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Association of American Cancer Institutes

PROTOCOL DEVIATIONS

IDENTIFY, DOCUMENT, TRACK, REPORT: A STEP-BY-STEP GUIDE

The AACI Clinical Research Innovation Protocol Deviations Working Group drafted the following recommendations addressing protocol deviations within cancer clinical trials.

Two examples (one that impacts participant safety and one that does not) are provided to demonstrate the steps throughout this guide.

WHAT IS A PROTOCOL DEVIATION?

- As defined by the FDA in "Compliance Program Guidance Manual, Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, December 8, 2008":
  - A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change.
  - A protocol deviation could be a limited prospective exception to the protocol (e.g., agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria).
  - Deviations are expected to occur and vary in the level of impact to research participant safety and overall data integrity. The evaluation, documentation, and prevention plan when a deviation occurs is critical.

EXAMPLE 1: IMPACTS PARTICIPANT SAFETY

Participant 6075 came in for their C2D1 visit on a study with an oral medication. The protocol schedule required an EKG to be completed at the visit. The protocol states that study medication should be held in the event that the QTcF is ≥450. The research coordinator/nurse made all of the necessary arrangements for the EKG.

The participant was anxious to get to their next appointment and asked if the study medication prescription could be prepared while they were waiting for the EKG. The research coordinator/nurse initiated the pharmacy dispensing process. The research coordinator/nurse was called away before the EKG was read by the investigator.

The participant assumed because the EKG procedure had been completed, they could go pick up the medication at the pharmacy. The participant picked up their medication and took their daily dose the following morning. The investigator reviewed the EKG the following day and the QTcF was noted to be 482.

EXAMPLE 2: DOES NOT IMPACT PARTICIPANT SAFETY

Participant 7540-004 dosed at 0830 hours and all subsequent required day 1 pharmacokinetic (PK) samples were collected per protocol. The protocol stated that a 72-hour (+/- 2 hours) PK sample must be obtained. The participant lived approximately 3 hours away from the cancer center and was caught in a snowstorm on their drive.

The participant arrived at 1035 hours and the sample was unable to be obtained until 1042 hours making it 12 minutes out of the protocol-required window.

IDENTIFY, DOCUMENT, TRACK, REPORT: A STEP-BY-STEP GUIDE

1. Confirm the Presence of a Deviation by Referring to the Protocol and Take Any Immediate Corrective Action

2. Evaluate and Review the Deviation

Policies may vary among institutions. Consult your institution's evaluation and review policy for the appropriate next steps.

3. Conduct a Root Cause Analysis

When conducting a root cause analysis, consider the "5 whys," think about it from different perspectives, and consider if it was a process, training, or communication issue. It isn't about assigning blame, but about documentation, prevention, transparency, accountability, and ownership. Issues should be addressed with a culture of "team failure, team solution."

4. Develop Corrective and Preventative Actions (CAPA)

Using the root cause as your guide, work with parties involved in the process to identify what could be done to prevent this deviation from occurring again.

5. Report to Sponsor as Required

This process may differ among institutions and/or based on the study. Review the protocol to determine how to report a deviation to the sponsor, and what information should be included.

6. Reporting Timeframes and IRB Reporting Policies

Policies may vary. Consult your institution's evaluation and review policy for the appropriate next steps.

STEP 1: CONFIRM PRESENCE OF A DEVIATION BY REFERRING TO THE PROTOCOL

Example 1: Impacts Participant Safety

- In the dose modification section of the protocol, it states the dose should be held for a QTcF ≥ 450. EKG should be repeated daily until the QTcF gets below 450, and then daily dosing may resume. The participant's QTcF required a dose hold that did not take place, resulting in a deviation.

- **Corrective Action:** The investigator contacted the patient and notified them of the prolonged QTcF and asked them to hold their dose immediately and return to the cancer center as soon as possible for a repeat EKG to ensure that the participant was safe. EKG was obtained and the QTcF was 460. The participant was instructed to continue holding their dose and to return to the cancer center daily for repeat EKG. The investigator contacted the medical monitor for further guidance.

