PREP Course 27: How to Avoid Common Audit Findings and Reduce Risk for Your Site?

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CME Disclosure Statement

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• Course Director and Course Planner, Kevin Tracey, MD and Tina Chuck, MPH have nothing to disclose.

• Sharon Hochman and JiYoung Choi have nothing to disclose.
Objectives

Discuss how to avoid today’s most common audit findings through practical, memorable application of the current Good Clinical Practice (GCP) E6 guideline, and as a result reduce risk to your research site.
Definitions related to Clinical Trial Audits & Monitoring

What are the Most Common Audit & Monitoring Findings

How to Reduce Risk?
Definition of Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
Definition of Monitoring

Monitoring is defined as “the act of overseeing the progress of a clinical trial, and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s)”  
[ICH 1.38]
Types of Quality assurance reviews

Federal
- OHRP
- FDA

Internal
- ORC
- Research Team
- Department Staff

External
- Sponsor
- Independent
- Cooperative Group
Common Audit Findings
Findings from FDA Inspection

Warning Letters

Lack of Investigator Oversight

Feb 21, 2014
NY, NY

- Failed to personally conduct or supervise the clinical investigation [21CFR312.60]

Lack of Safety Monitoring/Adequate Case Histories

Jul 17, 2014
Dearborn, MI

- Failed to protect the rights, safety, and welfare of subjects under your care [21CFR312.60]
- Failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21CFR312.62(b)]
FDA inspection occurred in June 2013 and protocols were reviewed for compliance. It was found that the site failed to personally conduct or supervise the clinical investigations 21 CFR 312.60 and failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60 and 21 CFR 50.20.]
Lack of Investigator Oversight warning letter

Feb 21, 2014 NY, NY

Failed to personally conduct or supervise the clinical investigations 21 CFR312.60

- The letter stated that When the PI signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trials, they agreed to take on the responsibilities of a clinical investigator at your site. The general responsibilities as a clinical investigator include ensuring that the clinical trials are conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60].

While certain study tasks can be delegated to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities.

It was found that the PI didn’t supervise adequately the individuals that were delegated specific tasks.
Failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60 and 21 CFR 50.20.

- Informed consent wasn’t obtained from 28 of 50 subjects enrolled in the protocol. 10 subjects were enrolled and given investigational drug prior to each signing the informed consent.

- The site sent a written response to the FDA and indicated that after serious noncompliance and the potential risk to subjects was discovered, on August 19, 2011, the CUMC IRB and the Department suspended Protocol (b)(4), the Department performed an audit of all available study records and, at the direction of the IRB, all 50 subjects were notified of the violations in the consent process and study procedures.

- A corrective action plan was put into place however it was deemed inaccurate by the FDA as it appears the corrective actions appear to represent actions taken by Columbia University Medical Center and do not reflect corrective actions that the investigator had taken.

This failure to obtain informed consent prior to involving subjects in research jeopardizes the safety and welfare of subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.
FDA inspection occurred for the investigational drug Albiglutide. 7 protocols were being monitoring as part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.
<table>
<thead>
<tr>
<th>Date</th>
<th>Location</th>
<th>Issue Description</th>
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<tbody>
<tr>
<td>Jul 17, 2014</td>
<td>Dearborn, MI</td>
<td>Failed to ensure that the investigation was conducted according to the investigational plan [21CFR312.60]</td>
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<td>- The letter states that The protocol states that the site will contact the subject and schedule a return visit within 2 weeks from the time the site received confirmation of the laboratory results indicating a needed dose adjustment. You failed to adjust the dose of Albiglutide within 2 weeks of receiving the laboratory results for Subject 006. Subject 006 had an HbA1c of 8.4% at Week 24 on November 9, 2009. However, you did not adjust the dose of Albiglutide until December 23, 2009, which is a delay of over 1 month.</td>
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<td>- In your September 2, 2013, written response to the Form FDA 483, you indicated that the delay in dose adjustment occurred due to the subject’s noncompliance, despite site staff instructions. However, you have not provided any documentation of your or your staff’s attempts to contact the subject to schedule a return visit for dose adjustment within the 2-week time frame.</td>
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<tr>
<td>Jul 17, 2014   Dearborn, MI</td>
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**Failed to protect the rights, safety, and welfare of subjects under your care [21CFR312.60]**

