



1. Purpose

The purpose of this operating procedure is to outline the procedures to be followed when a deviation or violation to the approved study protocol has been identified.

2. Responsibilities

Research Site: Responsible for reporting non-compliance issues to CERU.

CERU: CERU is responsible for identifying, following up and documenting protocol violations and deviations.

3. Procedures

3.1 Protocol deviations and violations are unplanned or unforeseen changes to procedures and algorithms found within the approved study protocol.

3.2 A **protocol violation** is defined as non-compliance with the study protocol and/or procedures that may impact study participant safety, the integrity of study data and/or study participant willingness to participate in the study.

3.3 Refer to study specific work instructions for the protocol violation definition being applied to a particular trial. Examples of protocol violations include, but are not limited to:

3.3.1 Failure to obtain informed consent.

3.3.2 Informed Consent performed by someone other than individuals authorized and trained to obtain consent.

3.3.3 Enrollment of a participant who did not fulfill all inclusion/exclusion criteria.

3.3.4 Performing study procedures not approved by the local Research Ethics Board (REB).

3.3.5 Failure to report a serious adverse event.

3.3.6 Failure to perform a required lab tests that, in the opinion of CERU or Qualified Investigator (QI), may affect participant safety or data integrity.

3.3.7 Investigational product dispensing or dosing error.

3.4 A **protocol deviation** is non-compliance with the study protocol and/or procedures that does not impact study participant safety, compromise the integrity of the study data and/or study participant willingness to participate in the study.

3.5 Refer to study specific work instructions for the protocol deviation definition being applied to a particular research study. Examples of protocol deviations include, but are not limited to:

3.5.1 Implementation of unapproved recruitment procedures.

3.5.2 Missing original signed and dated consent form (only a photocopy available).

3.5.3 Missing pages of executed consent form



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- 3.5.4 Failure to follow the approved study procedure that, in the opinion of CERU or QI, does not affect study participant safety or data integrity:
 - 3.5.4.1 Study procedure conducted out of sequence
 - 3.5.4.2 Failure to perform a required laboratory test
 - 3.5.4.3 Missing lab results
- 3.5.5 Over-enrollment
- 3.5.6 Enrollment of study participants after REB approval of the study expires
- 3.5.7 Failure to submit continuing review application to the REB before study expiration.
- 3.6 CERU may be made aware of a protocol violation/deviation through regular communications with the research site, via a case report form or during a site monitoring visit.
- 3.7 CERUC should document the protocol violation/deviation. This may be documented in a note to file or a form developed specifically for the trial.
- 3.8 Protocol violation and deviation documentation should contain at a minimum, the following:
 - 3.8.1 Study Participant Identification
 - 3.8.2 Classification as either a violation or deviation
 - 3.8.3 Description of the violation or deviation
 - 3.8.4 Follow-up/resolution
- 3.9 Whenever appropriate, CERU will provide training and support to the research site to ensure a previously reported protocol violation does not reoccur.
- 3.10 CERU will provide the research site with a copy of protocol violation/deviation documentation for their study regulatory files.
- 3.11 If the site has committed a protocol violation, CERU will inform the research site to contact their local REB to receive direction whether a report to the REB is required.
- 3.12 CERU and/or the Data Monitoring Committee (DMC) will evaluate protocol violations for serious and/or persistent non-compliance issues, and if deemed necessary, may amend the protocol or prematurely terminate a research site's participation in the study.

4. References

- 4.1 ICH GCP Section 4.5: Investigator - Compliance with Protocol
- 4.2 ICH GCP Section 5.20: Sponsor - Noncompliance