Frequent Research Study Audit Findings Requiring a Corrective and Preventative Action (CAPA) Plan

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Objectives

Define	Define the criteria used to identify what findings require a CAPA Plan
Identify	Identify frequent findings requiring a CAPA plan found during a research study audit by the CTQA Program
Explain	Explain what is needed to create an effective CAPA Plan

What Findings Require a CAPA?

Criteria used to identify what findings require a CAPA Plan:

- ❑Pose significant risk to the rights and/or safety of subjects
- ❑Jeopardize data integrity
- ❑Represent a major deviation from or deficiency in compliance with applicable regulations, guidelines, the protocol, standard operating procedures (SOPs) and/or policies

Frequent Findings Requiring a CAPA: Consent/HIPAA

- Missing consent/HIPAA authorization
- Lack of reconsent when required by the IRB
- Study procedures performed prior to obtaining informed consent
- Missing Conflict of Interest (COI) required consent language as applicable
- Missing 2nd parent signatures when the IRB has made a 45 CFR 46.406 or 45 CFR 46.407 child finding

Please Note: "Not reasonably available" does not apply to situations when a parent is at work, traveling, not immediately available by electronic means, or living in another state or country, without more to justify the investigator's inability to reach the parent and seek permission.

Examples of situations when one may reasonably conclude that a parent is not reasonably available could include the following situations:

- The parent is incarcerated and not contactable.
- The parent is on active military duty and not contactable.
- The parent's whereabouts are unknown.
- The parent is known and contactable but chooses not to be involved in the child's care.
- The parent is known but, upon inquiry, there is reason to believe that requesting permission would be inconsistent with the parent/child relationship, such as where there is reason to believe there is or has been domestic violence or other situations involving harm to the health or welfare of the child.

Frequent Findings Requiring a CAPA: Consent/HIPAA

- The Adult Consent/Parental Permission and HIPAA appear to be signed by an LAR without appropriate documentation:
  - Signed by Step-mother
  - Signed by guardian
  - Signed by Wife, who claimed to have a POA for previous medical condition, however, there was no documentation in EPIC

Frequent Findings Requiring a CAPA: Subject Rights/Safety

- Study personnel who do not have human subjects protection (HSP) training, which may be a result of the personnel not being added in IRBIS
- Documentation of protocol-specific training
- Unsubmitted or untimely submission of revised protocols/Investigator Brochures
- Discrepancies between the protocol/IB and/or the informed consent form
- Study tasks performed by study personnel not licensed or qualified to perform those tasks
- Missed safety assessments – including visits, procedures, infusion related vital signs
- Excessive protocol deviations
- Failure to follow the protocol required drug administration (e.g. dose reductions and dispensing errors)

Frequent Findings Requiring a CAPA: Subject Rights/Safety

- Inadequate specimen handling (e.g., specimen left in public area overnight)
- Use of an external email account to discuss patient care

  (see UNC-Chapel Hill Individual Email Address Policy)

- Protected Health Information left on an answering machine (see UNC HCS Privacy Guidelines)
- Use of personal cell/smart phones to collect, store and transmit information poses additional HIPAA privacy concerns as these devices may not be properly secured to protect stored protected health information (e.g., text messages, photographs, or emails)

Frequent Findings Requiring a CAPA: Documentation

- Documents signed by someone other than the subject or investigator
- Documentation of IRB approval for forms/subject logs
- Lack of documentation of clinical significance of laboratory results by an investigator
- Lack of documentation of adverse event assessment and attribution by an investigator
- Lack of investigational product management/documentation of accountability:
  - Dispensing
  - Compliance by subject (e.g., subject diaries and clinic notes)
  - Product returned
  - Discrepancies between product returned and product taken
  - Education and training (initially or ongoing)

Steps to Completing a CAPA

- Identify the problem
- Conduct a Root Cause Analysis (RCA) to identify the cause of the problem
- Develop an action plan to correct the problem and prevent recurrence
- Implement the plan
- Evaluate the effectiveness of the correction

