Effectively Preparing for and Responding to an FDA Audit: The Research Team’s Perspective

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Agenda:

- Objectives
- The Clinical Research Players
- Short Regulatory Roadmap to Clinical Research Compliance
- FDA Audit Triggers/Government Enforcement Trends
- Clinical Investigator Role - 1572
- Informed Consent
- Institutional/Hospital Role
- Commercial Sponsor Role – The Key Elements Needed
- Tips to Developing an Effective, Coordinated Clinical Research Audit
- Team Response to Audits/Inspection
Objectives

- Creating a Comprehensive Approach: protocol submission to Audit and Inspection,
- Establishing a Systemic Approach: Integration of Research Administrative Infrastructure – technically & operationally
- Educating PI: Regulatory Knowledge and Support
- Implementing Continuous Quality Improvement
- Lessons Learned

Objectives cont’d

- Practical Application – What to do when the Auditors call you
- Perspectives: Investigator, Institutional and Sponsor
- Response to Audit, Inspection, Monitoring
- Government Enforcement Trends
The Clinical Research Players

- Clinical Investigator (aka Principal Investigator or “PI”)
- Sponsors (Commercial, Academic or Public)
- Institutional Review Board (IRB) / Institution Research Integrity or Research Compliance Office
- Monitor and Contract Research Organizations (CRO)

Short Regulatory Roadmap to Clinical Research Compliance

- The IOM (FDA’s Investigations Operations Manual) – primary source for inspection policies and procedures [bible]
  - Inspections v. Investigations (consumer or industry complaints)
  - Subchapter 5.5 – Drugs; Subchapter 5.6 – Devices; Subchapter Biologics

- PI’s Statement of the Investigator for IND Studies (FDA Form 1572)
  - 21 CFR 50 (Protection of Human Subjects)
  - 21 CFR 56 (Institutional Review Boards)
  - 21 CFR 312 (Investigational New Drug Application / IND) (For Device studies, 21 CFR 812 (Investigational Device Exemptions / IDE) in place of 21 CFR 312)
Short Regulatory Roadmap to Clinical Research Compliance

- ICH GCP Guidelines of E6 (4.1 to 4.13): FDA embraces; not all instit’s inc. in FWA; but in int’l trial GCP applies

- Good Clinical Practices (GCP) – FDA Guidance (E6)

- IRB Policy: OHRP and FDA Regulations- Institutions that do not comply with OHRP must comply with FDA regulations regardless of source of funding

Types of FDA Audits and Triggers

- For cause
- Not-for-cause
- Expedited review (e.g., sponsor request) expedite marketing
- Adverse event/Unanticipated event
- New indication – drug or device
- Risks that Concern the Government Most-Current Trends
Overview of FDA Audit Process

- Review greater detail: investigator perspective
  - Pre-Audit
    - FDA contacts PI (phone call, unannounced)
    - Negotiate Date
    - FDA Arrives Onsite: Issues – Notice of inspection Form 482
  - Post-Audit Onsite:
    - FDA conducts audit, exit interview: Form 483
- Determination: Regional Audit Report to Washington
  - NAI: No Action Indicated
  - VAI: “Voluntary” Action Indicated (mandatory)
  - OAI: Official Action Indicated / Warning

FDA Review of Post Inspection Responses-change in Regulation as of 9-15-09 Federal Register pg. #1
Information Sheet Guidance

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

FDA Institutional Review Board Inspections

Additional copies are available from:

Office of Science & Health Coordination, Office of the Commissioner
Food and Drug Administration

http://www.fda.gov/orirp/publication.html

U.S. Department of Health and Human Services
Food and Drug Administration

January 2009
Clinical Investigator: Role/Responsibility
Main Requirements

General Requirements:
- Conduct in accord with investigator agreement, investigational plan (i.e. protocol) and regulations (312.60)
- Ensure the protection of human subjects; ongoing safety and welfare (312.60)
- Legally effective informed consent obtained (312.60)
- Documentation of informed consent process