- The letter stated that Subject 005 in Protocol GLP112756 was to receive an unscheduled replacement investigational drug, administered via a pen, at Visit 24/Week 16 on September 28, 2011. However, your study coordinator dispensed the wrong pen to the subject. The study coordinator placed a request into the Interactive Voice Response System (IVRS) for a replacement pen that was intended for Subject 006 enrolled in the same protocol, but the coordinator dispensed that pen to Subject 005.
# Findings from ORC Audits and Monitoring Visits

## Consent Process & Documentation
- Subjects were consented using unapproved consent forms.
- Consent process was not documented.
- Missing signed ICF

## Protocol Compliance & Subject Case Reviews
- Missing protocol required lab tests & assessments.
- Baseline and follow up tests performed out of given window.
- Discrepancy in accountability log.
- Not following randomization process as prescribed
- Not capturing which device was assigned to each patient
Findings from ORC Audits and monitoring visits

Safety data & Eligibility of subjects
- Lack of documentation and assessment of AE’s by clinicians
- Unreported AE’s
- Lack of source to verify eligibility
- Eligibility does not meet per protocol or is outside study window

Regulatory Compliance/ IRB/ GCP
- Protocol deviations were not submitted to the IRB. [HRPP Policies and Procedures]
- Inappropriate delegation of tasks
- Staff trainings missed or not updated
- Lapses in IRB approval
Tips to Reduce Errors/Mistakes: Enhancing Protocol Adherence

• Protocol design
  ➢ Focus on essential data points
    ❖ Explain significance in terms of study objectives (efficacy/safety) or subject protection
  ➢ Avoid ambiguity and vagueness
    ❖ Inclusion/exclusion criteria
    ❖ Adverse experiences
Tips to Reduce Errors/Mistakes: Enhancing Record Quality

- Clearly understand what records are to be maintained and how they should be completed
  - Original source data for critical study endpoints
  - Investigator verification on source documents
  - File enrollment notes
  - File study visit progress notes
  - File Case Report Forms
  - All records should meet the ALCOA test
## Tips to Reduce Errors/Mistakes: Enhancing Record Quality

<table>
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<th>A</th>
<th>• <strong>Attributable</strong> – Does the documentation clearly demonstrate who created the record and when, what happened, and when it occurred?</th>
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<tbody>
<tr>
<td>L</td>
<td>• <strong>Legible</strong> – Can the information be easily read and understood?</td>
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</table>
| C | • **Contemporaneous** – Was the information documented with timeliness?  
• **Complete** – Does the documentation include all of the necessary information? |
| O | • **Original** – Did you maintain the “source” of the information? (see GCP Glossary, Sections 1.51 and 1.52) |
| A | • **Accurate** – Does the information represent what actually happened? |

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Adapted from - FDA - GUIDANCE FOR INDUSTRY - COMPUTERIZED SYSTEMS USED IN CLINICAL TRIALS - ALCOA  
Tips to Reduce Errors/Mistakes: Enhancing Record Quality

• Minimize the need for transcription
• Document protocol required procedures
• Keep a regulatory binder
• Don’t throw anything away especially original documents
• Communicate with the IRB, ORC, and CRS
• Be audit ready – FDA will be inspecting the records
Tips to Reduce Errors/Mistakes: Enhancing Record Quality

- Any changes or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry; this applies to both written and electronic changes or corrections. The investigator should retain records of the changes and corrections (GCP E6 4.9.3)
- No Correction fluid or pencils should be used
- All staff working on the study should be delegated appropriately
Tips to Reduce Errors/Mistakes: Enhancing Record Quality

- All lab results should be assessed for clinical significance
- Staff obtaining consent of the subjects must understand the consent process and documentation requirements.
- Recording AEs appropriately and looking for trends over time
- Familiarity with your protocol and the adverse events reporting criteria and timeframes
How to Reduce Risks?
Building Quality into Clinical Trials

Quality is characterized by the ability to

- Effectively and efficiently answer the intended question about the benefits and risks of a medical question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure

While

- Ensuring protection of human subjects

Definition from October 2008 presentation on CTTI by Dr. Rachel Behrman, CTTI Co-chair and then Associate Commissioner for Clinical Programs, FDA (presently director of CDER’s Office of Medical Policy)
Building Quality into Clinical Trials

Elements of a quality clinical study include:

- Scientifically valid and ethically sound experimental design
- Adequate protection of subject rights, safety, and welfare
- Qualified personnel
- Adequate monitoring
- Current, complete, and accurate data

