Corrective and Preventive Action Plans (CAPAs): What they are and why you should care

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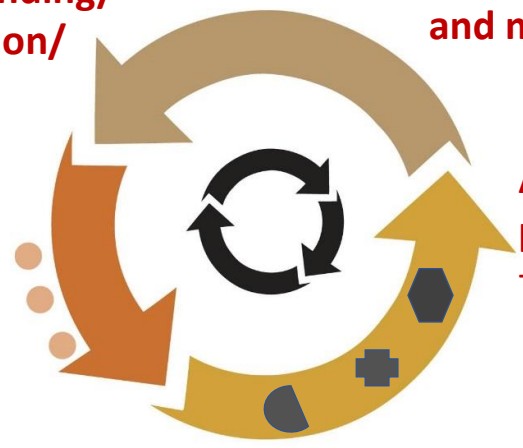
Objectives

- Define CAPA and state the purpose of CAPAs
- List components of a CAPA
- What makes a successful CAPA
- Apply CAPA principles when preparing for new studies

Quality System: continuous assessments for Quality

A bump in the Quality System



Quality System: continuous assessments for Quality

Quality checks and measures

Quality checks and measures

Quality checks and measures

Corrective and Preventive Action Plan (CAPA)

- A system for resolving quality issues
  - Resolve/correct problem and keep it from happening again
- Term originated in manufacturing field
- Required in FDA device/device manufacturing regulations
  - "Quality System Regulation" (21 CFR 820.100 and 21 CFR 211)

Regulatory perspectives…. CAPAs in Clinical Research

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.

FDA Guidance - Investigator Responsibilities, Oct. 2009

ICH GCP 2.13 (Principles)

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

ICH GCP 5.1.1

- The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements

What is a CAPA?

- Corrective and Preventive Action Plan
- Corrective Actions/Preventive Actions
- Documenting and communicating the plan to address the problem
  - Correct: REACTIVE steps to correct the immediate problem
  - Understand: IDENTIFY underlying cause(s) and extent of the problem(s)
  - Prevent: PROACTIVE steps to prevent future recurrence of the problem(s)
- Communication of the actions (assessment, approval)
  - Study team, IRB, FDA, Sponsor, Funder, etc.

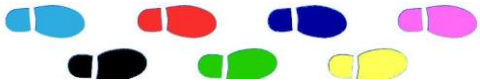
Case Discussion

- On next slide, we will review a case to consider as we move through elements of a CAPA plan.
- Please contribute to the discussion as we review the CAPA components and we consider each step in relation to the case.
  - Unmute and jump right in!
  - Raise your virtual hand in Zoom!
  - Drop your two cents in Chat!

CAPA Case

- Phase 2 NIH-funded study testing new study drug for condition X; IND held by main site PI
- Protocol detailed that the 1st infusion should take place over 2-3 hours, to minimize potential for some possible adverse effects
  - Protocol specified that concentration of the infusion should be 2 mg/1mL; dosing based on Subject BMI
- At one of the sites, a concern of quicker than expected infusions was brought to the subject advocate by a research nurse
- This led to the realization that many 1st infusions were taking between 20 min to 2 hours instead of the protocol requirement of 2-3 hours

Steps to a Successful CAPA Plan



- What happened? Evaluate the extent of the problem
  - Assess for harm/potential harm to subjects
- Determine the cause(s) of the problem
- Report to IRB, sponsor, other entities as applicable
  - May need updates as your CAPA is finalized
- Correct the problem as it relates to current subjects (if possible)
- Develop processes to ensure the problem is prevented in the future
  - Train on new processes! Document this training!
- Follow up assessment to ensure that all steps of the CAPA are successful
  - Document this assessment!

DOCUMENT EACH STEP!

1) CAPA Elements: Description of the Problem

- What happened?
  - Narrative of events – timeline w dates if applicable
    - Keep to facts
  - Extent of problem
    - Number of subjects affected/harmed
    - Number potentially affected/harmed
  - Could the problem extend beyond the study?

