Good Clinical Practice Update and Best Practices for Audit Readiness

Sandra SAM Sather, MS, BSN, CCRA, CCRC
Vice President Clinical Pathways, LLC

Presenter Bio

Sandra "SAM" Sather's has been in the clinical trial industry for almost 30 years and has worked as a study coordinator, monitor, auditor, site director, quality manager, trainer, and more.

She authored the latest CenterWatch book *The CRC's Guide to Coordinating Clinical Research.*

SAM continues to be dual certified by ACRP as a CCRC and CCRA for over 15 years. She sits on the ACRP Academy Board of Trustees. She owns a GCP consulting firm, Clinical Pathways, LLC, in Research Triangle Park in North Carolina.

Email: sam@clinicalpathwaysresearch.com

Session Objectives for You

- Discuss latest **GCP updates and audit findings** significance to investigational site best practices
- How to best avoid and also manage **issues that matter** for inspection readiness
- Apply the **ALCOAC** standard to support essential regulatory and source documentation

ICH E6 R2, Section 2 (13th Principle of GCP)

- 2.13 *Systems with procedures that assure the quality of every aspect of the trial should be implemented.*

- Adden 2.13: ***Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.***

Applicable to all GCP Stakeholders (investigators, sponsors, IRB)

Investigator Compliance and Oversight - ICH E6

- *4.1.3* The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
- *4.2.2* The investigator should have **sufficient time** to properly conduct and complete the trial within the agreed trial period.
- *4.2.3* The investigator should have available an **adequate number of qualified staff and adequate facilities for the foreseen duration** of the trial to conduct the trial properly and safely.

ICH E6 GCP (R2) Investigator Oversight

Investigator: Adden 4.2.5

- *Investigator is responsible for **supervising any individual or party to whom the investigator delegates trial-related duties and functions** conducted at the trial site.*

Investigator: Adden 4.2.6

- *If the investigator/institution **retains the services of any individual or party** to perform trial-related duties and functions,*
  - ***the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions** and*
  - *should **implement procedures** to ensure the integrity of the trial-related duties and functions performed and any data generated.*

ICH E6 GCP (R2) Investigator Oversight

Key Points:

- Investigators may delegate
- Delegates must be vetted for qualifications
- Procedures must be in place to support oversight.
- Must oversee their delegates.

Clarification of Investigator Responsibilities

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: **FDA Inspections of Clinical Investigators (2010)**

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-inspections-clinical-investigators

- *During an inspection at the site of a clinical investigator, FDA personnel typically verify:*
  - *who performed various aspects of the protocol* ***(e.g., who verified inclusion and exclusion criteria, who obtained informed consent, who collected adverse event data)****;*
  - *the degree of delegation of authority (e.g.,* ***how the clinical investigator supervised the conduct of the investigation****)*

. . . Etc.

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Clarification of Investigator Responsibilities

2009 FDA Guidance related to Investigator Oversight

- Supervision of the Conduct of a Clinical Investigation
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects

  – *21 CFR Part 312 and 21 CFR Part 812*

  – *Common practice to delegate certain study-related **TASKs** to:*
    - *employees,*
    - *colleagues, or*
    - *other third parties (individuals or entities not under the direct supervision of the investigator).*

  – *Investigator is responsible for providing adequate **SUPERVISION** and is **ACCOUNTABLE** for regulatory violations resulting from failure to adequately supervise.*

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Clarification of Investigator Responsibilities

FDA 2009 Investigator Responsibilities Guidance contents

- **Supervision of the Conduct of a Clinical Investigation**
  1. What is Appropriate Delegation of Study-related Tasks?
  2. What is Adequate Training?
  3. What is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?
  4. What are an Investigator's Responsibilities for Oversight of Other Parties Involved in the Conduct of a Clinical Trial?

- **Protecting the Rights, Safety, and Welfare of Study Subjects**
  1. Reasonable Medical Care Necessitated by Participation in a Clinical Trial
  2. Reasonable Access to Medical Care
  3. Protocol Violations that Present Unreasonable Risk

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Clarification of Investigator Responsibilities

FDA focuses on four major issues: Whether . . .

1. delegated individuals were qualified to perform such tasks,

2. study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study,

3. there was adequate supervision and involvement in the ongoing conduct of the study, and

4. there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible.

