

DEVIATIONS: DOCUMENTATION AND REPORTING

Introduction and Purpose

Deviations from the clinical research protocol, Good Clinical Practice (GCP) guidelines, or applicable federal regulations have the potential to place study participants at risk and can undermine the scientific integrity of the study, thus jeopardizing the justification for research. Therefore, deviations should be addressed and corrected where possible, and preventative measures should be established to prevent future occurrences from taking place.

Deviations must be documented according to the GCP guidelines, and must be reported to the Institutional Review Board (IRB) according to the guidelines set forth in this SOP and according to IRB policies & procedures. The IRB policies and procedures for deviation reporting in this SOP are for studies overseen by the University of Utah IRB. For studies using a central IRB (CIRB) or an IRB of record other than the University of Utah, the deviation reporting requirements for that board must be followed as well as the local reporting requirements for University of Utah Human Research Protections Program (HRPP).

The principal investigator (PI) is responsible for conducting clinical research in accordance with the current IRB-approved protocol, GCPs and applicable federal regulations. The PI may not make any changes to the protocol treatment or procedures without prior approval from the IRB except when necessary to protect the safety, rights, or welfare of study participants.

Definitions and Acronyms

Clinical Research: Clinical research includes all research involving human participants. It does not include secondary studies using existing biological specimens or data collected without identifiers or data that are publicly available.

Clinical Trial: Clinical trials are clinical research studies involving human participants assigned to an intervention in which the study is designed to evaluate the effect(s) of the intervention on the participant and the effect being evaluated is a health-related biomedical or behavioral outcome.

CAPA:	Corrective and Preventative Action
CFR:	Code of Federal Regulations
CIRB	Central IRB
ERICA:	Electronic Research Integrity and Compliance Administration program
FDA:	United States Food and Drug Administration

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GCP:	Good Clinical Practice
ICH:	International Council on Harmonization
IRB:	Institutional Review Board
PI:	Principal Investigator
SOP:	Standard Operating Procedure

Procedure

1. Identification of Protocol Deviations

- 1.1. Clinical research investigators and staff should be familiar with the study protocol, GCPs, and applicable federal regulations and strive to ensure that these are followed in the conduct of clinical research.
- 1.2. Deviations should be identified by the PI or research staff member as they occur. When a deviation is thought to have occurred, it should be verified against the study protocol, applicable regulations or relevant GCP principles.
 - 1.2.1. Protocols will generally have visit windows established for completion of scheduled procedures and assessments. Procedures and assessments that are completed outside the established windows are considered deviations.
 - 1.2.2. If a protocol does not establish windows and does not explicitly state exact timelines for procedures or assessments, then reasonable windows may be determined by the investigator, rather than incurring multiple deviations.
- 1.3. Deviations may be identified through routine monitoring visits or audits of the clinical research records. These deviations should be verified as above and presented to the PI for timely assessment and IRB reporting, if warranted.

2. Documentation of Deviations

- 2.1. All deviations, regardless of severity or outcome, must be documented. Deviations may be documented electronically (OnCore, REDCap, Microsoft Excel database, etc.), or written on a paper form (e.g. Protocol Deviation Log).
- 2.2. A clear, yet concise description of the deviation should be recorded, including a description of the regulatory requirement, GCP principle or protocol procedure that was not followed.

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- 2.3. The deviation record should include adequate attribution, including: date of deviation, identification of the study, subject ID, study visit, the date the deviation was identified, and identity of the individual recording the information.
- 2.4. If corrective action was taken to address the deviation, details describing the corrections should also be added to the record.

3. Deviation Review and Reporting

- 3.1. All Deviations will be reviewed and assessed by the PI.
- 3.2. Deviations noted by study staff or monitors will be communicated to the PI in a timely manner.
 - 3.2.1. Study staff should notify the PI of serious deviations affecting subject safety within 48 hours, whenever possible. If the PI is not immediately available, study staff will provide notification of serious deviations as soon as possible.
 - 3.2.2. Other deviations of less severity may be communicated to the PI at a monitoring visit close-out meeting, or in a regular study team meeting following discovery of the deviation.
- 3.3. For industry-sponsored clinical research, the protocol will typically contain requirements for deviation documentation and reporting to the sponsor. Study-specific requirements should be followed according to each protocol.
- 3.4. The PI will determine whether the deviation meets one or more of the following IRB reporting requirements:
 - **Intended to eliminate apparent immediate hazard** to a research participant (such as changing the dose of a medication due to toxicity)
 - **Caused possible harm to participants or others, or places them at increased risk of harm** – including physical, psychological, safety, economic, or social harm, such as breach of confidentiality
 - **Possible serious or continued non-compliance**
 - *Serious non-compliance* are deviations that result in significant harm (physical, psychological, safety, or privacy) or significantly increase the possibility or likelihood of harm to the health, rights or welfare of study participants.
 - *Continuing non-compliance* is a pattern of repeated actions or omissions to act (either serious or non-serious in nature) that suggests a future likelihood of recurrence and that indicates a deficiency in the ability or willingness to comply with the protocol, GCPs or regulations.