Case Quick Summary
- Protocol required 1st infusion over 2-3 hours to lessen adverse effects
- 1st infusions taking between 20 min to 2 hours instead of 2-3 hours

2) CAPA Elements: Causes of the Problem

- Root cause analysis (RCA)
  - Understand the system/process failure points to be able to fix them (not to assign blame)
  - Often have to assess multiple levels/processes/individuals
  - Perform as soon as possible after problems identified

Case Quick Summary
- Protocol required 1st infusion over 2-3 hours to lessen adverse effects
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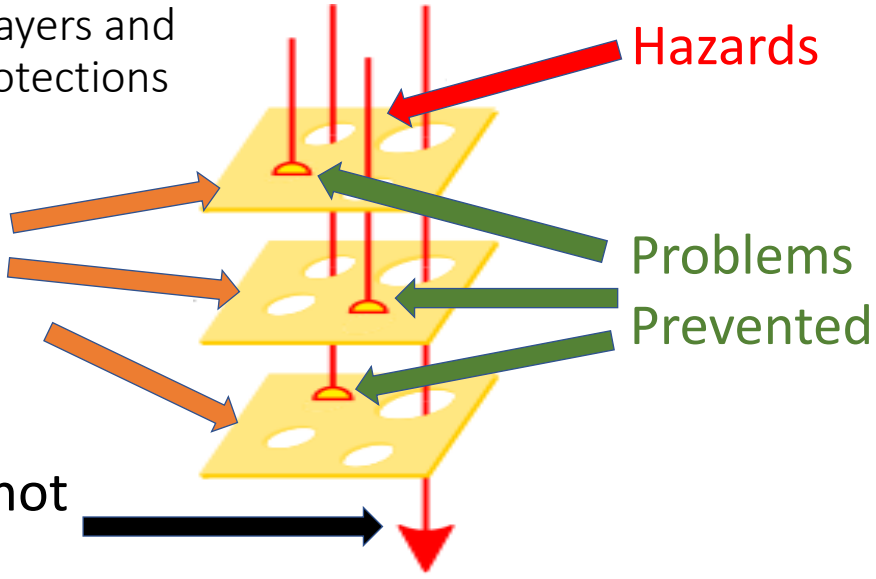
Swiss Cheese Layers and Holes in our Protections



- J. Reason, Human Error: models and management, BMC 2000;320:768
- https://en.wikipedia.org/wiki/Swiss_cheese_model

Root Cause Analysis: Questions to determine underlying cause(s)

- Identify the "near" problem…. work backwards…..
  - Also sideways, above and below, as relevant….
- 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?

Case Quick Summary
- Protocol required 1st infusion over 2-3 hours to lessen adverse effects
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"5 Whys" technique (aka the "Toddler technique!")

- State the problem: 1st infusion infused too quickly

Why 1

Why 2

Why 3

Why 4

Why 5

More on 5 Whys: P. Williams, BUMC PROCEEDINGS 2001;14:154–157

3) CAPA Elements: Corrective and Preventive Actions

- Corrective actions
  - What will you/did you do to correct the immediate problem?
- Preventive actions taken or to be taken
  - What processes are you putting in place to prevent the problem from occurring again in future?
- Most CAPAs will include new procedures/processes/workflows
  - Include new/updated SOPs, new tools or checklists, etc.
  - Changes to protocol: amendment submission
  - Trainings on new processes (DOCUMENT!)
    - Who was trained?
    - When was the training?
    - What was the training on?
    - How was it conducted?
    - Checklists

Case Cont'd.

- It was then found that pharmacy did not consistently prepare the bags at a 2 mg/1mL concentration as ordered by study MD (and per protocol), but by volume, and at a higher concentration. Volume and dose was on the label, but NOT concentration.
  - Pharmacy reported that study staff agreed to a range of concentration at the time of the meeting (PI not present)
- Nursing continued to follow study-provided documentation flowsheet and set infusion rate assuming 2mg/1mL concentration.
  - (would have needed slower rate for higher concentration/lower volume infusion)
- Thus, study drug delivered at higher dosages/timeframe than what was allowed by protocol (total dose was correct).
- 15 subjects had first infusions complete before the 2 hour requirement.
- No subjects were experienced adverse events.

Actions taken or to be taken

- What will you/did you do to correct the immediate problem?
- What processes are you putting in place to prevent the problem from occurring again in future?
  - Specifically, list what you need to do/have done to show you have addressed the action?

Case Cont'd.

