CAPA Plans: Solutions, not Blame

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February 25, 2014—Rochester NY
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The information regarding FDA inspections contained in this presentation was obtained from publicly available sources. My interpretation of this information is also my own.
Objectives

- What is the purpose of a CAPA plan?
  - Who should develop the CAPA?
- Why does conducting effective root cause analysis matter?
  - How, what, where, when and why matter more than who
- Applying the concepts and techniques to actual audit findings
  - Audience participation!
Corrective and Preventive Action Plans

- Something happens that
  - Is harmful or *potentially* harmful
  - Isn’t supposed to happen at all
  - Doesn’t happen the way it is supposed to
  - Is unexpected
  - Causes other problems
  - We don’t want happening again
Something happens....

1. Stop for my coffee
2. Come out of coffee shop to find a large dent in my car door....

“Good Morning”?

No such thing.
Purpose of CAPA

**Corrective Actions** = **Reactive Actions**

- **Correct** the immediate problem
  - It’s morning, I haven’t had my coffee yet….
- **Determine** what caused the problem
  - Again, it’s morning….
- **Eliminate** (correct) the source of the problem so that it does not happen again
  - Hey, just don’t get out of bed!
Purpose of CAPA

**Preventive Actions = Proactive Actions**

- Ensure the **Cause** and the problem does not happen again
  - On windy mornings....
- **B**lock the cause (or potential causes)
  - Use the drive through....
- **A**void the problem (or problems like it)
  - No more dents and dings (and no more ill temper)
Purpose of CAPA

- The “some things” that can happen in clinical research are far more serious
  - **Harm to the current study subject**
  - Harm to future study subjects
  - Inaccurate, incomplete, unreliable data
  - Drug, medical device, biologic may be approved (or approval may be denied) inappropriately
  - **Harm to future patients**
Who develops the CAPA?

- Why can’t “they” just tell “us” what to do and exactly how to do it?
  - How does “because they said so” thinking make you feel?
- Clinical investigator responsibility
- Practical, circumstantial expertise
  - One solution does not correct or prevent every problem
Why “root cause analysis”?

- Back to the coffee shop…..
- What if I had just gotten in my car, swearing at morning, swearing at jerks in parking lots, wishing I’d never gotten out of bed?
Why “root cause analysis”? 

To fix the problem effectively.....

it’s important to understand what the problem is
Why “root cause analysis”?

- Tylenol for knee pain (immediate correction) but what about the underlying cause (root cause) if that pain is frequent and effects mobility?
- Wouldn’t you want to eliminate that cause and avoid possibly falling or requiring surgery?
Analyze this....

- **Audit Finding:**
  - “The Drug Dispensing/Compliance Log (Form 16) for Visits 1, 3, and 4 do not include documentation of the Bottle Identification Number that was dispensed.”

- **CAPA Plan:**
  - “We will be careful to avoid repeating these mistakes.”
The “human” factor

- “Human error” is probably the number one “CAPA” response auditors receive

- Obviously.....
  - We are all human!
  - We all make mistakes (even auditors do!)

- But **why**?
  - Important to understand “why” ≠ “who’s to blame?”
Root Cause Analysis

- **The ‘5 whys’ of a problem**
  - ‘Why’ tends to make people ask ‘who’ before they ask more important questions

- **Remember, the purpose of a CAPA is to**
  - Correct, determine cause and eliminate the problem
  - Ensure the cause is blocked and similar problems avoided
Root Cause Analysis

The 5 ‘Ws’ (and be specific) instead

- What happened?
- Where did it happen?
- When did it happen?
- Who was involved?
- Weight (impact) of the problem?
Our Earlier Audit Finding

- “The Drug Dispensing/Compliance Log (Form 16) for Visits 1, 3, and 4 do not include documentation of the Bottle Identification Number that was dispensed.”
Incomplete drug dispensing log

- **What exactly happened?**
  - A drug dispensing log was not completed for three visits – 3 out of how many visits?
  - Is the log required per the protocol or study procedures? → Yes

- **What is the purpose of the log?**
  - To track specifically which bottles of drug by number were dispensed to which patient and at what visits
  - Why is that important?
Incomplete drug dispensing log

- **Where did this occur?**
  - Is the log completed where study subjects are seen (and where are they seen)?
  - Or…. *Are study subjects seen in the clinic but the log is filled out later in an office?*

- **When did it occur?**
  - 3 visits (1, 3, and 4) out of 5
  - What was different about these visits?
    - *Study coordinator did not go straight from clinic to study office*
Incomplete drug dispensing log

- **Who was involved?**
  - Study coordinator
  - Clinical investigator - Did not review and sign dispensing log

- **Impact (weight) of this problem**
  - How many study subjects are enrolled in this study?
  - How many visits was this a problem at?
    - One subject enrolled, 3 out of 5 visits **versus**
    - Ten subjects enrolled, 3 our of 5 visits for just this one subject
Root causes

- Investigator and study coordinator unaware of purpose of Drug Dispensing Log
- Log kept in office but study subjects seen in clinic
- Impact: Happened on first (and only) enrolled subject – Hmmm?....
Our Earlier CAPA

“We will be careful to avoid repeating these mistakes.”

