



Clinical Research Seminar

HOW TO DEVELOP A CORRECTIVE AND PREVENTIVE ACTION PLAN (THAT EVEN THE IRB AND FDA WILL LOVE)

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Case

- Protocol requires urine dipstick test be performed at Screening; Baseline; Weeks 4, 8, 12, 16, and 24; (24 hr urine test done if dipstick protein ≥30 mg/dL).
- Dipstick is a safety assessment... test drug dose may be changed, so missed protocol-required urine dipstick tests compromise subject safety.
- Subjects 1005 and 1018 did not have urine dipstick results recorded at baseline. Subjects 1021 and 1045 did not have urine dipstick results recorded at weeks 8 and 12 despite having elevated protein levels at week 4.

Objectives

- 1) Describe what a CAPA plan is and when it is required for studies approved by the BMC/BU Medical Campus IRB.
- 2) Describe the IRB process for reporting Major Deviations and Unanticipated Problems and when a CAPA is needed in the submission.
- 3) Describe how to develop a CAPA, including a "Root Cause Analysis."
- 4) List elements of a strong CAPA and provide examples of insufficient CAPAs.

What is a CAPA?

- CAPA = Corrective and Preventive Action Plan
- Documents and communicates how a problem was fixed and controlled
 - Outlines <u>REACTIVE</u> steps needed to correct the immediate problem.
 - Analysis to <u>IDENTIFY</u> the cause(s) of the problem.
 - Outlines <u>PROACTIVE STEPS</u> needed to prevent the problem from occurring in the future.

When Do You Need to Develop a CAPA Plan?

BMC/BU Medical Campus IRB approved Studies

 HRPP Policy (7.4.5) specifies that a CAPA plan must be submitted when reporting a <u>Major Deviation</u>

(including Unanticipated Problems (UPs) that are also major deviations)

IRB approved Studies with Ceded IRB Approval:

- WIRB/Hummingbird IRB
- Other IRBs (MGH, Other Universities, etc)

Major Deviations

HRPP Policies and Procedures (6.6.5.2) - Major Deviations

- Major Deviations are deviations that may

 harm the participant's rights, safety or well-being, or
 significantly damage the overall reliability of the study data, or
 represent noncompliance with IRB requirements that may be serious or continuing.
- Major deviations must be reported to the IRB within 7 days of the investigator or research staff becoming aware of the event.

Unanticipated Problems

OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

- <u>Unexpected</u> (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRBapproved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- <u>Related or possibly related</u> to participation in the research (meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at <u>a greater risk of harm</u> (including physical, psychological, economic, or social harm) than was previously known or recognized.

When is a UP a Major Deviation - ora Major Deviation and UP?

- When the UP harms or has potential to harm participant's rights, safety or well-being, or
- When the UP Significantly damage the overall reliability of the study data, or
- When the UP Represent noncompliance with IRB requirements that may be serious or continuing.

Algorithm for Reporting Unanticipated Problems, Adverse Events, and Deviations



How are Deviations and UPs Identified?

- Study Team/PI Observation
- Study Self-Audit
 - CRRO Website has tools available (<u>www.bumc.bu.edu/crro/tools/</u>)
 - RPN has slides available from recent self-audit presentation (<u>http://www.bumc.bu.edu/crro/past-rpn-workshops/</u>)
 - OHRA staff available for consultations (CRRO website-consultations)
- External Monitoring (Sponsor/ceded IRB/FDA etc.)
- Internal Monitoring/Auditing (OHRA routine QA Review and For-Cause Audits)
- Subject complaints

Deviations and UPs Reported to IRB via INSPIR RENI Report?



