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

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Audit Approach & Process

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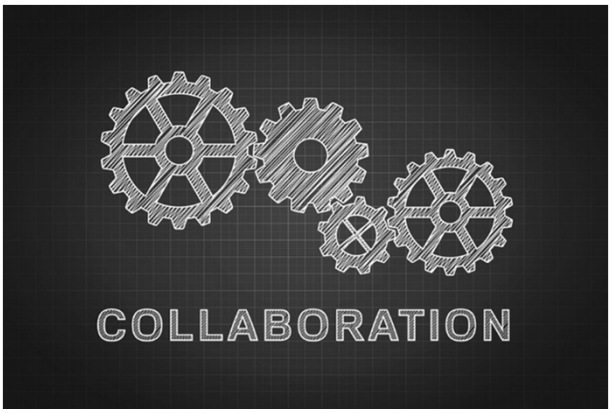
Audit Approach

- Assess
- Collaborate
- Empower
- Train
- Mentor



Learn the organization!

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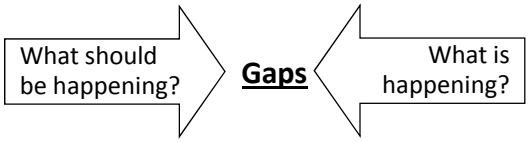
General Audit Approach

- Perform specific audits: compliance, process, study-specific



- 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!**
- **Cleary document** observations
  - Specifics: dates, subjects, regulations, data, safety, data integrity
- Identify **corrective and preventative action plans**
- Identify required reporting to appropriate entities

What's in a name?
Audit vs.
Quality Review vs.
Process Improvement

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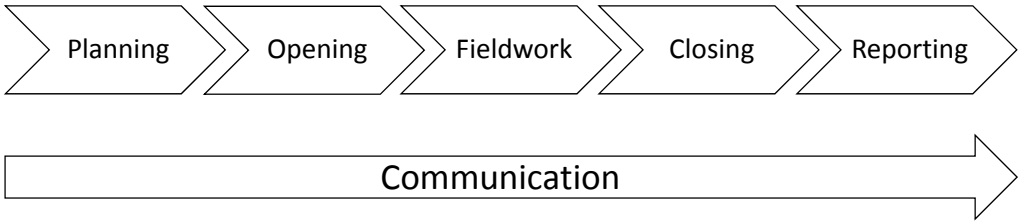
Audit Process



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GCP and Regulatory Review Audits

Guiding Principles: The 13 Principles of the International Conference on Harmonization Good Clinical Practices (ICH GCP):

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

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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**

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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

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IIT Risks: Regulatory, Compliance & Other

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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**

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Creating Risk Based Audit Plans & Sampling Techniques for IITs

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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?

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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

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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

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Success Story
&
Good Things!

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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

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A New Day…A New Process

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Engage a New External Firm

Study Team Feedback

A New Day…A New Process

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Roles & Responsibilities –
Policies & Procedures

Increased Communication with Leadership

A New Day…A New Process

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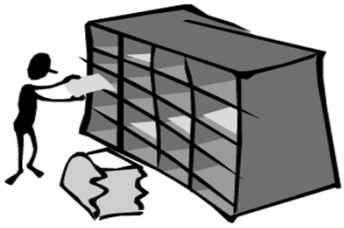
Sort Findings by Study Team Accountability and Infrastructure Issues.

Addressed Separately



A New Day…A New Process

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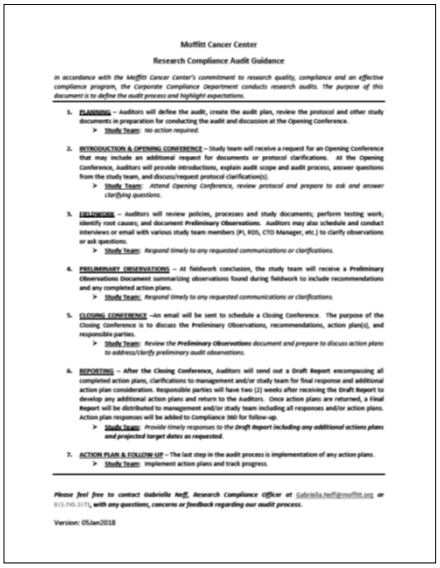
Audit Process Document



Moffitt Cancer Center

Research Compliance Audit Guidance

In accordance with the Moffitt Cancer Center's commitment to research quality, compliance and an effective compliance program, the Corporate Compliance Department conducts research audits. The purpose of this document is to define the audit process and highlight expectations.

