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Developing a Corrective and Preventive Action Plan (CAPA)

It is understood and accepted that problems can occur when conducting human subjects research. The purpose of this guidance is to help investigators and research personnel identify when a problem occurs, understand how to assess the root cause of the problem, how to identify what steps to take to correct or mitigate the problem, and how to provide a transparent and meaningful report to the IRB to satisfy ethical and regulatory reporting requirements.

A Corrective and Preventive Action Plan (CAPA) is a quality management strategy used often in the manufacturing and production industries to identify and rectify systematic defects and ensure they aren't repeated. Its use in research stems from the Food and Drug Administration (FDA) requirement that "each manufacturer shall establish and maintain procedures for implementing corrective and preventive action." (21 CFR 820.100(a))

The process of creating a CAPA can also be applied to addressing other problems such as noncompliance or unanticipated problems (termed nonconformance for the purposes of this guidance) that happen during the conduct of human subjects research. When nonconformance occurs and is reported to the IRB, the report to the IRB must include a CAPA to demonstrate how the problem will be corrected and prevented or mitigated in the future.

For the IRB to consider a CAPA to be appropriate, the IRB is looking for the Principal Investigator to provide a detailed report and propose a robust, effective and useful CAPA that will systematically address the nonconformance.

Simply stating things in the report to the IRB such as:

- The researchers will follow the protocol
- Research personnel have been re-educated
- Research personnel will be more careful
- Someone else will double-check

is not robust or effective, and it will not be useful for the IRB reviewer nor to persons implementing the CAPA.

This guidance outlines steps to develop appropriate CAPA plan:

1. Identify nonconformance (regarding the protocol and how study activities were or were not conducted, regulations, IRB policies and directives, etc.)
2. Evaluate risk and seriousness
3. Correct the nonconformance
4. Investigate the root cause of the nonconformance

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5. Develop preventive action plans
6. Implement preventive action plans
7. Assess and modify (as needed) the preventive action plan

1. Identify the Nonconformance

When someone identifies a situation of nonconformance, the first step is to provide some context around the issue.

The PI and study team should document and discuss the nonconformance, identify the reason it occurred and consider any immediate corrections that should be implemented taking into account the rights, safety and welfare of subjects and whether a subject has been harmed or is at risk of being harmed. Carefully evaluate the reporting requirements of the sponsor, IRB, and any regulatory agencies and report appropriately. The Children's Wisconsin IRB's reporting requirements are outlined in our Reportable Events/New Information Guidance. When an event occurs, the PI must consider whether subjects should be notified; however, the PI must submit any plan for notifying subjects to the IRB to obtain IRB and institutional approval before any written notification is sent.

Specifics are defined by asking these five questions:

- What is the nonconformance?
- Where in the process did the nonconformance occur?
- When did the nonconformance occur?
- How significant is the nonconformance?
- Who is responsible for the nonconformance?

A researcher's ability to begin and close an effective CAPA, and the IRB's ability to review and assess its acceptability at addressing or mitigating the nonconformance, is directly related to a thorough understanding of the situation.

2. Evaluate Risk and Seriousness

The PI should evaluate the risk and seriousness of the nonconformance and determine whether it meets prompt reporting requirements. See Children's Wisconsin IRB Reportable Events/New Information Guidance.

If, after careful review of the guidance, there is true uncertainty about whether to report something promptly, contact the HRPP (chwirb@chw.org) for further guidance. Alternately, you may report promptly to err on the side of caution but include a description of why you are uncertain at the time of the report. You can submit an initial report and then a follow up

report when additional information is known. The report could be withdrawn if it ultimately did not require prompt reporting.

When conducting the evaluation, consider the following:

- Effects on current and future subject's rights, welfare and safety
- Potential for the problem to occur in the future, affecting the same subject or other subjects who are in the study or other studies with the same parameters
- History of any previous similar nonconformance in this or another study conducted by the same PI or study team

Once CAPA specifics have been defined, and the effect and magnitude of the nonconformance has been determined, it's time to consider corrective and preventive actions.

3. Correct the Nonconformance

Once nonconformance occurs, immediate actions must first be taken to protect the rights, safety and welfare of the subject(s).