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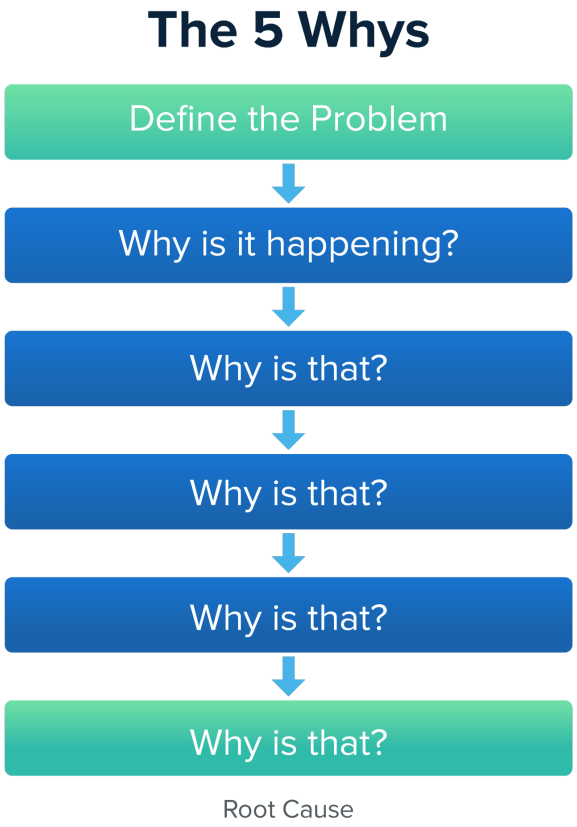
Root Cause Analysis (RCA)

- By conducting an RCA, you will be able to identify the root causes of problems
- Some methods of RCA:
  - Brainstorming
  - The 5 Whys
  - Flowcharting
  - Fishbone Diagrams
  - Affinity Diagrams



CAPA Implementation May Include:

- Correcting or implementing revisions to the documentation
- Retraining study personnel
- Re-consenting study subjects
- Revising your department SOPs
- Reporting to the IRB/FDA or other agency, as required

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Example #1 – Root Cause Analysis

Second Parent Signatures Not Obtained (Promptly reportable)

- Completed RCA – 5 Why's
  - Why did this happen? The PI was unaware that 2 signatures were needed, despite this information being included in the IRB approval letter
  - Why was the PI unaware? The PI, is a research scientist who inherited the project from the previous PI, who wrote the initial IRB in 2005. From examination of earlier records it does not appear the requirement for 2 parent signatures was ever consistently implemented, although most in prior years did have 2 parents.
  - Why did the PI not see the language requiring two parent signatures in the approval letters at subsequent renewals? The PI was not used to the approval letters containing language other than documentation of the approved protocol.
  - Why did the PI never become aware? The PI does not obtain consents himself; these are done by staff members, usually medical students or residents listed as Research Assistants who have relatively high turnover (typically 6 months to 1 year). Some of these obtained two signatures and some did not, so the training of these personnel was clearly inadequate.
  - Why was the training inadequate? This is a second failure on the PIs part, first to be aware of the necessary requirement, and second to provide consistent and documented training of personnel.

Example #1 – CAPA Plan

CAPA Plan:

- Put training procedures in place to be sure enrollment log is updated promptly with information about two parent signatures.
- Put monthly check procedures in place to be sure enrollment log matches consents, with documentation by a 'monthly check log,' signed by the PI.
- Make sure all personnel receive documented training about the need for two parent signatures, and appropriate justification if an exception is made.
- Each employee will review the appropriate documented IRB consent SOPs.
- Each employee will view informed consent training that was presented through the NRP, session dated 2/17/2022.

Example #1 – CAPA Plan Continued

- If two parents or an appropriate Legally Authorized Representative(s) are not present in most cases the study will not proceed. But in rare cases we would like to preserve the option to contact the second parent for a verbal consent by phone, with a witness on the line. We will apply for an IRB modification to do this.
- Responsible party: The PI, Dr. _____
- Due date: Will begin implementation of training and obtaining two parent signatures immediately
- Plan for effectiveness check: Check by Dept. Clinical Research Accountability Unit (CRAU) to see if monthly log completed, checked on a monthly basis for 3 months, then quarterly for one year.
- Outcome of effectiveness check: Report from CRAU to PI, cc'd to Admin Vice Chair
- Plan for amending the CAPA: Will assess progress at each CRAU oversight meeting to see if all items are now being appropriately implemented and are effective. If not, amend plan as needed.

