CAPA Best Practices:

How to ensure proper implementation of this integral component of a Research Quality System

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Objectives

- Define CAPA and state the purpose of CAPAs.
- List Components of a strong CAPA.
- Summarize process for a Root Cause Analysis (RCA).
- Explain how to best respond to audit findings.
- Describe what makes a good CAPA vs a poor/inadequate CAPA.

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.

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)

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 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

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

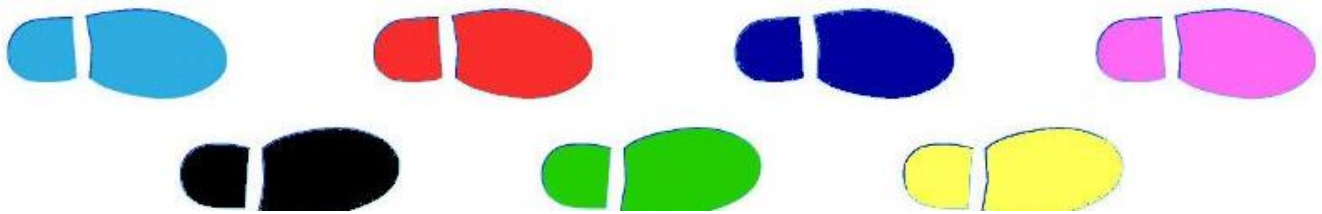
When do we need a CAPA?

- Depth of CAPA investigation and implementation should match the risk.
- Is the quality of the data and/or the safety of subjects *potentially* adversely impacted?

7-step Plan for Successful CAPA

- Evaluate the extent of the problem:
  - Assess for potential harm to subjects
- Determine the cause(s) of the problem
- Report to IRB, sponsor, other entities as applicable
  - Multiple updates may be necessary
- Correct the problem as it relates to current subjects
- Develop processes to ensure the problem is prevented in the future
- Train on new processes
- Follow up to ensure that all steps of the CAPA are successful

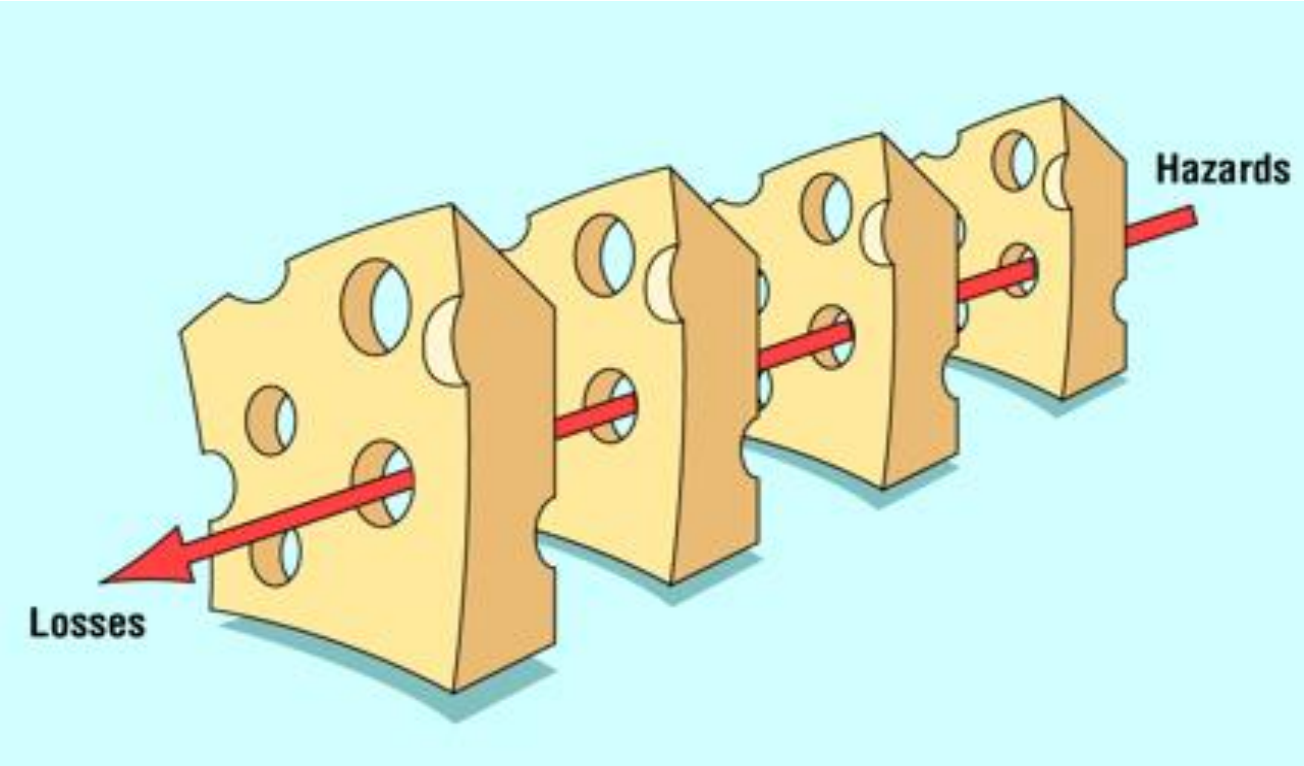
DOCUMENT EACH STEP!