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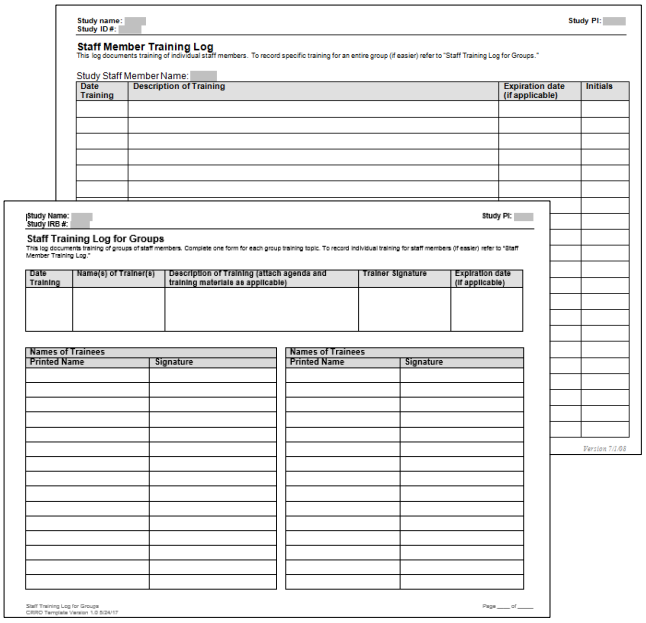
Tools to help

BUMC/BMC:
Training logs BUMC/BMC:
https://www.bumc.bu.edu/crro/tools/
- Scroll to Regulatory Files and to Staff Member Training Logs

CAPA Template BUMC/BMC:
https://www.bumc.bu.edu/irb/inspir-ii/irb-templates/
- Scroll to CAPA Plan template

UVM
https://commons.med.uvm.edu/dean/comclntril/SitePages/Regulatory%20Documents%20and%20Resources.aspx

UF:
UF provides the NIH sample Training Log for investigator's to customize for their own use - https://www.ctsi.ufl.edu/research/research-support/irb-consults/clinical-research-toolkit/
Scroll to Regulatory Binder Checklist (NIH) and to Training Log


Study name:
Study ID #:
Study PI:

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."

Study Staff Member Name:

Date Training	Description of Training	Expiration date (if applicable)	Initials

Study Name:
Study IRB #:
Study PI:

Staff Training Log for Groups
This log documents training of groups of staff members. Complete one form for each group training topic. To record individual training for staff members (if easier) refer to "Staff Member Training Log."

Date Training	Name(s) of Trainer(s)	Description of Training (attach agenda and training materials as applicable)	Trainer Signature	Expiration date (if applicable)

Names of Trainees	
Printed Name	Signature

Names of Trainees	
Printed Name	Signature

Staff Training Log for Groups
CRRO Template Version 1.0 8/24/17
Page ____ of ____

4) CAPA Elements: Reporting

- IRB
  - Reporting to the Reviewing IRB (IRB of Record)
  - If you are ceding review to an outside IRB, depending on your institution's policies, you *may* need to report to the relying IRB (i.e. your local IRB)
- Sponsor
- Lead site
- FDA
- Funder
- Other institutional entities

Reporting Policies for each Institution

University of Vermont

IRB Policies and Procedures
- RNI Reporting
- Non-compliance

Behind UVM firewall:
- Regulatory Documents & Resources
- 2019 RPN Workshop Presentation

MUSC

Policy IRB HRPP 10.1 Human Research Audit
- Item K – includes broad language on what should be included in a CAPA

Policy 4.14 Protocol Deviation
- Section IV describes the submission of a CAPA to the IRB

Protocol Deviation Report Form (example)
- This form is now a smart form submitted in eIRB as part of the reportable event along with other smart form pages

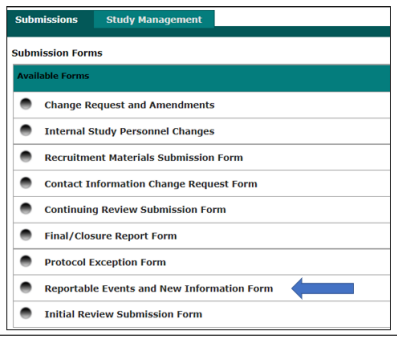
Reporting Policies for each Institution

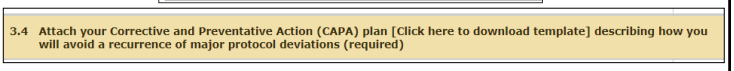
Boston University

- IRB CAPA Template (directs to templates page, not actual document)
- HRPP Policy 7.4.5 Submission of Reportable Events and New Information
- HRPP Policy 6.6.5.2 Major Deviations

General Resources
- CR Times article – May 2022 edition

- INSPIR (IRB system) Screenshots – RENI (Reportable Events and New Information Form)