Correcting the nonconformance is an action that should be taken as soon as possible. The specific action to take will be based on the nonconformance. For example, if the nonconformance involves use of an incorrect or inaccurate consent document, the corrective action would be to obtain consent from participants using an IRB-approved document that meets all applicable requirements. If the nonconformance involves administering an improper dose of study medication, the corrective action to mitigate risk may involve steps to counteract an overdose.

Immediate corrections should be focused on protecting the rights, safety and welfare of subjects and reporting the event. If there is a potential serious risk to one or more subjects, call the IRB for guidance before contacting all subjects, unless a delay may result in harm.

In some instances, investigators will not be able to correct the nonconformance. For example, participants may no longer be available to sign a revised consent document. In these instances, the CAPA should document the reason the nonconformance could not be corrected.

The report to the IRB must describe any immediate corrective action already taken, corrective actions that are planned, and/or reasons why corrective action is not possible for a specific circumstance. This may be submitted on the Reportable Event form if promptly reporting is required, or on the summary log if events are being reported at the time of Continuing Review or Status Report.

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4. Investigate the Root Cause of the Nonconformance

The next step is to determine **why** the nonconformance occurred. When nonconformance occurs in research, it's important to identify the cause(s) of the problem so that it can be resolved and prevented from occurring again. There can be multiple causes that contribute to one single event. The root cause is the initiating and most basic cause of a problem, which may have led to other problems. Eliminating the root cause should prevent recurrence of the problem(s).

Many CAPAs fail because the investigator automatically assumes the reason(s) for the nonconformance and does not thoroughly evaluate or investigate the cause. Causes of nonconformance could include:

- Lack of procedures to identify risks of noncompliance before study start-up
- Insufficient infrastructure/tools to prevent noncompliance (e.g. electronic systems, checklists, forms, reminder calendars, etc.)
- Lack of sufficient resources or qualified research staff to conduct the research
- Lack of understanding of the protocol requirements due to ambiguous language

A root cause analysis is the process of identifying and documenting the root cause and the downstream effect on the causal chain. Root cause analysis should focus on identifying underlying problems that may have contributed to an error rather than on mistakes made by individuals. The goal is not to blame but rather to gather knowledge to be able to educate and mitigate.

Finding the root cause of an issue isn't always easy. Sometimes it will require talking to many people and departments to understand what went wrong. Often it requires asking the questions that people tend to skip assuming the obvious answers. It often also requires writing the facts down in a systematic manner in order for the less obvious causes to become more visible.

Ask the "5 whys?" to find the root cause

The logic behind this method is simple: identify root causes by exhausting the question "why?" Brainstorm answers to questions like why did the event occur? Why were the conditions as such? Drill down further to sub-causes, ask why they occurred too.

The idea is that you'll make your way through all of the potential causes and end up identifying the one that doesn't have a proper answer to why? – The Root Cause.

For example:

1. *Why was the procedure not completed during the study visit?*

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Because the coordinator was not aware of the need for the procedure.

2. *Why was the coordinator unaware of the need for the procedure?*

Because the protocol involves multiple procedures at each visit and it is difficult to remember which procedures need to take place during a visit.

3. *Why can't the coordinator remember which procedures need to take place?*

Because no tools are available to help the coordinator remember.

4. *Why are there no tools?*

Because the PI and study team were new to research and didn't know that consideration should have been given at the outset of the study. There were no established processes for reviewing a protocol, identifying compliance risks, identifying needs and developing tools/checklists prior to study start-up.

As you can see, a thoughtful investigation into the root cause of a nonconformance event can lead to identification of important processes that can lead to reductions in noncompliance across multiple studies.

5. Develop Preventive Action Plans

Once the root cause has been established, an appropriate preventive action plan can be written.

There are two main components of a CAPA plan. One is to acknowledge and correct the existing errors that have already occurred (**Corrective** Action Plan) AND the other is to prevent the same or similar errors from occurring in the future (**Preventive** Action Plan). A CAPA can be protocol specific or more broadly applicable to a study team/department/institution process but this will largely depend on the error and result of the root cause analysis.