Elements of your CAPA

- Description of the problem
  - Narrative of events
  - Number of subjects affected/harmed
  - Number potentially affected/harmed
- The root and contributing causes for each finding
  - Include how this was determined
- Corrective actions and preventive actions taken or to be taken
  - Include description of new or changed processes and/or SOPs
  - Describe plan for training
  - Describe plan for evaluating the effectiveness
- Reporting

How did this happen?
The Swiss Cheese model



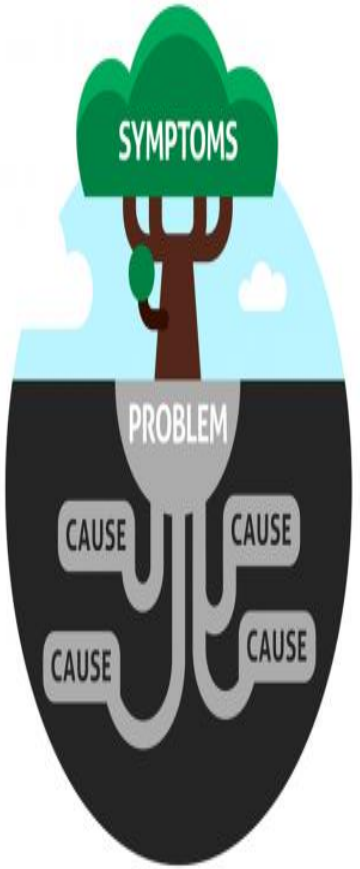
J. Reason, Human Error: models and management, BMC 2000;320:768

Two reasons for holes in the system

- Active failure: Unsafe acts by people in direct contact with the subject or system
- Latent conditions: Arising top level mngt./procedure developers, institutional culture, etc.
  - "Error-provoking conditions" within the workplace: inadequate staffing, insufficient training
  - Can create long-lasting holes or weaknesses in defenses

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

- 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 the underlying cause(s)

“5 Whys” technique (aka the “Toddler technique!”)

- State the problem: Urine dipstick result not recorded.
  - Why 1: Staff did not write down baseline urine dipstick result.
  - Why 2: Staff did not know they needed to record the results at baseline.
  - Why 3: Staff had not been trained on what data elements had to be captured at baseline visit.
  - Why 4: PI relied on the sponsor provided baseline CRF to specify what data points need to be captured at the baseline visit.
  - Why 5: PI believed sponsor would ensure all needed data points would be placed on the baseline CRF.

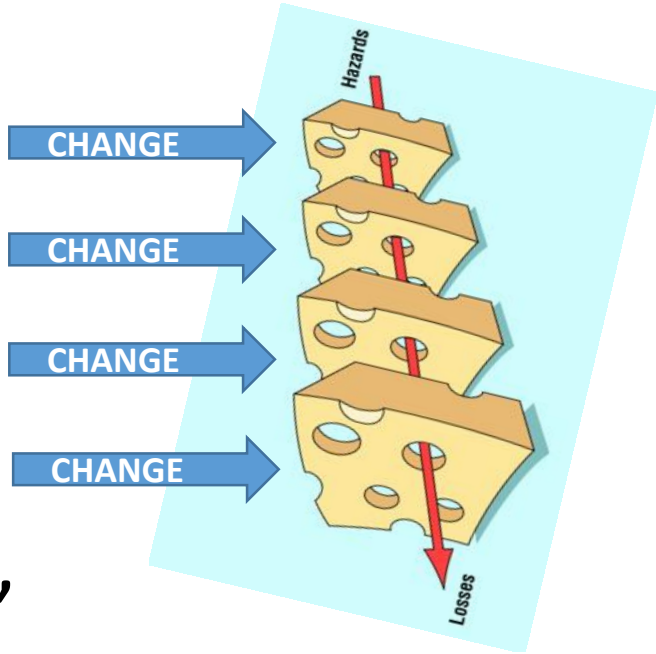
More on 5 Whys: P. Williams, BUMC PROCEEDINGS 2001;14:154–157

