to a sponsor's concern re. a site
- At the request of an FDA division
- For certain pivotal studies or products that are of special interest to the FDA

Preparing for an FDA Audit

How are individual sites selected ?

- Large volume of work
- Work outside of field of specialty
- Efficacy too good
- Toxicity too low
- Pivotal study
- Large # of subjects or too rapid enrollment
- Lab results inconsistent with other investigators
- Publicly visible study

Preparing for an FDA Audit

Steps in the Process

Step 1: FDA Selects Sites

Step 2: FDA Investigator (District Office) contacts site

a. May give advance warning or may not.

b. Try to accommodate suggested dates if at all possible. May become suspicious if site requests an extensive delay.

Preparing for an FDA Audit

Preparing for the Visit: Interacting with the Auditor

- Be businesslike and friendly but do not offer information if not requested.
- If asked a question you don't know the answer to, say you will find out, do not try to make up an answer.
- Do not offer anything to the auditor except for water, coffee, or tea. Provide them with directions to sites for breakfast/lunch, etc.
- Assist with all requests for information except for financial data or personal data.
- Don't be afraid: If you conduct your study well, there is nothing to worry about.

Preparing for an FDA Audit

The Note to File: A Useful Tool

- Clarify or add information regarding site specific regulatory file requirements
- Clarify or add information regarding source document standards
- Document and address any issue that is protocol and/or site specific that cannot be resolved without a change from previously approved procedures.
- A Note to the Study File **defines the issue and clarifies** what the site has been instructed to do or what the site has agreed to do.

Preparing for an FDA Audit

The Note to File

A Note to the Study File
Is NEVER written as an exemption from:

Protocol eligibility criteria
Protocol deviation reporting
Serious Adverse Event reporting
Institutional Review Board and any other applicable regulatory/contractual requirements.

Preparing for an FDA Audit

Steps in the Process-Continued

Step 8) If deficiencies are found, the auditor will present a Form 483. The PI may respond to this verbally during the exit interview and in writing thereafter.

Step 9) The Auditor will write up the findings in an Establishment Inspection Report (EIR) that will be submitted to HQ for evaluation.

Preparing for an FDA Audit

Steps in the Process-Continued

Step 10) FDA will classify the inspection and send a letter to the site. It will be classified as follows:

- NAI (No Action Indicated)
- VAI (Voluntary Action Indicated)
- OAI (Official Action Indicated) The dreaded Warning Letter. Generally requires prompt corrective action by the PI/site and a written response to the FDA

"...FDA may initiate a process to disqualify the clinical investigator from receiving investigational products in the future if the investigator has repeatedly or deliberately failed to comply with applicable statutory or regulatory requirements...."

Preparing for an FDA Audit

Useful Links

http://www.fda.gov/

http://www.fda.gov/oc/gcp/guidance.html#guidance

http://www.fda.gov/foi/warning.htm

www.ich.org

http://www.usajobs.gov/