FDA Inspections: Real Experiences & Lessons Learned

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Learning Objectives

- Explain how to prepare for a FDA inspection: Practical considerations for preparation and for the days the FDA inspector is on-site.
- Describe aspects of medical device inspections.
- Describe real-life experiences shared from UR research staff.

What is an Inspection?

- An act by a *regulatory authority(ies)* of conducting an official review of documents, facilities, records and any other resource deemed by the authority(ies) to be related to the study
- Conducted by:
  - OHRP
  - FDA

(ICH E6, 1996)

FDA Inspections

- Bioresearch Monitoring Program
  - Investigators, IRBs, Sponsors, CROs
- Types of Inspections
  - Study-Directed (**advance notification**)
    - Typically after NDA or PMA submitted for marketing approval
    - Typically select high enrolling sites or those who participated in the most studies of the IP
  - Investigator-Directed (no advance notification)
    - Complaints, investigate possible regulatory violations

(Hiers, Rhea, & Kelly, 2014; Liu & Davis, 2009; Steele, 2014)

Preparing for An Inspection

- Preparation should start from the beginning of the trial. Good motto: “Always be prepared.”
- If you’re not already, get organized!!
  - Are all of your essential documents (including the regulatory file, subject-specific files & IP accountability forms)…
    - Available? Up-to-date? Accurate? Complete?
- Have SOPs available
- Arrange for:
  - E-record access? IDS?
  - Retrieve items from off-site storage

Preparing for a FDA Inspection

- When you get “the call”…Ask for:
  - ➢Name & contact info of inspectors
  - ➢Reason for inspection
  - ➢What study(ies), investigator(s), locations(s) will be inspected
  - ➢Anticipated start & end dates
  - ➢Who should be available
  - ➢What should be available

(Copeland, 2014; Hiers, Rhea, & Kelly, 2014; Liu & Davis, 2009; Steele, 2014)

Additional Resources

- FDA Reminder Card
- FDA Audit Preparation Resource Checklist

Preparing for a FDA Inspection

- Reserve a conference room for the FDA Inspector(s) to use
  - Avoid clinical areas and where other research material is
  - Quiet with limited access/traffic
  - Phone access
- Meet the Inspector in a predetermined location (lobby)
- Set a schedule to check in on progress

The Inspection Begins…

- Upon arrival:
  - Verify inspector credentials (photo ID)
  - Request/Accept FDA Form 482 Notice of Inspection
  - Confirm purpose
  - Provide inspector with a “host”

(Copeland, 2014; Hiers, Rhea, & Kelly, 2014; Liu & Davis, 2009; Steele, 2014)

During the Inspection

- Be available
  - Interviews, clarifications, additional documentation
  - Be prepared to provide an escorted facility tour (to where specific aspects of study were/are performed)
- Answering questions…
  - Take your time & be concise (and honest)
  - Ask for clarifications
  - If you don't know the answer, write down the question and get back to reviewer or refer to appropriate individual

During the FDA Inspection: What will they look at?

- Who performed different aspects of the study
- How authority has been delegated (and was it followed)
- How/where data has been recorded
- Orientation/training of study staff
- Whether or not the PI and delegated staff have followed the protocol
- Was communication with the IRB satisfactory
- IP accountability
- Informed consent process and consent forms
- Adverse assessment and reporting (as applicable)
- Record retention
- How CRA communicated with PI and evaluated study progress

(http://ictr.johnshopkins.edu/wp-content/uploads/import/1556-FDA%20Audit%20Preparation%20checklist_NAV_03JAN13_.pdf)

During the Inspection

- PI should set aside time each day to talk with inspector
- Inspector has the right to access & copy study records
    - If providing copies:
        - Make a copy for yourself
        - Mark Inspector's copy as "confidential" and your copy as "copy"
        - *Only give the Inspector copies that are specifically requested*
        - Inspector will source verify data

(Copeland, 2014; Hiers, Rhea, & Kelly, 2014; Liu & Davis, 2009; Steele, 2014)

During the FDA Inspection:

- Advice:
  - Stay calm & stick to the facts
  - Don't guess or speculate
  - Don't volunteer additional information or elaborate unnecessarily
  - Don't argue
  - Keep a log of questions asked by the inspector

(Copeland, 2014; Hiers, Rhea, & Kelly, 2014; Liu & Davis, 2009; Steele, 2014)

Exit Interview/Discussion

- PI must be present
- Audit findings – ask clarifying questions
- Clarify misunderstandings
- May issue Form FDA 483 Inspection Observations, if indicated

(483 FAQs: http://www.fda.gov/ICECI/Inspections/ucm256377.htm)

Common Findings

OHSP-QI Reviews

- Regulatory file documentation
- Consent form errors
- Protocol adherence
- Subject eligibility
- Source documentation

BIMO Investigators

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate IP accountability
- Inadequate communications with IRB
- Inadequate subject protection – failure to report AEs, informed consent issues

(FDA BIMO Metrics, 2014)