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Clarification of Investigator Responsibilities

FDA gives common examples of **inappropriate** delegation

*1. **Screening evaluations**, including obtaining medical histories and assessment of inclusion/exclusion criteria, conducted by individuals with inadequate medical training (e.g., a medical assistant)*

*2. Physical **examinations performed by unqualified personnel***

*3. Evaluation of **adverse events** by individuals lacking appropriate medical training, knowledge of the clinical protocol, and knowledge of the investigational product*

*4. Assessments of **primary study endpoints** (e.g., tumor response, global assessment scales) by individuals lacking appropriate medical training and knowledge of the protocol*

*5. **Informed consent** obtained by individuals who lack the medical training, knowledge of the clinical protocol, or familiarity of the investigational product needed to be able to discuss the risks and benefits of a clinical trial with prospective subjects*

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What is Adequate Investigator Oversight?

Investigator should have:

- *Sufficient **TIME** to properly*
  - *Conduct and*
  - *Supervise the clinical trial*
- *Intensity of supervision should be:*
  - ***Appropriate to staff,***
  - ***Nature of the trial, and***
  - ***Subject population***

Reference: 2009 FDA Guidance: Investigator Responsibilities

What is Adequate Investigator Oversight?

- FDA notes common factors that may compromise the investigator's ability to provide adequate supervision:
  - *Inexperienced study staff*
  - *Study staff demanding workload*
  - *Complex clinical trials, e.g., many observations, large amounts of data collected*
  - *Large number of subjects enrolled at a site*
  - *Subject population seriously ill*
  - *Conducting multiple studies concurrently*
  - *Conducting a study from a remote (i.e., off-site) location;*
  - *Conducting a study at multiple sites under the oversight of a single investigator, particularly where those sites are not in close proximity*

Reference: 2009 FDA Guidance: Investigator Responsibilities

What is Adequate Investigator Oversight?

- Investigator should develop a ***Plan*** *for* <u>supervision</u> *and* <u>oversight</u> *of a clinical trial*
  - *Even for individuals who are highly qualified and experienced*
- Plan might include the *following elements per* ***particular trial when applicable****:* 10 items…

Reference: 2009 FDA Guidance: Investigator Responsibilities

Elements of a Plan for Adequate Supervision

1. Routine meetings *with staff to review trial progress + update staff on any changes to protocol or other procedures*

2. Routine meetings *with sponsor's monitors*

3. Procedure *for "**timely**" correction and* ***documentation*** *of problems identified by study personnel, outside monitors or auditors, or other parties*

4. Procedure *for documenting* ***or reviewing*** *the performance of delegated tasks in a satisfactory and "**timely**" manner*

e.g., observation of performance of selected assessments or independent verification by repeating selected assessments.

Reference: 2009 FDA Guidance: Investigator Responsibilities

Elements of a Plan for Adequate Supervision

5. Procedure *for ensuring that the consent process is and study subjects understand the nature of their participation and risks*

6. Procedure *for ensuring that source data are accurate, contemporaneous, and original*

7. Procedure *for ensuring that information in source documents is accurately captured on the CRFs*

8. Procedure *for dealing with data queries and discrepancies identified by the study monitor*

Reference: 2009 FDA Guidance: Investigator Responsibilities

Elements of a Plan for Adequate Supervision

9. Procedure(s) *for ensuring study staff comply with the protocol and adverse event assessment and reporting requirements*

10. Procedure *for addressing medical and ethical issues that arise during the course of the study in a timely manner*

Reference: 2009 FDA Guidance: Investigator Responsibilities

Investigator Oversight Case Example

In your experience what is the biggest areas that challenge investigator oversight?

ALCOA: documentation!