RENI submission

Additional required information for reporting major deviations is:

- A description of the deviation; and
- Identification of whether the deviation resulted in an Unanticipated Problem (reported on the same form)
- <u>Corrective and Preventive Action Plan</u>.

http://www.bumc.bu.edu/ohra/



Corrective and Preventive Action Plan (CAPA)

- A system for resolving quality issues
 - Resolve problem and keep from happening again
- Term originating in manufacturing field
- CAPAs required in FDA device and pharma regulations:
 - "Quality System Regulation" (21 CFR 820.100 and 21 CFR 211)
- Clinical trials/research studies....
 - Complex system
 - Your product is the data
 - Ensuring quality at every step in your study helps to ensure
 - A quality "product" your data
 - Safety of subjects (and ultimately, future patients)

A Research study as a quality system

(paraphrased from 21 CFR 820.100)

- Analyze processes to identify potential causes of "nonconforming product"
- Investigate causes of nonconformities
- Identify the actions needed to correct/prevent problem
- Verify corrective and preventive actions to ensure they are effective
- Implement and record needed changes in methods and procedures
- Ensure information related to quality problems is disseminated to those responsible for assuring quality of product
- Submit relevant information on identified quality problems and corrective and preventive actions for management review
- Document activities and results



A Research study (or organization) as a quality system

- 4 main components of a quality system...
 - Say what you do
 - Do what you say
 - Prove it
 - Improve it



From CTTI Summary of Expert Meeting, 2010, Developing Effective Quality Systems in Clinical Trials: An Enlightened Approach

From FDA Guidance....

The PI should ensure....

"A procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study."

CAPAs are the responsibility of the study PI.....

FDA Guidance Investigator Responsibilities, Oct. 2009

Why a CAPA?

- Documents and communicates how the problem was fixed and controlled
 - Outlines REACTIVE steps needed to correct the immediate problem.
 - Analysis to IDENTIFY the cause(s) of the problem.
 - Outlines PROACTIVE STEPS steps needed to prevent the problem from occurring in the future.

What to do when you encounter a problem

- Assess potential for harm to subject(s)
- Notify PI
- Immediate corrections to protect current subject(s)
- Initial reporting to IRB, Sponsor, FDA, etc. (depending on seriousness)
- Assess causal factors (Root Cause Analysis)
- Implement corrective and preventive actions
- Further reporting to IRB, Sponsor, FDA, etc. to update if necessary
- Evaluate effectiveness of CAPA

Root Cause Analysis (RCA)

- Understand that clinical research studies are complex systems
- Often will have to assess multiple levels/processes/individuals
- Perform as soon as possible after the problems identified
- Include all individuals involved in the error



Root Cause Analysis

- You will put time, energy, possibly money into fixing the problem
- You have responsibility for the rights and welfare of study participants and for the quality of the "product".... your data.
- So it's imperative to do "due diligence" to ensure you understand the <u>true underlying CAUSES(S).</u>
- The key to fixing and preventing problem



Root Cause Analysis

- Data Collection
- Causal factor charting
- Root cause identification
- Recommendation generation/implementation
- Evaluate implementations





Rooney and Vanden Heuvel, Root Cause Analysis for Beginners, Quality Progress, July 2004

Root Cause Analysis

- Identify the problem....
- Review processes, interview those involved
- What happened?
- How did it happen?
- Why did it happen? When? Where?
- What were contributing factors?
- Who was involved?** Who was affected?
- How often did it happen? How many were affected? How serious is the problem? How extensive is the problem?
- Usually these questions will lead you to an underlying causal process



"5 Whys" technique

- State the problem: I missed a meeting at work
 - Why 1: I left my house late
 - Why 2: I overslept
 - Why 3: My alarm clock didn't ring
 - Why 4: My alarm clock was broken
 - Why 5: My dog's tail swept my alarm clock off the nightstand during the night



Fishbone diagram technique

- Show causes of specific problem/non-conformity
- Map out various levels
- Cause/effect



F. Feldstein, Investigate; CAPA Management in Clinical Research, Sept. 2014

Insufficient detail on CAPAs.

- "You have not adequately addressed how you will improve your supervision of study staff in future..."
- "You did not specify the corrective actions you will take to address these violations in the future..."
- "... you indicate that you have the following corrective action: Investigators are required to sign a document prior to randomization that states that Inclusion Criteria have been met. Your response is inadequate because it is insufficiently detailed You have not provided details regarding the document that investigators are required to sign and you have not submitted a copy of that document."
- "However, although you promised certain corrective measures in your response, you did not specifically address your failure to collect the protocol-specified screening blood samples."