Corrections/Preventions

- Different levels within the research infrastructure may have contributed to the problem (remember the Swiss cheese!)

thus

- Changes may be needed at multiple levels
  - Institutional policies
  - Department/clinic policies
  - Processes for study team working on multiple studies
  - Internal study processes specific to a particular study
- Example: study team, department, pharmacy, GCRU/clinical center, etc.

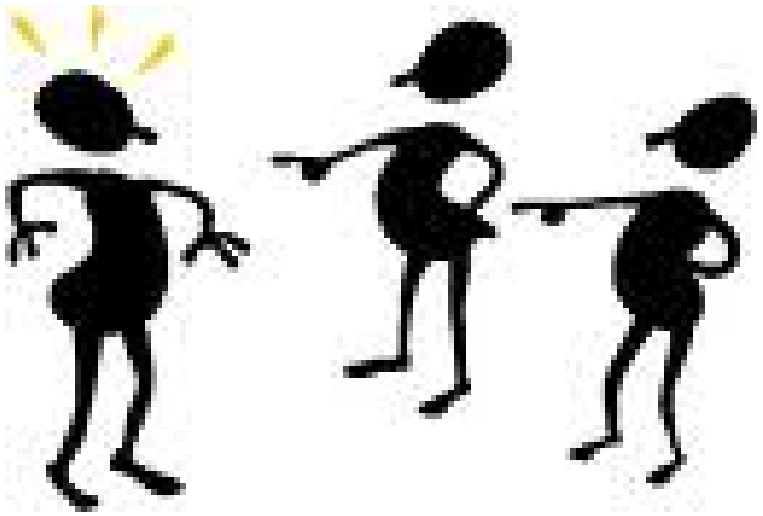


Who gets the blame?

20 inspections … 23 parties blamed

Highest, at 39%? …… **Study Coordinator**

Scientific Misconduct: The F Word, Stan Woollen, 2001



"When an investigator blames colleagues, it's meaningless to the FDA…"

- Adil Shamoo, PhD, Bioethicist

"FDA cites investigators for poor recordkeeping…. blaming staff" Clinical Trials Compliance, J. Harzbecker, Dec. 2005

Corrections/Preventions: Own the Problem(s)

"Prior to the detailed replies, I wish to clearly state that I understand I am responsible for oversight of all activities that occurred at our site regarding this protocol. We do not dispute any of the findings of the inspection and we acknowledge the serious nature of the observations and have taken action both in the past and now to directly address these specific issues and help ensure similar research-related issues do not occur at our site on any current or future study."

"Unfortunately, our study coordinator was not sufficiently trained on the process of obtaining informed consent. She also did not understand the electronic IRB system and the importance of ensuring that when there are amendments to the study there needs to be a new consent form printed from the system. This contributed to the issues raised in the audit. We have provided training to the study coordinator."

Don't be this investigator!

Clues to deficient CAPAs: FDA Warning Letters

Not enough detail

- Not addressing why the problem occurred
- Not describing the extent/pervasiveness
  - # times/#subjects/#studies, etc.
- Not detailing timeframe of the corrective actions
- Note detailing how you assess effectiveness of the corrective actions

"… you identified the problem and have established certain corrective actions…. You identified and addressed the integrity of the investigational procedures and data in other clinical investigations in which the terminated research nurse was involved. However, we find that you have not adequately addressed how you will improve your supervision of study staff in future…."

Clues to deficient CAPAs: FDA Warning Letters

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."

Clues to deficient CAPAs: FDA Warning Letters

Insufficient detail to determine if CAPA will correct the problem….

- Poor root cause analysis!

"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."

Clues to deficient CAPAs: FDA Warning Letters

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

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

Clues to deficient CAPAs: FDA Warning Letters

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

"You noted you were unaware at the time of the study that the xxx assessments for these subjects were not completed properly, and this violation was not brought to your attention by either your staff or monitors… We wish to emphasize that as the clinical investigator, it was your ultimate responsibility to ensure that these studies were conducted properly…"

Clues to deficient CAPAs: FDA Warning Letters

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 …"

Also keep in mind….