Case example of lack of investigator oversight:

- Refer to the Investigator Warning Letter and next slide

Lack of Investigator Oversight FDA Warning Letter Case Example

- *"In your response you stated that the **violations were caused by errors on the physicians part and inadvertent errors on the part of the supervisor, the study coordinator**.*
- *You also stated as corrective actions that a "summary with specific criteria will be made available to the physicians to review prior to the enrollment of each patient" and that the inspection findings were reviewed with the appropriate research staff and co-investigators .*
- *Your response **is inadequate**. As a Clinical Investigator, you are responsible for ensuring that all study staff are adequately trained and qualified to perform study tasks delegated to them.*
- ***You may delegate study tasks to other qualified personnel, but you may not delegate your responsibility to ensure that all study tasks are correctly performed."***

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Origin of the Greatest Areas of Risks for Sites

Sponsor	IRB	Participants	Site / Self
Protocol Monitoring	Locale aspects	Vulnerability Adequate medical care Compliance Recruitment/ Retention	Talent / Retention Budget Compliance Resources Governance

Regulatory Guidance:

- ICH 2016 E6 R2 Addendum
  - Section 4 Investigator
- FDA 2009 Guidance
  - Investigator Responsibilities
- FDA 2010 Guidance
  - Inspections of Clinical Investigators

Stages of Research:

- Pre-study, During, Post

Risky to rely on Sponsor/CRO for compliance

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Same as 2016

FY17 Clinical Investigator Inspections Classified*
Common Clinical Investigator Deficiencies*

- Failure to follow the investigational plan/agreement or regulations, or both
- Protocol deviations
- Inadequate recordkeeping
- Inadequate subject protection – informed consent issues, failure to report AEs
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Investigational product represented as safe/effective

Looks like there has been some improvement between 2016 to 2017, but the same top deficiencies

* Clinical Investigator (CP 7348.811) deficiencies identified in FDA Form 483 issued at close of inspections.

FY17 Sponsor/Monitor/CRO

Common S/M/CRO Deficiencies*

- Inadequate monitoring
- Failure to bring investigators into compliance
- Inadequate accountability for the investigational product
- Failure to obtain FDA and/or IRB approval prior to study initiation

Inadequate Monitoring (sponsor Oversight) unchanged since 2013 risk-based monitoring (RBM) approach changes

Too early to tell the benefit of RBM for compliance?

*Sponsors, Contract Research Organizations, and Monitors (CP 7348.810) deficiencies identified in FDA Form 483 issued at close of inspections.

Most Significant Audit Findings are Linked to the Following:

Not Following the Protocol

- **Deviations**
  - Consent
  - Screening
  - Endpoint procedures
  - Investigational product
- **Preventable**
- **Anticipated**
- **Effective Management of Issues (later in the training)**

Inadequate Documentation

- **Adverse Events**
  - Documentation Completeness
  - Discrepancies Between Source
- **Informed Consent**
  - Incomplete Forms
  - Poor Documentation of Process
- **Duplication and inaccuracies between EMR and study source**

Define GCP Issues That Matter

- What is an Issue That Matters?
- How are they expected to be handled?
- Case Example
- Questions and Answers

Focus on What is Essential

ICH E6 (R2) ADDENDUM
5.0 Quality Management

- *Implement a system to manage quality throughout all stages of the clinical trial*
- ***Focus on trial activities essential** to ensuring human subject protection and the reliability of trial results.*
- *Methods used should **be proportionate to the risks***

Quality management includes:

- *Design of efficient clinical trial protocols,*
- *Tools and procedures for data collection and processing*
- ***Collection of information that is essential to decision making***

What MATTERS, Prevent Issues That Matter

ICH E6 GCP

5.20 Noncompliance

- *5.20.1 Noncompliance with the protocol, SOPs, GCP, and / or applicable regulatory requirement(s) by:*
  - ***an investigator/institution, or***
  - ***by member(s) of the sponsor's staff***

  Should lead to prompt action by the sponsor to secure compliance.

ICH E6 GCP(R2)

5.20 Noncompliance
ADDENDUM

- *When significant noncompliance is discovered, the sponsor should:*
  - *Perform a **root cause analysis** and implement appropriate **corrective and preventive actions**.*
  - *If required by applicable law or regulation the sponsor should inform the regulatory authority(ies) when the noncompliance is a serious breach of the trial protocol or GCP.*