PDCA Cycle

- **Act**
  - Standardize
  - Continual Improvement

- **Plan**
  - Policy
  - Resources
  - Objectives

- **Check**
  - Audits
  - Monitoring
  - Verifications

- **Do**
  - Processes
  - Training
PDCA: Plan

• Study and Site Feasibility:
  ➢ Site capacity, Study Team/Resources, Accrual

• Protocol Design:
  ➢ Endpoints, Eligibility Criteria, Data Quantity, Monitoring, Randomization, IP handling and administration
PDCA: Plan

• Patient Safety:
  ➢ Informed Consent, Withdrawal Criteria, Subject Retention, Signal Detection and Safety Reporting, DMC and Stopping Rules

• Study Conduct:
  ➢ Training, Data Recording and Reporting, Data Monitoring and Management, Statistical Analysis
PDCA: Do

• Develop Protocol:
  ➢ Simple & promote collection of Quality Data without compromising study objectives
• Understand Institutional Policies, Clinical Research Guidelines, Regulations
• Generate & Follow Departmental SOPs
• Train on Institutional Mandatory & Study Specific Trainings
PDCA: Do

• Implement a process to oversee trials through out the study period (study start to end)
• Create and Utilize applicable worksheets, checklists, & CRFs to collect minimal necessary data
• Implement processes for data safety monitoring
• Delegate tasks to qualified study personnel
PDCA: Check

• How are the processes?
  ➢ Consent & Documentation
  ➢ Monitoring
  ➢ Oversight & Team Meeting
  ➢ Communication (internal & External)

• Way to Improve a process?
  ➢ Study Review
  ➢ Team Review
PDCA: Act

• Corrective Action/ Preventive Action
  ➢ Correct errors & Plan to stop recurring.

• Improved Processes
  ➢ Reduce time & resources

• Protocol/ Consent Amendments
  ➢ Better information/Clear direction

• Departmental SOPs update
  ➢ Better standardized procedures
PDCA Cycle

Continual
Quality
Improvement
Case Study #1

It is noted during a monitoring visit that the investigator did not document review of the subject’s abnormal labs by an investigator.

The PI states that in his clinical practice, labs are reviewed on-line and action is taken when needed.

To avoid future issues, what would you advise the site does before the next monitoring visit to ensure compliance?
As you are performing a QA review on your study files, you find the following:

1. Dates for the subject, the witness and the investigator on 6 consents were written with the same color ink and in the same handwriting.
2. Seven of 12 subjects did not make a selection for future use of specimens on their consent form.
3. The enrollment note for 6 subjects was written the day before your QA review, but you note that consent was obtained over 3 months ago.

Which ALCOA deviations can you identify?
Case Study #3

An investigator initiated study that is more than minimal risk study has a safety evaluation plan per the protocol to be done every six months at a team meeting. The process of the safety evaluation for this study is to have an initial review of all AEs and lab results of the subjects by the PI and a co-investigator independently. Afterwards, in a team meeting both evaluations are reviewed again and any different opinions and safety trending are discussed further to make a congruent decision. On average, the study has enrollment of 25 subjects monthly.

Since the safety evaluation is scheduled every six months, the investigators wait a couple of months to review and evaluate subjects’ charts for safety except for any serious adverse events or unanticipated problems. When it is a time to review, they spend an extensive amount of time to go through each subject’s charts for any adverse incidents and lab results for any clinically significant abnormalities. One investigator notes the reviews on a post-it to present at the meeting. Another investigator noted on a notepad to summarize at the meeting.
Case Study #3 continued

- What do you think?
- Does this study have an appropriate data and safety monitoring plan?
- Do investigators appropriately perform safety evaluation?

The safety monitoring plan seemed to have an appropriate monitoring plan. Any AEs and/or Lab results should be reviewed and evaluated by an investigator in a timely manner. They should have been reviewed all AEs and lab test results on a regular basis as oppose to review them all at once.

- What would be the better way to shorten review time of safety evaluation?

Have system to evaluate the safety data in a timely manner. To be effective and efficient of reviewing safety data, utilization of AE log is recommended. By utilizing AE logs, study team can save time of gathering and evaluating data that should be done on a regular basis. In addition, the investigators should document their evaluations in an appropriate forms and/or templates and file in a regulatory binder as a proof of review.

Additional Tip: Remember to document outcome of safety evaluation at the meeting. What was the outcome from the meeting? Was there a need of updating safety information in the protocol? Should eligibility need to be updated? Make sure to document and file it!