- Don’t promise corrective/preventive actions that could never realistically be carried out
  - Try to get the “just right” (think “Baby bear” ☺)
  - What is feasible, with the expected positive effects
  - Example: “Site staff will review the EMR for all subjects for AEs on a weekly basis.” *(There are ~100 subjects.)*

- Make sure to DO WHAT YOU SAY YOU WILL DO
  - If you find that you cannot, amend the CAPA (and get it approved)
  - Ex: “All protocol deviations have been entered on a deviations log.”
    - A deviation log was never created and instead deviations were entered in the EMR
      - What is the potential problem with this practice?

- Recognize that problems in one study can likely mean problems in other studies
  - Your CAPA might have to involve other studies under the PI and/or using the same study staff

Activity 1

Instructions: Review the examples below, some from real (but modified) draft or final CAPAs. Provide constructive advice on needed modifications.

Example 1: Reporting AEs to Sponsor

- Finding: Multiple SAEs not reported to the Sponsor within the protocol-specified timeframe (48 hours).

- Response: All AEs were reported according to the [institution name] IRB policies and procedures. As all care delivered through this trial has been "standard of care" there are no safety concerns for research subjects regarding these observations….We acknowledge that the timing of reporting was delayed during the early phase of the study in 2013, and have already worked diligently in 2014 to comply with the timing required by the protocol. There are multiple examples of our compliance with the required reporting timeframe [list of subjects].

Activity 1

Instructions: Review the examples below, some from real draft or final CAPAs. Provide constructive advice on needed modifications.

Example 1a: Reporting AEs to Sponsor

- Finding: Multiple SAEs not reported to the Sponsor within the protocol-specified timeframe (though they were reported to the IRB).

- Response: In order to improve communications internally between study team members, a review of enrollment logs and occurrence of hospital admissions and/or assessment of medically significant events will be conducted by the PI at weekly/biweekly research meetings to cross check with study investigators and further improve timing of SAE reporting.
- Study coordinator will perform bi-weekly follow-up phone calls to study participants to monitor admissions or medically significant events outside of BMC and will inform study investigators immediately regarding such events … study investigators will report AEs to the Sponsor according to the protocol.

Activity 1

Instructions: Review the examples below, some from real draft or final CAPAs. Provide constructive advice on needed modifications.

Example 2:

- Finding: Subject 011 enrolled in xxx, the Source Document Worksheet for Visit 17 contains discrepancies regarding the fundoscopy exam. The document originally noted in that the fundoscopy exam was performed on Jan. 11, 2011 but the entry of "yes" for the performance of the exam was crossed out, and a notation of "not performed" was added. On June 2, 2011, the words "not performed" were crossed out, with the word "error" entered above that crossout. The document also contains another late entry, dated June 2, 2011, with fundoscopy examp findings. In addition, the document contains the undated entry, "visual acuity and fundoscopy were done but not documented – missed documentation." We were unable to determine whether the fundoscopy exam was performed on Jan. 11, 2011 or June 2, 2011.
- Response: All discrepancies in the study records noted in the finding were directly related to our poor documentation practices. We failed to document the fundoscopy exam properly because the physical exam worksheets did not contain a section to capture fundoscopy exams. In addition, missed assessments were due to a confusion of the protocol; the fundoscopy exams were not required for every visit and some were inadvertently missed, while others were captured when they were not required. We revised source documents to include the physical and fundoscopy exams on the required visit dates, as required by the protocol. The staff have been re-educated on proper source documentation and on GCP. In addition, moving forward, we will document all required assessments at the time of subjects' visits to avoid late entries.

Activity 1

Instructions: Review the examples below, some from real draft or final CAPAs. Provide constructive advice on needed modifications.

Example 3:

- Finding: Audiometry reports that were represented as reports for subject 3 at visit 2 and visit 3 are obscured audiometry reports that were originally for other subjects…..

- Response: The CRO site monitor instructed our study coordinator to obscure identifying subject information. In addition, our study coordinator made errors in transcribing the subject information. The errors in transcribing the subject information were not intentional and involved only 5% of all audiograms that our site generated. Where applicable, we have instituted additional measures and procedures to address the inspection findings.