Describing corrective actions without developing SOPs

 "Your corrective actions to ensure reporting of deaths to FDA and IRB include: reconfiguring your team, holding an IRB training for staff, informing staff that you must be notified immediately of any subject's death....

We are unable to undertake an informed evaluation of your response because you did not provide documentation further explaining your corrective action plan, for example, an SOP that shows your staff is to notify you immediately upon becoming aware of any death...."



Insufficient detail to determine if CAPA will correct the problem

 "You indicated that you have added a "clinical trials link" to your site's EMR to provide access to study information for study staff..

Your response is inadequate because you did not provide sufficient information to enable us to evaluate the adequacy of your corrective action plan..... it is unclear how adding a "clinical trials link" to your site's EMR will ensure that protocol requirements will be met for studies conducted at your site."



Not providing detail on corrective actions that the clinical investigator him/herself is taking

 "We are concerned that the majority of the corrective actions appear to represent actions taken by xxx Medical Center and do not reflect corrective actions that you personally have taken."



Indicating that the PI doesn't understand his/her responsibilities as clinical investigator

 "You noted that you were unaware at the time of the study that the xxx assessments for these subjects were not completed properly, and that this violation was <u>not brought to your</u> <u>attention by either your study staff or sponsor monitors</u>.

We wish to emphasize that as the clinical investigator, it was your ultimate responsibility to ensure that these studies were conducted properly..."



Not providing documentation that corrective measures have been done or when they will be done

 "Although you stated that your SOP has been put into effect and that your research coordinators are well aware of this requirement, you failed to provide documentation that your research staff have been adequately trained in this SOP."



Explaining how the violation occurred but not providing a corrective action



What makes a deficient CAPA? (a few more....)

- Not addressing *why* the problem occurred
- Not describing the extent/pervasiveness of the problem
 # times, #subjects, # studies, etc.
- Not detailing the timeframe of the corrective actions
- Not detailing how you assess if the corrective actions worked
- Not reporting deviations and CAPA to all applicable entities/authorities





A great plan may not pass IRB or FDA muster if you don't:

- TAKE RESPONSIBILITY
- APPROPRIATELY ASSESS CAUSES OF THE PROBLEM
- DEVELOP/MODIFY WRITTEN PROCESSES (SOPs)/PROTOCOL
- TRAIN STAFF ON NEW PROCESSES
- EVALUATE TO ENSURE YOUR CAPA WORKS
- DOCUMENT EVERY STEP OF YOUR CAPA
 - Training
 - SOPs
 - Assessment of whether CAPA initiatives are effective





If you develop SOP(s) or modify the protocol as part of your CAPA

- Ensure the SOP addresses the root cause(s)
- Ensure SOP details procedures to fix and prevent the problem
- Train staff on this new SOP
- Document training (when, what, who, who)
- Perform self-assessment to ensure SOP worked as part of the CAPA



Study name:

Study ID #:

Staff Member Training Log This log documents training of individual staff members. To record specific training for an entire group (if easier) refer to "Staff Training Log for Groups."

Templates to Assist you in Documenta

In CRRO website http://www.bumc.bu.edu/crro/

- under Resources
- go to Research and Regulatory Tools and Resources
- scroll to Study Regulatory Files
- click on Regulatory Binder Tab Inserts

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Case revisited

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- Subjects 1005 and 1018 did not have urine dipstick results recorded at baseline. Subjects 1021 and 1045 did not have urine dipstick results recorded at weeks 8 and 12 despite having elevated protein levels at week 4.

CAPA Plan:

 "We have instructed our study coordinator to be more careful to ensure this dipstick test is done."

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What do you think?

Helpful guidance

Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects <u>www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM18</u> <u>7772.pdf</u>

IRB Continuing Review after Clinical Investigation Approval <u>www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf</u>

Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring guidance <u>www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM26</u> <u>9919.pdf</u>

FDA Inspections of Clinical Investigators <u>www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf</u>

FDA Inspectional Objectives for CAPAs

https://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm170612.htm

Questions?