FDA Inspection Follow-Up

- Inspector submits Established Inspection Report to FDA
- Report is reviewed & assigned classification

No Action Indicated (NAI)	Voluntary Action Indicated (VAI)	Official Action Indicated (OAI)
• No objectionable conditions or practices found (or conditions did not justify further action) • Response from site not required	• Objectionable conditions or practices found but FDA is not prepared to take or recommend any admin/regulatory action • Letter may be issued (which may or may not require a response)	• Regulatory and/or administrative actions will be recommended • May include issuance of Warning Letter • Response required

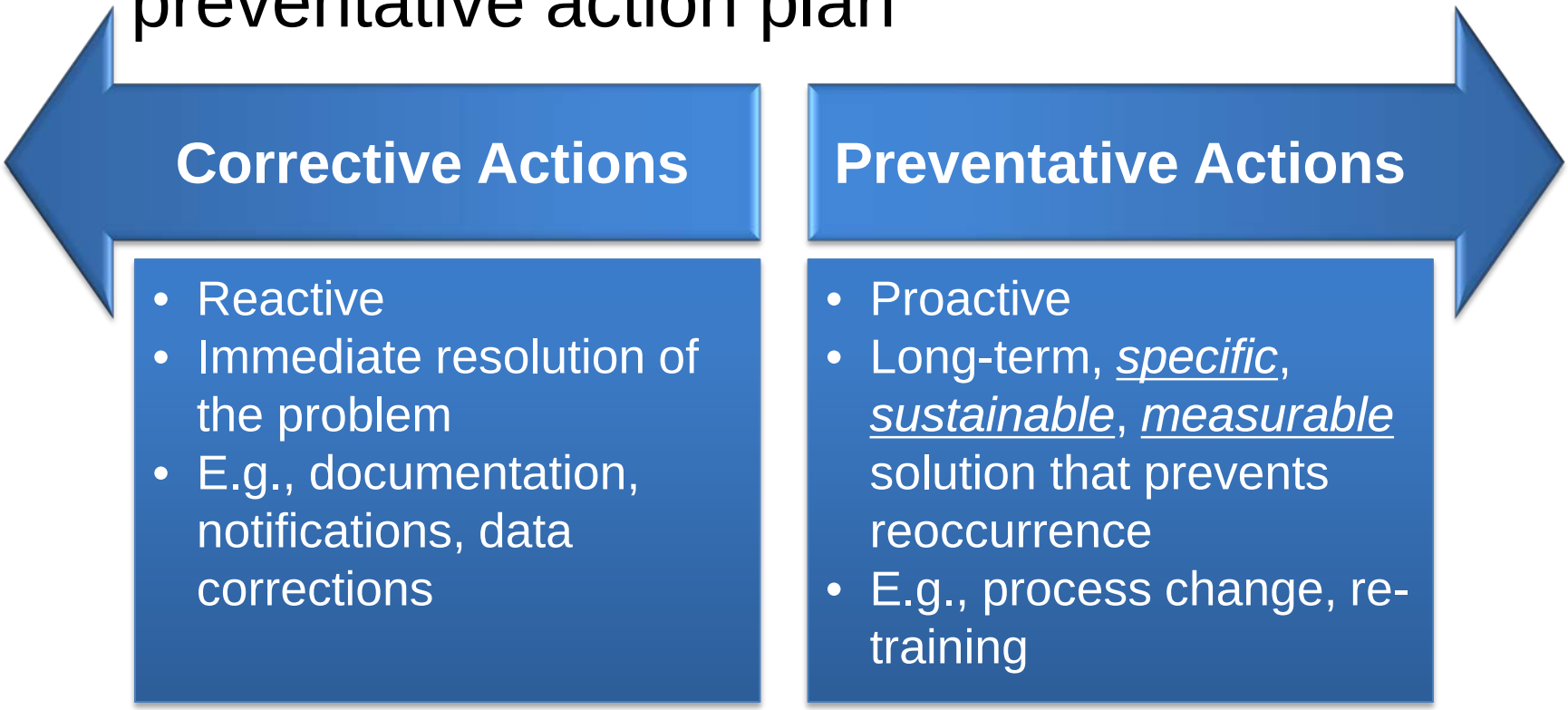
(Copeland, 2014; Hiers, Rhea, & Kelly, 2014; Liu & Davis, 2009; Steele, 2014)

Responding to Findings

- Step 1: Determine why the finding occurred?
  - Root Cause Analysis
    - 5 Whys; Cause and Effect, Fishbone Diagrams
  - Why ≠ Who
  - E.g., Missing data point
    - Data management error?
    - Subject refused to answer?
    - Subject inadvertently missed the question?

Responding to Findings

- Step 2: Develop a corrective and preventative action plan



(Divers, 2014; Masarek, 2014)

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OHSP-QI Regulatory File Contents Description

ICH EG – Section 8: Essential Documentation

OHSP Self Audit Tools

BIMO Site Audit Checklist (will be available on SCORE website)