CAPA - DOs

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

CAPA - DOs

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

Food for thought…… "PA-CAPA"

- Is the idea of a CAPA too *REACTIVE*?
- Think of this idea of research as a quality system…
- Think of YOUR study…. what can you ensure is in place to emphasize PREVENTION rather than waiting for problems to arise?

- **Well-written protocol**
- **Well-trained staff**
- **PI Oversight**
- **A "culture" that promotes questions from staff when something doesn't "feel right."**

- **Detailed written SOPs**
- **Appropriate delegation of responsibilities**
- **Adequate monitoring**
  - **Of subjects**
  - **Of study conduct and processes**

Activity 2

Instructions: Review the findings below and break into small groups to discuss the next steps, including specifics of the CAPA. You may have to make some assumptions on causes to come up with corrective/preventive actions, that is OK.

Please refer to Activity 2 handout.

Need assistance?

- BMC/BU Medical Campus
  - Clinical Research Resources Office
    - www.bumc.bu.edu/crro
    - 617-358-7679
  - BU/BMC Institutional Review Board (IRB)
    - www.bumc.bu.edu/irb
    - 617-358-5372

- UVM/ UVM Medical Center
  - Office of Clinical Trials Research
    - clinicaltrials@med.uvm.edu
    - 802-656-8990
  - UVM Research Protections Office
    - IRB@uvm.edu
    - 802-656-4050

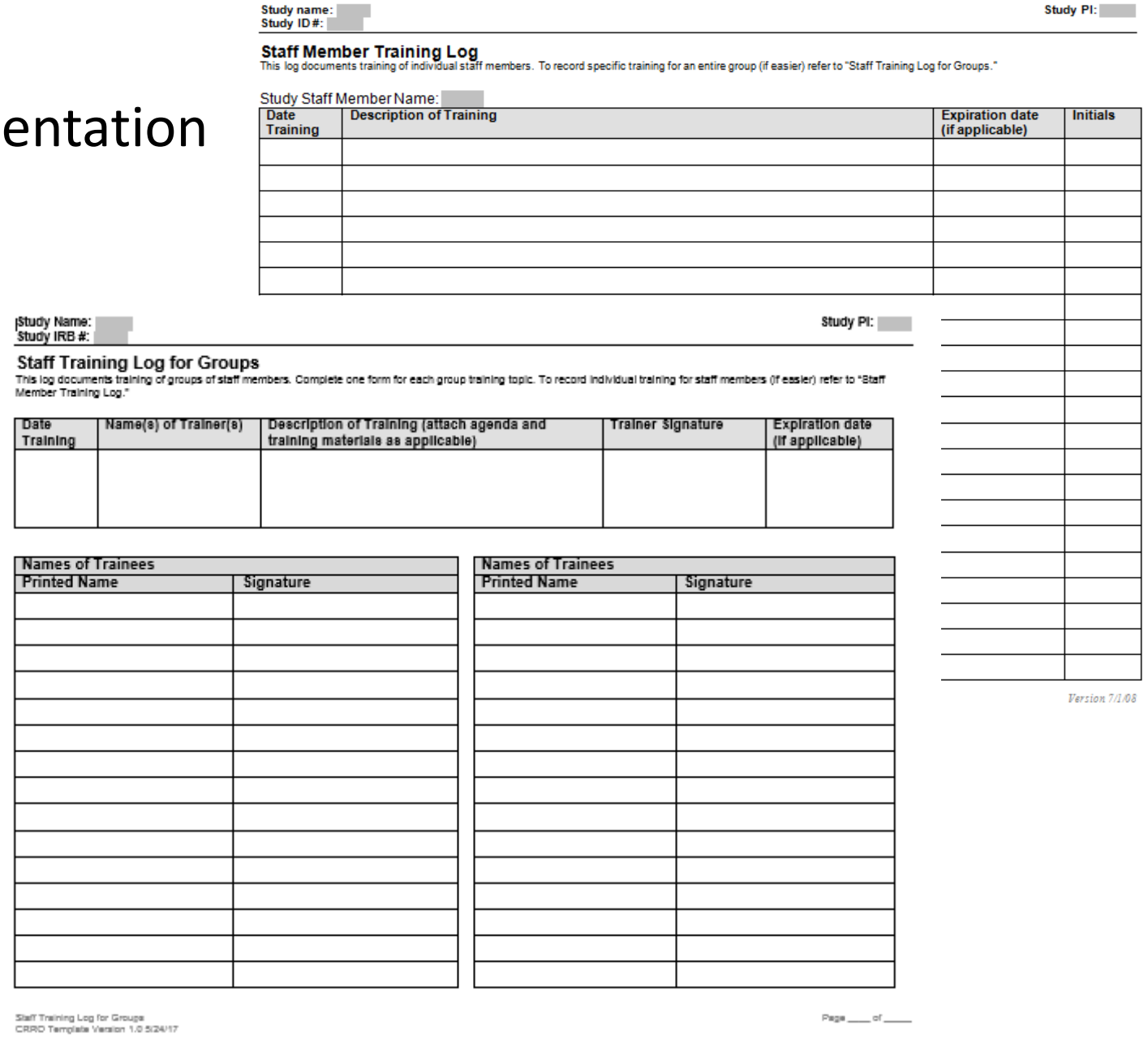
Templates to Assist you in Documentation