Example 2: Does Not Impact Participant Safety

- In the study procedures section, it states that the 72-hour PK must be obtained within +/- 2 hours from the time of dosing on day 1.
  - NOTE: If the protocol used the word "**should**" instead of "**must**," this would **not** be considered a deviation.

- **Corrective Action:** The PK was obtained as soon as possible after the patient's arrival and the actual time of draw was noted on the requisition form. The study sponsor was notified in accordance with the protocol requirements

STEP 2: EVALUATE AND REVIEW THE DEVIATION

Example 1: Impacts Participant Safety

- The research coordinator/nurse referred to the departmental SOP on deviation reporting, which indicated that the deviation needed to be reviewed with the investigator within 24 hours and due to the potential impact on patient safety, sponsor notification was required within 48 hours.
- The research coordinator/nurse reviewed the deviation with the investigator to determine the impact on patient safety and the potential for corruption of study data and documented the PI's assessment.
- This information was recorded in the departmental CTMS as required.
- The SOP indicated that manager review was the next step followed by regulatory review.
- The deviation along with the PI's assessment was reviewed for IRB reporting requirements. Per the institutional guidelines, this situation required reporting to the IRB.

Example 2: Does Not Impact Participant Safety

- The research coordinator/nurse reviewed the departmental SOP on deviation reporting.
- The situation was discussed and reviewed with the investigator
- The PI evaluated the deviation, and it was recorded in the institution's CTMS.
- The IRB reporting requirements were reviewed, and this deviation did not meet the reporting requirements.

STEP 3: CONDUCT A ROOT CAUSE ANALYSIS

Example 1: Impacts Participant Safety

There were several issues that led to this deviation:

- The patient knew that they had to have an EKG but was not aware that the procedure was part of the safety parameters required prior to treatment.
- EKG results were reviewed by the investigator the next day.
- The patient was able to pick up their medication from the pharmacy with no communication about the safety parameters for the treatment.

Example 2: Does Not Impact Participant Safety

- The root cause of this deviation was an unexpected snowstorm. There was nothing the patient or study team could have done to prevent this from occurring.

STEP 4: DEVELOP CORRECTIVE & PREVENTATIVE ACTIONS (CAPA)

Example 1: Impacts Participant Safety

- To correct the identified root causes, the investigator will be aware of the EKG and be available to read it to determine if any dosing modification is required and the study coordinator/nurse should implement a plan for communicating the safety parameters from the investigator, research staff, and pharmacy to the patient, allowing all involved parties to be aware of the plan.
- Additionally, they should implement a medication dispensing process that ensures an “OK to treat” determination is made before dispensing the medication.
- Finally, they should consider having research staff deliver oral medications to the patient once the safety parameters have been reviewed, rather than have the patient go directly to the pharmacy.

Example 2: Does Not Impact Participant Safety

- There was nothing that would have prevented this deviation from occurring.

STEP 5: REPORT TO SPONSOR AS REQUIRED

Example 1: Impacts Participant Safety

- The protocol indicated that in the case of a deviation that could have impacted participant safety, the study team should get in touch with the medical monitor for further guidance.
- The PI contacted the medical monitor to notify them about the deviation and to identify if any additional procedures should be taken to protect the participant. This correspondence was retained in the participant's research record.

Example 2: Does Not Impact Participant Safety

- The protocol gave no guidance on sponsor reporting parameters. All documentation regarding the deviation was retained in the participant's research record.

STEP 6: REPORTING TIMEFRAMES AND IRB REPORTING POLICIES

Example 1: Impacts Participant Safety

- Policies may vary among institutions. Consult your institution's evaluation and review policy for the appropriate next steps.

Example 2: Does Not Impact Participant Safety

- Policies may vary among institutions. Consult your institution's evaluation and review policy for the appropriate next steps.

ADDITIONAL RESOURCES

1. U.S. Department of Health & Human Services Office for Human Research Protections: Recommendation on Protocol Deviations
2. U.S. FDA Guidelines on Corrective and Preventative Actions

AACI thanks the 2023 Clinical Research Innovation (CRI) Education and Operation Subcommittee for authoring this guide.
For questions, please contact AACI CRI at cri@aaci-cancer.org

AACI Association of American Cancer Institutes