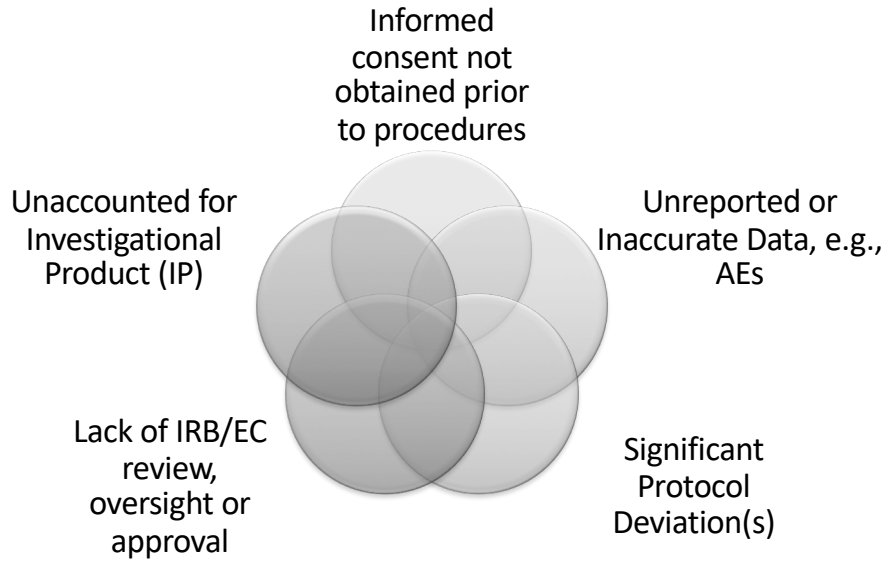
And the FDA says in Investigator Warning Letters . . .

- *Your response is inadequate in that **you did not describe a corrective and preventive action plan.***
- *Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to prevent the recurrence of these violations in future clinical studies.*

What is an Issue That Matters? Definition

- Issues that **considerably impact**:
  - **patient safety, rights, and well-being;**
  - **data integrity and/or scientific rigor;**
  - **compliance with regulatory requirements; and/or**
  - **trust in the clinical research enterprise.**
- **Examples?**

Escalation & Issues That Matter



Question (for Sites/Sponsors/CROs/IRBs/Vendors)

At an organizational level

- **Do you have a clear definition of what are significant issues that require escalation and cross functional action planning?**
- **Is this supported throughout your clinical quality system (across departments / projects)?**
- **If yes, where? Is it working for you?**
- **Common weak links**

Question

What is the main reason we find out **why** an issue that matters occurred?

a. So the deviation will not happen again

b. To ensure properly assigned interventions

c. To document the cause in the study file

Issues That Matter Management Process (ALCOA)

- **Identify non-compliance (issue that matters)**
  - Escalate (report, notify)
  - Immediate Action (ensure subject safety), if applicable
  - Define Issue
- **Investigate the root cause of the problem**
- **Identify actions needed to correct and prevent recurrence**
- **Confirm that the actions are completed**
- **Monitor that the actions were effective**

Issues That Matter Management Process (continued)

Also:

- Ensure follow-up is planned to re-evaluate the situation and effectiveness of the intervention (action plan)
- Ensure that information is disseminated to the appropriate people, e.g., ethics committee, compliance, investigator
- Submit information for management review on identified problems and actions taken for involved stakeholders
- Process is not necessarily linear or completed at the same time
- Anyone involved in oversight activities needs training, practice and support to perform these activities

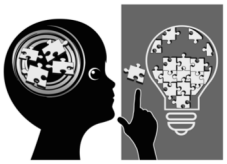
Example Discussion

- You are one of 50 sites globally.
- Vaccine study that requires multiple visits and doses. Dose dependent on subject health assessment /labs.
- 45 subjects enrolled at your site.
- Only 2 AEs have been reported in the eCRF across all subjects.
- CRO monitoring has been regular and with only minor issues.
- Sponsor audit revealed significant documentation deficiencies.
- Only 2 subjects have documentation related acceptable health status for subsequent vaccines.
- The CRO monitor followed up after the audit and documented that they "retrained" your study coordinator on the protocol requirements.
- Monitoring Visit report/ follow-up letter review notes:
  - The monitors requested you place a "note to file" in the subjects' charts noting the deviation and investigator perceived health status.
  - The monitors requested the study coordinator at the sites to report the issue to the IRB.

Example Discussion (continued)

From what you know:

- Is there an Issue That Matters? Why?
- Handled Adequately? Why or Why Not?
- Does the management of the issue that matters include all elements of the process to manage an issue?
- What is missing or inadequate?
- More you need to know?