Reporting Policies for each Institution

University of Florida

- HRP Policy 112 Reportable Events

Investigator Guidelines
- Deviation Reporting – Event Reporting – Adverse Events, Unanticipated Problems Involving Risks to Subjects of Others, Protocol Deviations, and Other Problems

Example - Submission of Reportable Events through myIRB:
Reportable Event
1.0 What are you submitting?
- Regulatory Noncompliance
- **Protocol Deviation: risk to subjects or research integrity (*Deviation/Non-Compliance* smartform)**
  - 1.0 Describe what occurred
  - 2.0 Date of occurrence
  - 3.0 Date of discovery
  - 4.0 Did this occur in order to eliminate an apparent immediate hazard to subjects?
  - 5.0 Did any study subjects experience an adverse effects or unanticipated problem?
  - 6.0 Explain why this issue does or does not affect the integrity of the research data
  - 7.0 What action have you taken to directly address this issue? CORRECTIVE PLAN
  - 8.0 What have you done to prevent this from reoccurring? PREVENTIVE PLAN
- Adverse Event that is Serious and Unexpected (5 day form)
- Miscellaneous
- DSMB Report

5) CAPA Elements: Plan for Evaluation

- Plan for future evaluation (audit) of your CAPA
  - Was it effective in correcting/preventing the problem?
  - Did the problem reoccur?
- How
  - Internal audit to assess compliance to the CAPA
    - Self-audit (see CRRO tools; scroll to end; see UVM tools)
    - Request a QA review from your Institutional QA team
  - Address deficiencies (new CAPA?)
  - Document what you did!

Identify principles of a successful CAPA

1. Implement a Corrective and Preventive Action (CAPA) process and document CAPA procedures
2. Investigate and identify the root causes of quality problems
3. Verify or validate CAPAs for effectiveness and prevent possible adverse impact on finished products
4. Implement and record changes in methods and procedures as part of actions taken and disseminate those records to the research team.

A typical CAPA investigation should be comprised of the following general steps:

1. *State the problem clearly and completely - Facts no judgments*
2. *Invest the appropriate time and effort to implement the documented investigation procedure conduct a thorough evaluation*
3. *Document the investigation process as it's conducted*
4. *Analyze the root cause of the issue and identify all actions needed to correct and prevent recurrence*

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

Include Enough Details

FDA Observations from FDA Warning Letters:

- "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."

Develop the Appropriate Materials to Support Your Plan

"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…."

Correct and Preventive Actions should be feasible and realistic

- What can be done to address the issue and have the expected positive effects
- Implement the plan, put it into action
  - Train the research team, document the training
- Assess if the plan is working
  - Did implementation of the corrective action plan go as planned?
  - Is it addressing the issue, have we corrected/prevented future instances?
- Adjust the plan if it is not addressing the issue
  - Make sure you resubmit the plan to the IRB for review!

Case

Researcher and their coordinator are reviewing the report from a recent QA review/monitoring visit on their investigator initated study:

Findings in the report are as follows:

- The protocol states participants must have a Hemoglobin of $\geq$10.0 g/dL for at least 30 days prior to enrollment.
  - 8/10 enrolled participants did not meet this criterion for baseline Hemoglobin.
- Documentation of Training Log is incomplete
- Delegation of Authority Log is not current
  - Key personnel were updated in June, the new staff are engaged in the research activities
- Subject 003, 004, 006 Day 28 visit were completed outside of window per the IRB approved protocol.
- Adverse events (AEs) were noted on Subject 003, 004, 007 that have not been reported per IRB policy and Subject 008 AE was not reported in a timely manner.

What do we need to do for CAPA to address these findings?

Proactively planning for success - Preventive Actions

What causes a CAPA to be written?
Deviations!

Deviations – departure from the approved protocol/study plan

- Can never get away from deviations, things are going to happen

  we are all human and some of us are very busy humans who are asked to do many things at once

- But you can learn to **anticipate deviations** and **plan procedures** that can help prevent them from occurring

Anticipation: Prior to implementation – before study starts

- Review protocol:
  - Read the protocol in full – even several times!
  - Are there any procedures that aren't clear or might be interpreted differently?
  - Are there procedure windows that could be hard to meet because of clinical reasons, staffing reasons, participant reasons?
  - Are there procedures that must happen before other procedures?
  - Do the eligibility criteria make sense for safety or clinical reasons? Are they appropriate for the patient population? Are they clear enough to prevent deviations?
- Is there formal training available? Is the training adequate for all procedures? Are there gaps in training?
- Dry-runs – start at screening through the final data collection – are there points of confusion or things that took longer than usual, are there things that were forgotten? Do these as a team and run more than one with different leads.Do all the above with the entire study team – there may be differences between team members about what they understand
- Is there a Table of Events that a visit checklist can be developed from?
- Are there non-research staff members involved?
- Are there clinical procedures or labs that must be done within a shorter window than standard practice?