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3.4.1. The PI must determine whether the deviations meet the IRB-reporting criteria listed above. The following scenarios are some examples (not an exhaustive list) that should be used as a guide in making these determinations:

- *Failure to obtain informed consent prior to performing protocol related tests or procedures.* Prior to obtaining consent, administration of investigational drug/treatment, or invasive study procedures, such as exposure to radiation, have enough risk of potential physical harm to warrant reporting to the IRB. However, standard-of-care procedures such as a routine blood test prior to obtaining consent may not be of sufficient risk to be reported.
- *Use of an outdated or incorrect informed consent document.* This will generally require IRB reporting based upon the type of information that was not provided or was provided incorrectly to the participant. The inadvertent use of an outdated consent form having no differences with the current version may not warrant IRB reporting. However, once this deviation is noticed, continued use of an outdated consent form, or use of an outdated form when the current version contains changes to the Risks or Study Procedures section should be reported to the IRB.
- *Enrollment of a study subject who did not meet all inclusion criteria, or met one or more exclusion criteria.* Safety-based eligibility criteria such as ECG parameters, liver function test lab values, or prohibited concomitant medications, if not met, can place study participants at greater risk of physical harm and deviations from these criteria should be reported to the IRB. Deviations from eligibility criteria that establish baseline parameters such as body mass index or that are slightly outside screening timeframes, however, may not increase risk to study subjects and not warrant IRB reporting, unless missing data is needed for assessment of the primary study objective.

3.4.2. Additional examples of deviations that meet the requirements for IRB reporting are listed below.

- Administration of an incorrect investigational drug, assignment of an incorrect investigational device, or dose error significantly greater than the protocol-specified dose
- Failure to implement a protocol-specified dose modification for safety/toxicity

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- Treatment with drug/device or a treatment delay beyond the period allowed in the protocol
 - Failure to perform a study visit or procedure that may affect subject safety or the primary objective of the study
 - Breach of confidentiality, as defined by [IRB guideline](#)
 - Enrollment, treatment or data collection without IRB-approval of the study, after IRB approval has expired, or after acknowledgement of study closure and Final Report from the IRB
 - Conducting study procedures at an unapproved site
 - Minor deviations that may not individually require reporting, but that are continually repeated without correction or implementation of a protocol amendment
- 3.5. The PI will use his or her clinical expertise combined with careful consideration of the clinical research protocol, subject safety, and applicable regulations to determine if the deviation meets the IRB reporting requirements.
- 3.6. The assessment for IRB reporting by the PI should be documented in the electronic or paper-based record, and should be signed or initialed and dated by the investigator.
- 3.7. If the deviation is determined reportable to the IRB, the study coordinator or clinical research coordinator should work with the PI to complete the deviation report in ERICA.
- 3.7.1. Each section of the report template should be completed with sufficient detail to effectively describe the deviation to IRB administration and board reviewers.
- 3.7.2. The report section to describe the plan to prevent the deviation from occurring in the future is particularly important. Corrective and preventative action plans (CAPA) should be carefully developed, so that when implemented, they address the root cause of the problem and prevent further occurrences. If the CAPA involves re-training, this training should be documented.
- 3.8. The PI must submit the complete report in ERICA within 10 working days from the date that the deviation is identified or the study team is notified of the deviation.

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- 3.8.1. If the deviation report is not submitted to the IRB within 10 working days, a written explanation for its tardiness must accompany the report. Late reports may be assessed by the IRB as additional non-compliance.
- 3.9. The IRB will evaluate the deviation report to determine if it had a significant effect on risk to study participants' safety, rights or welfare, or had an effect on the integrity of the scientific data.
 - 3.9.1. The IRB review may result in a request for additional information, which the PI must respond to within the requested timeframe.
- 3.10. After IRB review is complete, the PI will be notified of the outcome, which may include the determination of "Serious Non-Compliance" and/or "Continued Non-Compliance". Such determinations may require additional corrective and preventative actions to be carried out by the PI and study team.
- 3.11. IRB deviation reports and supporting documents should be retained with the study records.
- 3.12. If the study is under the review and approval authority of a CIRB or an IRB of record other than the University of Utah, the deviation reporting requirements of that IRB must be followed. Local deviations that meet the University of Utah IRB reporting criteria for prompt reporting, must also be submitted according to that policy for review by the University of Utah HRPP.

Materials Required

- IRB-approved protocol and informed consent form
- Protocol Deviation Log, or other department-specific or study-specific deviation documentation form, or electronic data capture system
- Access to ERICA (IRB electronic application and document system)

References

- 45 CFR Part 46.103(b)(5)
- ICH Guidance for Industry E6(R2): Good Clinical Practice, Section 4.5
- University of Utah IRB SOP 902: Protocol Deviations

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Document Approval



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DATE

Revision History

Version Date	Change Summary
12Nov2019	Original Version
26Jun2020	Version #2 – minor updates for clarity and ease of reading

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