- What might the CAPA be now that the causes are understood?
  - To correct the immediate problem (bottle identification numbers not logged), *what might be done*?
  - To eliminate the source (causes) of the problem, *what might be done*?
  - To prevent the causes (and similar problems) from re-occuring, *what could be done*?
Frequency and Impact

- Two important factors to consider in a root cause analysis and to assist with developing effective CAPA are
  - *Frequency* of the problem
  - The *impact* (or potential impact) of the problem
Frequency and Impact

- Why is this important to root cause analysis and to effective CAPA? Back to “human error”…..
  - If a study related form is filled out wrong once or twice, or only filled out wrong by one person, is that different than a form being filled out wrong repeatedly or filled out wrong by numerous people?
  - Does an effective CAPA depend on the answer to these questions?
Frequency and Impact

1) What if someone in the US records the date as 25/2/14, what is the impact?
2) What if they record the date as 3/5/14 but it is a global study, is that different?
   - Is an effective CAPA different for 1) than it is for 2)?

One way to help evaluate the difference is to assess the risk
Frequency and Impact = Risk

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- Note that Impact is weighted, as it should be relative to subjects rights, safety and welfare

**Frequency and Impact = RisI**

* 25/2/14 – US Only Study *

- Fairly obvious what the correct date is, right?
- Assume it happens occasionally *for a study visit*

# 3/5/14 – Global Study #

- Could be March 5th, could be May 3rd
- Problematic anytime the month and/or day are ≤ 12?

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- Continual: 5
- Frequent: 3
- Occasional: 2
- Rare: 1

- Continual impacts can be extremely severe.
- Frequent impacts are problematic but not catastrophic.
- Occasional impacts have minor consequences.
- Rare impacts are negligible.
Frequency and Impact = Risk

FDA Warning letter issued 19 Nov 2013 to Sreedhar Samudrala

- Two clinical trials of an inhaled medication for moderate COPD in patients with cardiovascular disease
  - “Failed to ensure that the investigation was conducted according to the investigational plan [protocol] per 21 CFR 312.60”
FDA Warning Letter, 11/19/13

- Protocol #1 required a FEV$_1$/FVC ratio of $\leq 0.70$ at screening
  - 11/31 subjects did not meet this criteria
- Protocol #2 required FEV$_1 \geq 50\%$ and $\leq 70\%$ of predicted normal values calculated using NHANES III reference equations at screening
  - 4/31 subjects did not meet this criteria (3 above, one below the requirement)
Also, in protocol #2, one subject did not meet the age criteria for enrollment and one subject was not being treated for any of the cardiovascular conditions required for enrollment per protocol.

How would you assess the frequency and impact of these inspection (audit) observations?
## Frequency and Impact = Risk

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Dr. Samudrala’s written response stated, “Investigators are required to sign a document prior to randomization that states [whether] Inclusion/Exclusion Criteria have been met. All investigators and study staff personnel were re-educated. A new spirometer was purchased to replace the spirometer that was inadequate for the study.”
Not surprisingly, the FDA stated, “Your response is inadequate because it is insufficiently detailed with respect to your corrective action plan. You have not provided details regarding the document that investigators are required to sign, and you have not submitted a copy of that document. You also have not provided details or documentation regarding the re-education that took place. Without this information, we cannot assess whether these corrective actions are adequate to prevent further occurrences of this type of violation.”
FDA Warning Letter, 11/19/13

- Do you think a root cause analysis was done?
- Do you think “signing a document” will correct and prevent re-occurrence?
- And who said anything about an “inadequate spirometer”??
Effective CAPA Require Facts

- **Facts** are necessary and critical for effective problem solving
  - Ask the people involved
  - Go to the location where the error occurred
  - Look at the documents
  - It’s about what happened, how and why it happened, not *who’s to blame*
Laboratory aide cuts herself with a pathology knife…. 