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

- Under Resources in the top menu
- Select Study Documentation Tools
- Scroll to Regulatory Files
- See Customizable templates to the right

On IRB website
http://www.bumc.bu.edu/irb

- CAPA template
  - Go to INSPIR II in the right menu
  - Click on IRB Templates under INSPIR II



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

Version 7/1/08

Staff Training Log for Groups
CRRO Template Version 1.0 5/24/17

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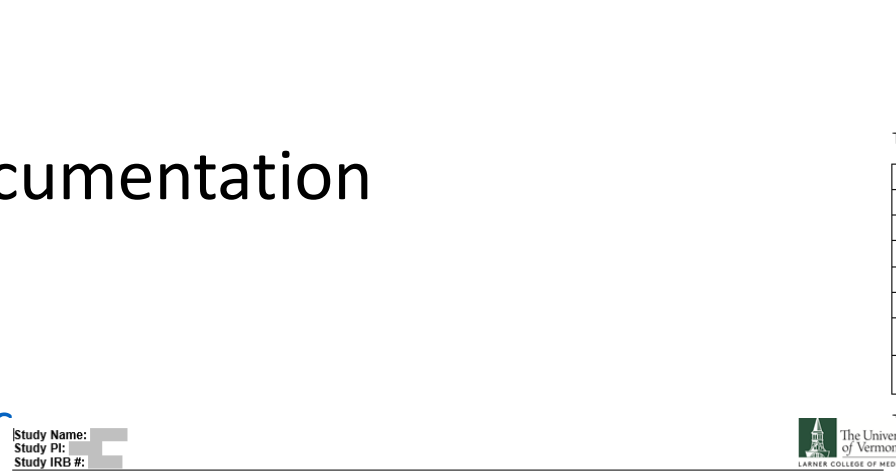
Templates to Assist you in Documentation

On UMV website:

https://commons.med.uvm.edu/dean/~omclntril/SitePages/Regulatory%20Guidance%20Resources.aspx



Study Name:
Study PI:
Study IRB #:

Staff Training Log for Groups

This log documents training of groups of staff members. Complete one form for each group training topic (i.e. protocol training, amendment training, REDCap training). 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