Anticipation: After implementation – after enrollment starts

- Review protocol amendments:
  - Read the protocol – not just the amendment, are the changes consistent throughout the protocol
  - Are there any procedures that aren't clear or might be interpreted differently?
  - Are there procedure windows that could be hard to meet because of clinical reasons, staffing reasons, participant reasons?
  - Are there procedures that must happen before other procedures?
  - Do any visit checklists need to be updated?
  - Should retraining be done? Even if the sponsor requires retraining – this is often just "read and sign" – often not actually adequate for learning
  - Do non-research staff members need to be updated about protocol amendment
- Onboarding new staff: Review previous slide – what applies to new staff even if study is ongoing?
  - New research staff and new non-research staff members, especially important if floor staff are doing any procedures
- When scheduling for participants – check for required windows against holidays, vacations, clinic/lab closures, weather issues
  - Check for both participants AND staff
  - Often useful to, at time of consenting and throughout enrollment, to talk about timing of visits and specifically ask about vacations

Standing Meetings and Open Communications

- Set to occur on regular basis
- Are not routinely canceled
- Have set, recurring agendas
  - Recruiting and enrollment, enrolled participants and upcoming visits, adverse events, deviations, upcoming IRB submissions, planned amendments, staff time off, etc
  - Discuss successes and problems or issues
- Use agendas to take notes - maintain as part of study documentation
- Involve primary team members, can involve others as needed on rotating or as needed basis
- Should occur fairly often during startup planning/initiation and can occur less often as enrollment and study procedures become routine
- Should not occur less than monthly

Reactive Process: Writing a CAPA because of a finding/deviation

Proactive Process: Study planning and implementing processes to prevent deviations

Processes are often repeatable, duplicatable across studies

- ★ Less effort each time you implement - expectation setting, understandable process
- ★ Provides "selling point" for industry sponsored studies and multi-site studies during site selection processes
- ★ Success often has trickle-down/across benefits - models good practices for other teams

Documents are often repeatable, duplicatable across studies

- ★ Templates for logs, checklists, MOPs

Identification of protocol "pain points", often similar across studies

- ★ Ask for clarification from sponsor or lead team before enrollment starts
- ★ Write/amend protocol to clarify or correct those known pain points
- ★ Work with clinical care team early in process to prevent pain points

Spending the time doing this WILL take time and WILL slow down study startup timelines as you start to do this – but will drastically reduce errors and deviations, time spent in reporting and correcting those issues, and increase general goodwill with sponsors/lead teams/institutional stakeholders. Will take less time each new study is implemented with the same proactive process – **work smarter, not harder.**

Apply CAPA principles to preparing for new studies

Finding Example	Common "Preventive Actions"	Study Initiation and Startup Planning
Participants did not meet eligibility criteria	• Retraining • Checklists • Amend protocol if eligibility aren't appropriate	• Develop MOPs or Checklists • Review eligibility in protocol
Visits not done within window	• Checklist • Shared visit calendars • Amend protocol for more appropriate window	• Review protocol for issues with windows • Develop MOPs or Checklists
AEs not reported in timely manner	• More frequent team meetings • Develop MOP about reviewing and reporting AEs	• Standing meetings with study team • Develop MOPs
Delegation Log not current	• Onboarding of new staff will include log completion • Meetings will include regulatory log review	• Develop onboarding checklist • Meeting includes standing agenda items
Documentation of Training log not complete	• Onboarding of new staff will include log completion • Meetings will include regulatory log review	• Develop onboarding checklist • Meeting includes standing agenda items

Practice makes perfect! Using Annotations!

Put a stamp (any kind) in the box of which animal you prefer!
(Dogs rule, cats drool)

Apply CAPA principles to preparing for new studies during initiation and startup planning			
How likely are you to be able to implement these things for your next study?	**Unlikely**	**Maybe**	**Definitely**
Develop MOPs or Checklists			
Review protocol for issues with windows			
Schedule standing meetings with study team - and keep them!			
Develop onboarding checklist			

CAPAs, Quality Systems, Future Planning