1. **PLANNING** – Auditors will define the audit, create the audit plan, review the protocol and other study documents in preparation for conducting the audit and discussion at the Opening Conference.
   - Study Team: *No action required.*
2. **INTRODUCTION & OPENING CONFERENCE** – Study team will receive a request for an Opening Conference that may include an additional request for documents or protocol clarifications. At the Opening Conference, Auditors will provide introductions, explain audit scope and audit process, answer questions from the study team, and discuss/request protocol clarification(s).
   - Study Team: *Attend Opening Conference, review protocol and prepare to ask and answer clarifying questions.*
3. **FIELDWORK** – Auditors will review policies, processes and study documents; perform testing work; identify root causes; and document Preliminary Observations. Auditors may also schedule and conduct interviews or email with various study team members (PI, ROS, CTO Manager, etc.) to clarify observations or ask questions.
   - Study Team: *Respond timely to any requested communications or clarifications.*
4. **PRELIMINARY OBSERVATIONS** – At fieldwork conclusion, the study team will receive a Preliminary Observations Document summarizing observations found during fieldwork to include recommendations and any completed action plans.
   - Study Team: *Respond timely to any requested communications or clarifications.*
5. **CLOSING CONFERENCE** –An email will be sent to schedule a Closing Conference. The purpose of the Closing Conference is to discuss the Preliminary Observations, recommendations, action plan(s), and responsible parties.
   - Study Team: *Review the **Preliminary Observations** document and prepare to discuss action plans to address/clarify preliminary audit observations.*
6. **REPORTING** – After the Closing Conference, Auditors will send out a Draft Report encompassing all completed action plans, clarifications to management and/or study team for final response and additional action plan consideration. Responsible parties will have two (2) weeks after receiving the Draft Report to develop any additional action plans and return to the Auditors. Once action plans are returned, a Final Report will be distributed to management and/or study team including all responses and/or action plans. Action plan responses will be added to Compliance 360 for follow-up.
   - Study Team: *Provide timely responses to the **Draft Report including any additional actions plans and projected target dates as requested.***
7. **ACTION PLAN & FOLLOW-UP** – The last step in the audit process is implementation of any action plans.
   - Study Team: Implement action plans and track progress.

Please feel free to contact Gabriela Neff, Research Compliance Officer at** Gabriela.Neff@moffitt.org **or** 813-745-3175, **with any questions, concerns or feedback regarding our audit process.

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A New Day…A New Process

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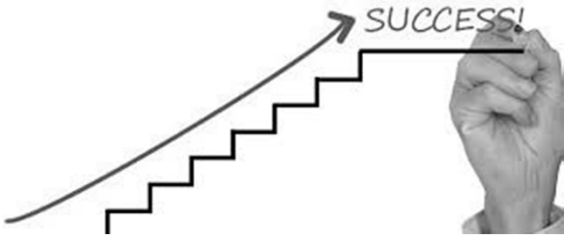
Audit Process - Steps

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



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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

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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**

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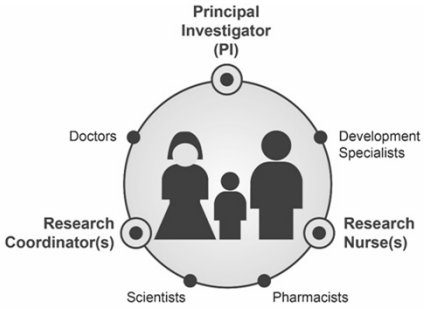
Please audit me!



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Summary

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

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Thank You

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