Version 1.0 11/16/18

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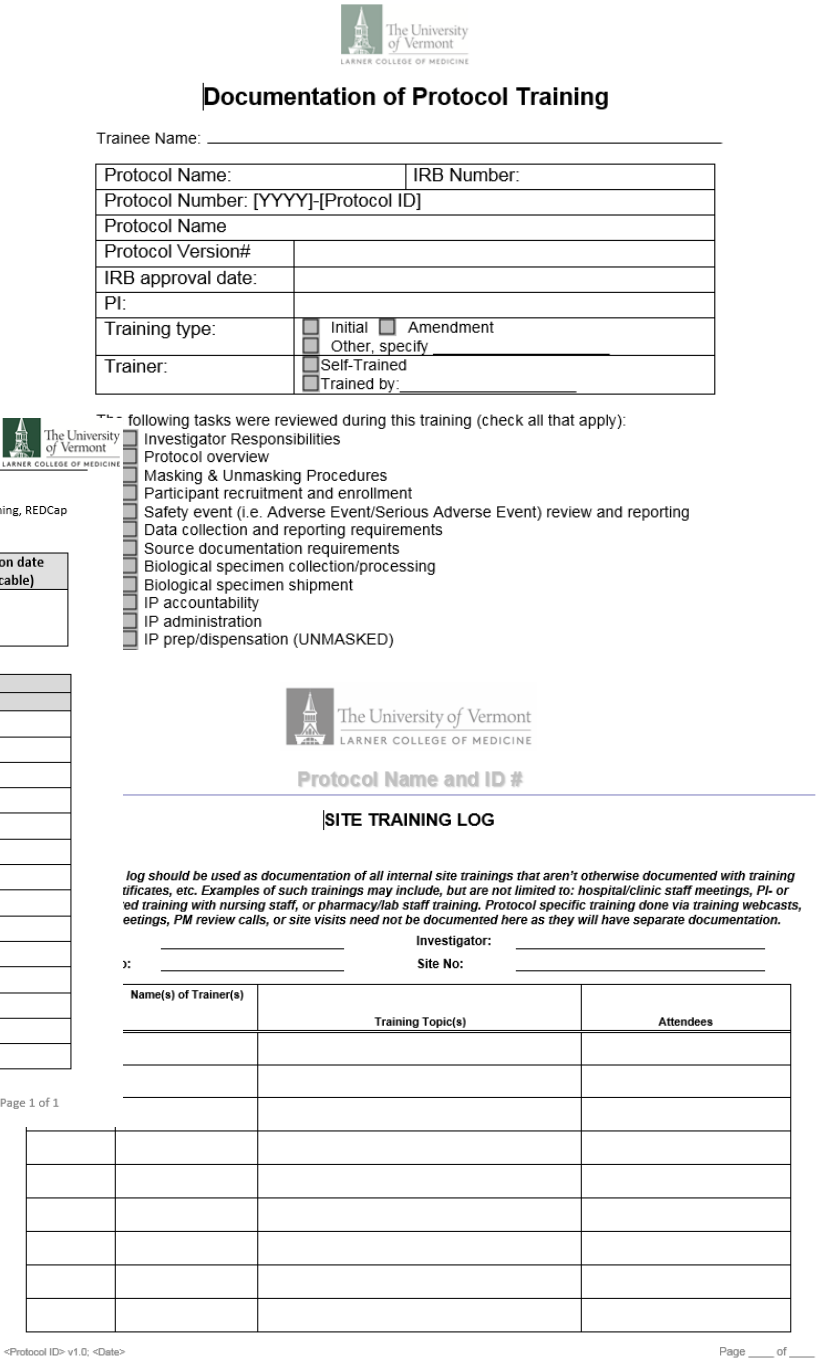

Documentation of Protocol Training

Trainee Name: _____

Protocol Name:	IRB Number:
Protocol Number: [YYYY]-[Protocol ID]	
Protocol Name	
Protocol Version#	
IRB approval date:	
PI:	
Training type:	☐ Initial ☐ Amendment ☐ Other, specify _____
Trainer:	☐ Self-Trained ☐ Trained by: _____

The following tasks were reviewed during this training (check all that apply):

- ☐ Investigator Responsibilities
- ☐ Protocol overview
- ☐ Masking & Unmasking Procedures
- ☐ Participant recruitment and enrollment
- ☐ Safety event (i.e. Adverse Event/Serious Adverse Event) review and reporting
- ☐ Data collection and reporting requirements
- ☐ Source documentation requirements
- ☐ Biological specimen collection/processing
- ☐ Biological specimen shipment
- ☐ IP accountability
- ☐ IP administration
- ☐ IP prep/dispensation (UNMASKED)

The University of Vermont
LARNER COLLEGE OF MEDICINE

Protocol Name and ID #

SITE TRAINING LOG

log should be used as documentation of all internal site trainings that aren't otherwise documented with training tificates, etc. Examples of such trainings may include, but are not limited to: hospital/clinic staff meetings, PI- or ed training with nursing staff, or pharmacy/lab staff training. Protocol specific training done via training webcasts, eetings, PM review calls, or site visits need not be documented here as they will have separate documentation.

Investigator: _____

Site No: _____

Name(s) of Trainer(s)	Training Topic(s)	Attendees

<Protocol ID> v1.0; <Date>

Page ____ of ____

Helpful guidance

- Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects https://www.fda.gov/media/77765/download
- IRB Continuing Review after Clinical Investigation Approval https://www.fda.gov/media/83121/download
- Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring guidance https://www.fda.gov/media/116754/download
- FDA Inspections of Clinical Investigators https://www.fda.gov/media/75185/download
- FDA Inspectional Objectives for CAPAs
- https://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm170612.htm

Thank you!