Investigators should identify methods to eliminate the root cause. For example, in the illustration above, the preventive action plan could include:

1. Obtaining training and mentoring to those new to research.
2. Developing a new procedure describing a process to review new protocols, identifying any compliance risks and establishing tools to reduce each identified risk.
3. Developing a checklist to help the research staff identify every required protocol procedure for each visit.

During this step, any changes to established processes should be reviewed by the impacted departments and managers. Something that positively impacts your work flow could have a

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major negative impact on another's or result in noncompliance with other institutional policies/procedures.

Preventive action plans could include things like:

- Regular review and self-audits of the research
- Establishing regular training and refreshers with the research team
- Holding frequent study team meetings to discuss challenges or glitches that come up
- Creating study specific tools, for example:
    - calendars
    - checklists that require the responsible party's signature *(checklists are often very useful tools because a checklist can simultaneously ensure compliance and provide documentation of research activities)*
    - template orders

However, specifics of a plan will depend on the specifics of the research and the root cause identified.

In general the preventive action plan should be:

- Specific to address the root cause as identified.
- Robust yet simple enough to actually be implemented and consistently followed.
- Measurable and set up so that it can be monitored to determine its effectiveness; a monitoring plan should be described in the report to the IRB.
- Include target achievement dates.
- May include additional corrective actions.
- Should clearly demonstrate how the PI, who is ultimately responsible for the conduct of all aspects of the research, is involved in the plan.

Below is a list of questions to ask while developing and implementing your CAPA plan. The answers to these questions should be part of the thorough description of the plan in the report to the IRB:

Who

a. Who is going to change?
b. Who is impacted by this change?

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c. Will Principal Investigator be involved in the change?
d. Who is going to teach/implement the change?
e. Who is going to track the changes?

What

a. What specific events, failures, deviations, exceptions or noncompliance occurred that resulted in the need for this CAPA plan?
b. What is the root cause of each?
c. What is going to change?
d. What is the corrective action that will be taken?
e. What is the preventive action that will be taken?

When

a. When is the CAPA going to be taught?
b. When is the CAPA going to be implemented?
c. When is the CAPA going to be evaluated?
d. When does the IRB require an update on the results of this CAPA plan?

Where are the changes being made?

How

a. How is the change proposed by the CAPA going to occur?
b. How will those affected by the proposed change be educated?
c. Is education/reeducation part of the plan? What type of education will be used?
d. How will the implementation of the CAPA be tracked? (objective and measureable)
e. How does this plan correct the event, problem, failure, deviation, exception, or noncompliance?

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f. How does this plan prevent the event, failure, deviation, exception, noncompliance from occurring again?

6. Implement Preventive Action Plans

It is not enough to simply tell the IRB what the preventive action plan is, it must be implemented and executed over time as well.

- Once the plan is implemented, investigators should keep records describing when and how each element of the plan was achieved.
- All others involved in conducting this research should be aware of the corrective and preventive action plan, particularly if their role on the research team is key to implementing this plan.

7. Assess and Modify the Preventive Action Plan

Every good CAPA process should have a built-in effectiveness checking mechanism to verify and validate that the CAPA plan is working.

- If your CAPA is applicable to a departmental process, consider whether this ongoing evaluation/monitoring should occur at the departmental level rather than at an individual study/protocol level.
- Track the effectiveness of the plan itself. After its first use, ask: Was it easy to understand and follow? Effective writing is critical to your CAPA process, it will ensure your plan and reports are clear, impartial, easy-to-understand (for both the research team carrying this out and the IRB members who review it) and complete.
- Consider holding training sessions or obtaining team review and feedback on the draft version of your CAPA procedure before it is submitted to the IRB. Use the feedback to revise the procedure and clarify difficult, confusing or vague steps.
- Maintain documentation of your ongoing evaluation of the effectiveness of your CAPA. Documenting CAPAs is another vital CAPA factor to take into account. If the CAPA is not thoroughly documented, auditors, regulators and the IRB will assume it was not done or that investigators did not consider the nonconformance to be a serious matter.

If your evaluation demonstrates that the CAPA is not effective, you should amend your CAPA and begin the cycle of training, implementing and evaluating again.

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In closing, it is important to remember that the ultimate goal of a CAPA plan is to protect the rights, safety and welfare of study participants; however, all members of the research team will benefit from a well-written and executed CAPA as part of the overall conduct of human subject research.