Oversight of Investigative Article:
- Only under supervision of investigator should study article be administered (312.61)
- Maintain meticulous records of study article (312.61)
- Maintain study article in area away from conventional therapies
- Ensure limited number of personnel with access to study article
Clinical Investigator: Main Requirements
cont’d

Record Keeping
- Prepare and maintain accurate/complete case histories; include all observations and data pertinent to the study per subject \((312.62)\)
- Retain records for 2 years following the date of market application approval or 10 years ( whichever is greater) \((312.62)\)

Clinical Investigator: Main Requirements
cont’d

Reports to Sponsor
- Disposition of test article \((312.62)\)
- Prompt reporting of adverse effects caused by or probably caused by test article \((312.64)\)
- Supply accurate financial disclosure statement ( initially and update annually) \((312.64)\)
Clinical Investigator: Main Requirements cont’d

IRB Oversight (312.66):
- Assure qualified IRB responsible for protocol review (initial, continuing, amendments)
- Prompt reporting of any changes (expected and unexpected) in research activity
- Investigator must “promptly report” (5-10 working days) any Adverse Event (AE) that is considered an Unanticipated Problem (UP)
  - For IDE studies Unanticipated Adverse Device Effect (UADE) ASAP; no later than 10 working days

FDA Form 1572: Statement of Investigator
Informed Consent: Joint Responsibility of the Clinical Research Players

- Investigator / IRB / Institution / Sponsor- Must ensure that rights of Research Participant are Protected
- What is and is not Informed Consent

Institution: Role/Responsibility

- Establish Culture of Compliance
- Education/Training:
  - Regulatory Compliance
  - Research Integrity and Responsible Conduct of Research
- Policies / Training
- Self-Audit and Monitor
- Manage Internal Investigations
- Manage Documentation
- Risk Assessments / Set up Internal Controls, / Preventive Measures, e.g.,@ Rush: EQuIP program
- Conduct Due Diligence
Institution: Role/Responsibility
cont’d

- Educate and Inform Research Community:
  - direct researchers to Institutional Policy on Audits
  - If none, draft one!

- Conduct institutional evaluations and inspections at your institution – obtain benchmark data on research community:
  - knowledge and preparedness

- Give presentations on Audits
- Conduct a mock-audit in public forum
Coordinate activities with Research Integrity/Compliance or Internal Audit

Collaborate with Institutional Review Board Administration

Ensure communication among the parties involved, as needed e.g., Investigator, Research Team, IRB personnel, Pharmacy, Medical Records
Open Lines of Communication

- Institutional official makes assistance available to research team subject to audit
- Assign staff to work closely with research team point person, make sure individuals understand need to communicate and relay information to institutional staff, to avoid surprises
- Ensure thorough meticulous review of all records

Sponsor: Role/Responsibility and Different Types

- Sponsors, IRBs, Clinical Investigators, Monitors, Contract Research Organizations (CROs), Non-clinical (animal) laboratories and Bioequivalence Analytical Laboratories
  - Sponsors can be commercial pharmaceutical or biotech companies (“Commercial Sponsor”), doctors, medical institutions, foundations, voluntary groups, or federal agencies such as the National Institutes of Health (NIH)

- Commercial Sponsor working independently, with another Commercial Sponsor or Commercial Sponsors) working with one or more Public or Academic Research Institution (common models)
Sponsor: Role/Responsibility and Different Types cont...