Example #2 – Root Cause Analysis

Reconsent not obtained from any subjects or parents as required (promptly reportable)

- Completed RCA – 5 Why's
  - Why did this happen? The PI did see this requirement. Having some experience trying to contact subjects by phone for reconsents and finding it to be impossible, he did not have the personal time or additional personnel to do this. Did not have any ideas regarding an alternative plan.
  - Why were no alternative ideas suggested and implemented? It is clear that this is the step that should have been taken, i.e., some negotiation could have taken place to meet this requirement. We will suggest some possibilities below that can be done, and will accept recommendations as to what needs to be done.
  - Why was there a need for additional consents, and how could this requirement be fulfilled? Does it need all 500+ reconsents? Due to new information that may affect the subject's rights

Example #2 – CAPA Plan

CAPA Plan:

- Will send to the IRB a consent addendum to obtain the reconsent. It will say what has changed since the original consent was obtained and ask for a signature and return. If not returned, we will follow up via telephone. If there is no response, we will document the effort that was made.
- Responsible party: The PI, Dr. _____
- Due date: We expect this progress to be complete within 6 months of the agreement with the IRB on how to implement
- Plan for effectiveness check: Progress to be reported to the Dept. CRAU at the monthly and then quarterly meetings.
- Outcome of effectiveness check: Report from CRAU to PI, cc'd to Admin Vice Chair
- Plan for amending the CAPA: Will assess progress at each CRAU oversight meeting to see if all items are now being appropriately implemented and are effective. If not, amend plan as needed.

Example #3 – Root Cause Analysis

Legally authorized representative (Promptly Reportable)

- Completed RCA – 5 Why's
  - Why did this happen? The PI was not aware of the LAR requirements
  - Why was the PI not aware of the LAR requirements? These are technical but critical requirements that the PI should have been aware of. Our consents are obtained the day of surgery, so the assumption was that the person who consented the surgery would be able to provide consent for research. While this assumption may have been correct in most cases, it does not preclude the necessity for documenting the authority, or account for situations (such as a Foster Care child) who would also need State authority.

Example #3 – CAPA Plan

CAPA Plan:

- Preventative actions are to put training procedures in place to be sure the person signing the consent on behalf of the subject is an LAR, and if other than a parent documenting that authority for consent version, assent and HIPAA forms.
- Include this information in monthly check procedures to be sure the LAR documentation is correct.
- Each employee will review and document training for the appropriately documented IRB consent SOPs.
- Each employee will view informed consent training that was presented through the NRP, session dated 2/17/2022.
- In addition, we have implemented the form from the CTQA website on the Informed Consent Process and HIPAA Authorization Documentation.
- For corrective action, those subjects without adequate documentation of LAR signature will be removed from the study

Example #3 – CAPA Plan Continued

- Responsible party: The PI, Dr. _____
- Due date: Will begin implementation of training immediately
- Plan for effectiveness check: Progress to be reported to the Dept. CRAU at the monthly and then quarterly meetings.
- Outcome of effectiveness check: Report from CRAU to PI, cc'd to Admin Vice Chair
- Plan for amending the CAPA: Will assess progress at each CRAU oversight meeting to see if all items are now being appropriately implemented and are effective. If not, amend plan as needed.

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Summary

- The best approach is to identify potential problems or risks and implement new processes to mitigate those risks as they are identified.
- Each event can be used as a teaching tool to prevent future recurrence.
- The CTQA program can assist with:
  - Setting up systems and processes at the beginning of a trial
  - Friendly compliance review during a study
  - Support prior to and during FDA inspections or Sponsor audits

Resource Links:

- Resources Related to UNC Research - Links to internal and external resources (FDA, OHRP, NIH, Associations, Policies, etc.):

Resources Related to UNC Research - UNC Research

- ICH GCP E6(R2) dated 9Novemer 2016:

GUIDELINE FOR GOOD CLINICAL PRACTICE (ich.org)

- Office of Human Research Ethics – Standard Operating Procedures:

Standard Operating Procedures (unc.edu)

- Office of Clinical Trials - Links to Forms/Templates (Deviation log, SAE log, Start-up Checklist, Training log, SOP templates, etc.):

Forms & Templates - UNC Research


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