Based on Using the Issues That Matter Management Process - Version 2

- The issue was discussed internally at the site and escalated as required.
- The root cause was determined to be that the investigator documented when there was an AE, but not when the subject was stable.
- The source document prompt did not include a confirmation question of the subject's health. The source was updated with a version date in the footer.
- During a staff meeting the issue was discussed related to the potential for other studies and how this could be a risk for lack of documentation.

The study coordinator did not complete the note to files as requested by the monitor. Rather the investigator noted in the subject's source that the subject had no AEs and per protocol was eligible for the next vaccine. This is not contemporaneous, so it is dated real time.

Associated meeting minutes and training documentation links to the actions of the investigator. The investigator stated outside of research, the EMR does not ask for verification of health status, but rather negative charting.

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Inaccurate, Incriminating, and Incomplete NTF (Examples from FDA Warning Letters)

- *In addition, we note that a CV for Ms <<redacted>> was never obtained as documented in a Memo to File signed by you and Ms. <<redacted>>; therefore, it is not clear if Ms. <<redacted>> was qualified to perform the duties that were delegated to her."*
- *Nine months later the subject signed the correct version assent; the coordinator back dated the signatures as stated in your note to file dated almost a year later.*

Inaccurate, Incriminating, and Incomplete NTF (Examples from FDA Warning Letters) continued

- *125 NTF generated for deviations noted at the site.*
- *"Our investigation found that [sponsor] failed to take any action to secure compliance while the study was ongoing except to generate numerous memos to file after all subjects had completed the study."*
- *"These memos to file were to serve as a mechanism to train the investigator. . . because the majority of memos were generated after all subjects had completed the study, there wasn't much value in training the clinical investigator."*
- *"As noted previously, memos to file are inadequate to address the falsification (backdating) of study documents."*

Documentation of Investigator Non-compliance Management (Issue That Matters)

- Ensure the Issues That Matter Management Process is followed
- Should link to the investigator/sponsor/IRB correspondence
- Should have acknowledgement from the Investigator
- Requires study team coordination and tracking
- Included in action item tracking and management
- Documentation at site and sponsor develops over time
- After the study is done it is up to the investigator/site to evaluate that efforts were effective or repeat the process

"If it's not documented, it didn't happen"
"If it's not written, it didn't happen"
"If you can not tell who entered the info, it did not happen"

Record related issues are among the most common deficiencies in regulatory site inspections

Did you know?

ALCOA/ALCOA-C/ALCOACCEA?

ALCOA FDA 2007 Guidance for 21 CFR Part 11	**ALCOA-C** ICH E6(R2) Section 4.9.0 Investigator Responsibilities 2016	**ALCOACCEA** EMEA CDISC 2007 Reflection paper
Attributable	Attributable	Attributable
Legible	Legible	Legible
Contemporaneous	Contemporaneous	Contemporaneous
Original	Original	Original
Accurate	Accurate	Accurate
	Complete	Complete
		Consistent
		Enduring
		Available when needed

In any form . . . Paper or Electronic

ALCOA-C Common Areas of Challenge?

- A: Attributable
- L: Legible
- C: Contemporaneous
- O: Original
- A: Accurate
- C: Complete

ADDENDUM

1.63 Certified Copy

A copy (irrespective of the type of media used) of the original **record that has been verified** (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Warning Letter – Investigator

Failed to maintain adequate and accurate case histories

- For 3 subjects, the dates next to the subjects' signatures on the consent forms were initially dated 6/8/06 and then changed to 6/15/06. For subject 8202, the date was then revised back to 6/8/06 and multiple date changes were made to most of the pages in the Screening Visit Source Documents for these subjects. No documentation was provided to explain these changes
- For 5 subjects, Karnofsky performance scores were revised by the study coordinator at various times for various study visits without documentation explaining the changes

Ref. No. 09-HFD-45-03-03

Questions? Thank you! Summary

- Discuss latest **GCP updates and audit findings** significance to investigati best practices
- How to best avoid an **ssues that matter** for inspection readin
- Apply the **ALC C** rt essential regulatory and source

THANK YOU!

SAM Sather
Clinical Pathways, LLC
samsather@clinicalpathwaysresearch.com