- **Public, Academic, Foundation Research Entity** as Sponsor
  - Independent clinical study without support from a commercial sponsor

- **Cooperative Research** – Multiple/single Clinical Investigators from different Research Institutions working on a study

Sponsor Perspective on Audits: Key Elements Needed

- Commercial Sponsors Get Audited by the FDA / Regulatory Agencies, Audit other members of the Research Team and Get audited by Collaborators/Partners

- Key Elements Needed for a Successful Audit
  - PI's active role in the Clinical Research Process
  - Adherence to Regulatory Requirements and IRB/Institution’s Own Written Procedures
  - Financial Disclosure
  - Adherence to the Research Protocol
  - Staff Signatures
  - The IC Process
  - Reporting Requirements
    - AEs and SAEs
Sponsor Perspective on Audits: Key Elements Needed

- “An Ounce of Prevention”
- Crises Management= Having the Team in Place
  - “Always Ready” with a Clear Chain of Command
- Importance of Written Policies
- Compliance Program
- Internal Investigations
- Close Communication with Legal Department
- Avoid Misinformation by Only Speaking in One Voice through Communications folks

Developing an Effective, Coordinated Research Team Response to Audits

Edvard Munch 1893 The Scream
PI Inspection Tips to Developing an Effective Response to an Audit

cont’d

- Review Key Study Documents
  - Informed Consent Form
  - Protocol (Amendments)
  - Source Documents
  - Investigational Article Accountability Records
  - Unexpected Problems

- Assign a site escort/facilitator
- Assemble all study documents in 1 place
  - Document staff responsibilities and training
  - Request all subject medical and research charts
- Prepare list of investigator’s studies
- Reserve adequate work space for field investigator during inspection
- Assure accessible photocopier
Make 2 copies of all documents FDA investigator requests during site visit

FDA investigator interviews site staff directly involved in trial activities

- **Answer**
  - Politely, cooperatively, ask for clarification, factually, briefly, within one’s expertise (seek expert), directly (remain within scope), without speculation or guesswork

- **Avoid**
  - Unsolicited questions, hypothetical questions, long delays to requests, affidavits

Audit preparation starts before the study commences.

- Know your study
- Know your study subjects
- Be organized
- Call in resources (e.g., IRB, ORI, Research Compliance)
Institutional Tips to Developing an Effective Response to an Audit

- Make sure the research community understands the importance of contacting the appropriate institutional official
- Ensure close communication between the institutional official, the investigator and research team, and the IRB
- Assume the role, if warranted, of liaison with the FDA auditor, RTOG, OHRP, etc.

Institutional Tips to Developing an Effective Response to an Audit cont’d

- Meet with the research team before the audit (at least once) more often as needed
- Represent the institution at the outset of the audit, introduce yourself, your role, provide your card/contact info and let them know you are readily accessible
- Coach the research personnel on how to interact with the auditor
- Be present at the exit interview
Sponsor Tips to Developing an Effective Response to an Audit

☐ Sponsor will be looking for:
  ☐ Were all dropouts with reasons reported to the Sponsor?
  ☐ Who recorded information in the records and what records were maintained?
  ☐ If study records were not maintained by the Investigator, was the Sponsor notified?
  ☐ Were periodic reports submitted to the Sponsor and how?

Sponsor Tips to Developing an Effective Response to an Audit cont’d

☐ Have Processes and Procedures to Prevent:
  ☐ Inadequate consent forms
  ☐ Inadequate accountability for test article
  ☐ Failures to adhere to study protocol
  ☐ Inadequate and inaccurate records
  ☐ Failures to inform IRB of changes

☐ Take Immediate Corrective Action when Necessary and Communicate Same / Be Able to Show Steps Taken
Maintaining a Culture of Compliance
Research Team

- Establish Culture of Compliance
- Policies / Training
- Self-Audit and Monitor
- Manage Internal Investigations
- Manage Documentation
- Risk Assessments / Set up Internal Controls / Preventive Measures
- Conduct Due Diligence

Note: Role of the Compliance Officer in Regulatory Visits, Audits and Investigations to be covered at 11 am on Monday, Oct. 19 during Juliann Tenney and Carole Klove's Breakout Session

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It Has Been Our Pleasure To Present This Material. Feel Free To Contact Us If You Wish To Discuss Further.

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