Investigator Initiated Trials (IITs): Addressing the Challenges of Auditing IITs for Compliance and GCPs

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Agenda

• Identify the unique regulatory and operational challenges of IITs, as well as, the associated risks
• Discuss suggestions for risk-based audit plans, sampling and testing techniques for IITs
• Share success stories and lessons learned conducting IIT audits at a designated cancer center
Audit Approach & Process

Audit Approach

• Assess
• Collaborate
• Empower
• Train
• Mentor

Learn the organization!
General Audit Approach

- Perform specific audits: compliance, process, study-specific
  
  What should be happening?  \(\Rightarrow\) Gaps  \(\Rightarrow\) What is happening?

- What are the causes of the gaps? (e.g., isolated incident, broad internal control deficiency, lack of knowledge/training)
- Collaborate with audit client: Communicate! Communicate! Communicate!
- Clearly document observations
  
  - Specifics: dates, subjects, regulations, data, safety, data integrity
- Identify corrective and preventative action plans
- Identify required reporting to appropriate entities

Audit Process

Planning  \(\rightarrow\) Opening  \(\rightarrow\) Fieldwork  \(\rightarrow\) Closing  \(\rightarrow\) Reporting

Communication

What’s in a name?  
Audit vs. 
Quality Review vs. Process Improvement
GCP and Regulatory Review Audits


1. Ethical principles
2. Risk / Benefit
3. Human Subject Protection
4. Investigational Product (IP) information
5. Protocol: scientifically sound & detailed
6. Institutional Review Board (IRB)
7. Physician qualifications & oversight
8. Staff training
9. Informed consent
10. Data
11. Privacy & Confidentiality
12. IP manufacturing, handling, storage & use
13. Quality systems & procedures

GCP and Regulatory Review Audits

- Review SOPs / Policies & Procedures
- Review regulatory documents, trial master file, informed consent documents and process
- Confirm informed consent process, date of consent against study related procedures and appropriate documentation of consent
- Confirm subject eligibility
- Validate protocol compliance
- Verify reporting of adverse events and serious adverse events (SAEs)
- Validate all source data against Case Report Forms and orders with medical documentation
- Evaluate Investigational Product (IP) accountability and handling
- Review quality of data
- Analyze physician oversight
GCP and Regulatory Review Audits: Document Request / Review

- Protocol, all protocol versions, investigator’s brochure (IB), Instructions for Use (IFU) and any other related study documents
- Standard Operating Procedures (SOPs); Policies & Procedures
- Regulatory documents:
  - Institutional Review Board documents (approvals, correspondence, acknowledgement letters, correspondence, roster)
  - Correspondence – Internal (study team), External (Sponsor)
  - FDA 1571/1572, Investigator statement, Safety Reports, DSMB Reports, Financial Disclosures
  - Serious Adverse Event reports, other
- Informed Consent Forms: all IRB approved versions, and all signed consent forms for each subject
- Delegation of Authority Log
- Credentials: CVs, licenses
- Training: Protocol specific; general (e.g. GCP, HSP, IATA)
- Logs: Screening & enrollment logs, monitoring logs, etc.
- Investigational Product (IP) – drug / device: accountability & dispensing logs, temperature logs, calibration logs, as applicable
- Laboratory Documentation: CLIA, CAP, normal ranges, specimen logs, temperature logs, chain of custody SOP
- Case Report Forms
- Publications

IIT Risks: Regulatory, Compliance & Other
Selected Regulatory, Compliance & Other Risks

- Lack of monitoring
- Lack of oversight of the investigational product
- Adverse event reporting to funder & IRB inconsistencies
- Lack of adherence to institutional policies
- Lack of an IND or maintaining an IND

- Lack of regulatory documents
- Unclear protocols; ghost written protocols
- Lack of insurance coverage or indemnification

Creating Risk Based Audit Plans & Sampling Techniques for IITs
Risk Based Audit IIT Study Selection

- Risk ranking & complexity scoring of IITs for **audit selection**.
  
  For example:
  - Is there an **IND or IDE** involved?
  - Is there a strong **monitoring** function?
  - Are certain **therapeutic areas** higher risk?
  - What is the **past experience** with investigator or clinical team?
  - What do past audit or monitoring results reveal?
  - When was the study last audited or monitored?
  - Have there been **changes in personnel**? PI? Coordinator?
    Regulatory staff?

Risk Based Audit Plans & Sampling

- For example:
  - **Informed consent** review selection
    - All or a sample
  - Subject selection
    - Different arms, screen failures, most recent subjects enrolled
  - When to **start an audit** on a new IIT
    - Before subjects are enrolled
    - After first subject
  - Areas to audit
    - Determine during planning
  - **Full audit versus focused audit**
    - Audit after changes implemented
  - Audit to institutional SOPs, GCP/protocol compliance or both
Other Areas to Consider

• Review of protocol
  • Alignment with institutional policies and procedures
  • Document concordance

• Training
  • All personnel must be trained on protocol
  • Site Initiation Visits

• Delegation of Authority
  • Contractual obligations with funder
  • Billing compliance matters

Success Story
&
Good Things!
Old Audit Process

• Non-professional external staff
• Confrontational
• Punitive
• Repetitive findings
• Recommendations did not consider infrastructure deficiencies
• No flexibility for corrections to the final report
• Lack of communication with study staff and leadership
• Lack of CAPA item accountability
A New Day...A New Process
Engage a New External Firm

A New Day...A New Process

Roles & Responsibilities – Policies & Procedures

Increased Communication with Leadership

A New Day...A New Process
Sort Findings by Study Team Accountability and Infrastructure Issues. Addressed Separately

A New Day...A New Process

Audit Process Document

A New Day...A New Process
Audit Process - Steps

1. Planning
2. Introduction & Opening Conference
3. Fieldwork
4. Preliminary Observations
5. Closing Conference
6. Reporting
7. Action Plan & Follow-up

Good things that happen from IIT audits

- Identified need for and increased **training** by adding learner platforms for refresher training, started mentoring programs, initiated a Co-Op study training program with local college
- Increased monitoring
- Increased **monitoring** and resources for investigational product accountability
- Implemented new IIT **protocol templates**
- Increased **protocol writing support** to investigators for IITs for protocol consistency and clarity
- Revised **amendment review** and **tracking** processes
MORE good things that happen from IIT audits

- Created SOPs and guidelines to determine who should be listed on regulatory documents (e.g. DOA & 1572)
- Implemented new processes to label informed consent forms scanned into the medical record
- Established workgroups to solve bigger process issues
  - EMR issues with investigation product (IP) times & IP administration documentation
- Created templates for eCRFs to address data matters
- Created process to manage IB receipt and distribution in a timely manner
- Identified clinical trial billing issues
- Identified need to better manage external sites
Summary

• Collaboration is the best approach
• Planning the audit is critical
• Use a risk-based approach
• Communicate! Communicate! Communicate!
• Celebrate successes!

Thank You

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