- She must need “re-training”…. 
  - Asking the 5 whys revealed: The knife was left by the sink; the area was not cleared from the previous day; clearing is not a habit; there is no procedure for how/when to clear the cleaning area

- Interviewing her to assess What, Where, When it happened revealed…. 
  - History of intimidation by physicians in her previous department so she didn’t want to move it
  - Weight (impact): She needed 15 stitches!

- Looking at the knife…. 
  - Revealed the cutting edge was not readily apparent

Source: Techniques for Root Cause Analysis, Patricia M Williams, BUMC Proceedings 2001;14:154-157
Effective CAPA

- How do you know you have the right root cause?
  - Go back to all your ‘Ws’ and see if the causes you identified explain the problem if.....

- Root causes of incomplete drug dispensing log were determined to be:
  - Locational (needed to be in the clinic)
  - Vocational (PI and study coordinator did not understand purpose)
  - Procedural (PI was not required to sign a protocol required form)
Effective CAPA

- Be **SMART**
  - **S**pecific, **M**easurable, **A**ttainable, **R**elevant, **T**ime-bound/Trackable
  - Describe not just *what* you’re going to do but *how*, by *when* and by *whom*

- For **high risk** problems, strongly advisable to include a plan to check at a later date to ensure your CAPA was effective
  - Plan to fail....
Let’s Look at an Audit Finding Together

- The protocol states, “If a non-anemic subject becomes anemic during the study, this will constitute a condition which precludes further participation in the study, and the subject will be paid for participation to date. Anemia is defined as hemoglobin below the lower limit of normal.” The following three subjects are documented as becoming anemic during the study in the protocol deviation log but were not withdrawn in accordance with the protocol.
Let’s Look at an Audit Finding Together

a. Subject 001: Labs were suspended when the subject was found to be anemic at Visit 2. The subject’s PCP re-ordered labs with a result of 35. Blood draws were then resumed.

b. Subject 007: This subject was found to be anemic based on the blood draws completed at Visit 12. Blood draws were initially suspended and then resumed at Visit 16, which with the subject remained anemic. Further blood draw were discontinued.

c. Subject 010: This subject was found to be anemic based on blood draws completed at Visit 4. Blood draws were discontinued until the subject was assessed further. [No follow-up on this case documented in the protocol deviation log].
Let’s Look at the Investigator’s Response

- Investigator’s response: “Because participation in the trial yields many data points in addition to the labs, these subjects were not discontinued as their input was still of value to the study. These instances, and any others that occur, will be listed as protocol deviations and reported to the RSRB. Regarding Subject 010 who was anemic, a follow up will be conducted on this subject, and reported to the RSRB under separate cover.”
I need a note taker to volunteer…. 😊

- How would your 5 ‘Ws’ proceed?
  - What happened?
    - Be specific….be more specific….keep going
  - Where?
  - When?
  - Who was involved?
  - Oooops, missing a W…….
Let’s Look at an Audit Finding Together

**Weight (impact)?**

- Let’s assume the “frequency” was 3/10 subjects
  - But what about that statement in the Investigator’s response: “These instances, and *any others that occur*….”?
- Let’s assume it is a investigational drug to treat ulcerative colitis….
  - How would you assess impact of not withdrawing non-anemic subjects that develop anemia while on study?
  - Is your risk assessment *different* if it is an investigational drug for knee pain?
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Let’s work on the CAPA together

Corrective Actions = Reactive Actions

- **Correct** the immediate problem
  - What might that be?
- **Determine** what caused the problem
  - Your 5 ‘Ws’
- **Eliminate** (correct) the source of the problem so that it does not happen again
  - What are your proposed corrective action(s)?
Purpose of CAPA

Preventive Actions = Proactive Actions

- Note: These may, or may not be the same as some your corrective actions
- Ensure the **Cause** and the problem does not happen again
  - Would checking effectiveness at a later date be appropriate for this situation?
- **Block** the cause (or potential causes)
- **Avoid** the problem (or problems like it)
To Summarize....

- Problems in clinical research such as non-compliance with the protocol, Investigator’s Brochure, regulations, IRB approval, study procedures or your own procedures
  - Creates risk for current and future study subjects
  - May impact approval (pro or con) for drugs, medical devices, biologics
  - Creates potential risk for future patients who may (or may not be able to) receive the treatments we’re researching today
To Summarize….

- Audits help to identify problems (or potential problems)
  - Protect research subjects rights, safety and welfare
  - Educational for study staff
  - Educational for the IRB
- Effective CAPA correct and prevent such problems
  - Really understanding the facts and identifying the cause(s) is critical
- It’s about solutions, not blame!
Questions?
Contact Information

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“It takes less time to do a thing right than to explain why you did it wrong.”

- Henry Wadsworth Longfellow