

Guidance and Procedures for Investigators

Topic: Reporting Protocol Violations

Protocol Violations

Protocol violations are considered to be any change or departure (i.e. “deviation”) from the study design or study procedures of a research protocol that affects the subject’s rights, the risk/benefit ratio of the study, safety or well-being and/or completeness, accuracy or reliability of the study data. Essentially, a protocol violation is a deviation from the “flight plan” or protocol itself.

In many cases, protocol deviations that will be defined as violations will fall into one of the following 5 categories:

1. The violation has harmed or posed a significant or substantive risk of harm to the research subject.
2. The deviation has compromised the scientific integrity of the data collected for the study.
3. The deviation is a willful or knowing breach of human subject protection regulations, polices, or procedures on the part of the investigator(s).
4. The deviation involves a serious or continuing noncompliance with federal, state, local, or University human subject protection regulations, polices or procedures.
5. The deviation is inconsistent with the University’s Human Research Protection Program’s (HRPP) research, medical, or ethical principals.

The following are examples of protocol deviations (this list is not intended to be exhaustive). Note that any of these deviations is a protocol violation:

- Variations or errors in drug dosing/dispensing/storage
- Use of prohibited medications
- Enrolling subjects who did not meet the inclusion/exclusion criteria
- Research subject met withdrawal criteria during the study but was not withdrawn
- Unauthorized (i.e. not IRB Approved) persons (faculty, staff, students, residents, etc.) participating in the conduct of a research study
- Premature “unblinding” of research treatment or data
- Loss or corruption of samples and/or data
- Failure to obtain informed consent prior to initiation of study-related procedures
- Use of an unapproved or expired consent document or oral consent procedure
- Incorrectly performed or missing protocol-required tests and procedures
- Incorrect handling of biological samples
- Changing the protocol without prior IRB approval

- Falsifying research or medical records
- Performing tests or procedures beyond the professional scope or privilege status (credentialing)
- Breach in confidentiality
- Inadequate or improper informed consent procedures
- Failure to submit Data Safety Monitoring Board (DSMB) reports to OPHS in a timely manner (see section 18.4 “Submission of DMSB Reports to OPHS” for policy).
- Failure to report unanticipated problems involving risks to subjects or others, and adverse events (serious and/or unexpected) in a timely manner (see section 7.4 “Defining and Reporting Unanticipated Problems Involving Risks to Subjects or Others, and Adverse Events” for policy)
- Protocol deviations/violations identified by sponsor monitor visits, or study coordinator that may affect the safety of the participant or the integrity of the study data.

Protocol violations should be reported to OPHS within **10 working days** of discovery. This report must use the appropriate procedures described below.

For Clinical Trials:

A letter, signed by the Principal Investigator, must be submitted which contains the following information:

- IRB Project #, Subject ID #, Date(s) of the Event(s)
- Description of the protocol violation
- How the event deviated from the protocol
- Date the study sponsor was notified of the violation
- Investigator’s assessment regarding any effect on subject risk as a result of the violation. Include a description of additional treatment the subject required as a result of the violation.
- Corrective action plan describing what will be implemented in order to avoid the violation from reoccurring in the future.

If applicable, please also submit supporting documentation from the study sponsor.

For Non-Clinical Trials:

Investigators should complete and sign the “Protocol Violation Reporting Form,” and submit the form to OPHS for review. Submission of this form does not preclude additional investigation or inquiry by OPHS or the IRB. The form is available on the OPHS website at:

<http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm?pageName=IRB%20Forms>

Minor Protocol Violations

Minor protocol violations are considered to be those changes or alterations in the conduct of the study which do not have an impact on the subject’s rights, safety, or well-being or completeness, accuracy, or reliability of the study data. The following are examples of minor protocol deviations:

- A minor variation in clinic visits/follow up (e.g. “Day 10 visit” on day 14) if no protocol medication, treatment, or supervision is missed.

- Collection of study data (e.g. temperature reading) performed incorrectly by subject or subject's parent/guardian
- Withdrawal of subjects for logistical reasons (e.g. moved out of town)
- Changes in the formatting of an IRB approved study questionnaire (for example: font size, font face, margins, etc)

The OPHS/IRB does not require that minor protocol deviations be reported by the investigator. However, if the study sponsor requires that the deviation be reported to the IRB, the IRB will provide acknowledgement of receipt and review of the deviation. In any case, investigators should contact OPHS staff for guidance in determining if a deviation should be reported as a protocol violation if they are unsure.

Reporting of Errors that Occur During the Informed Consent Process

Examples of informed consent errors include the following:

- Subject undergoes study procedure(s) prior to giving informed consent (**this is a protocol violation and should be reported as such**)
- Subject signs an outdated or incorrect version of the consent form
- Subject undergoing research intervention is not re-consented when new information is incorporated into the consent form
- Other consenting error the study sponsor requires be reported to the IRB.

Errors that occur during the informed consent process must be reported to OPHS within **10 working days** of discovery using the appropriate procedures described below.

For Clinical Trials:

A letter, signed by the Principal Investigator, must be submitted which contains the following information:

- IRB Project #, Subject ID #, date the error occurred
- Description of the consenting error
- Date the study sponsor was notified of the error
- Investigator's assessment regarding any effect on subject risk as a result of the error. Include description of follow up procedures undertaken to correct the error.
- Corrective action plan describing what will be implemented in order to avoid the error from reoccurring in the future.

If applicable, please also submit supporting documentation from the study sponsor.

For Non-Clinical Trials:

Investigators should complete and sign the "Protocol Violation Reporting Form," and submit the form to OPHS for review. Submission of this form does not preclude additional investigation or inquiry by OPHS or the IRB. The form is available on the OPHS website at:

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Guidance for Avoiding Protocol Violations

The Principal Investigator is the responsible party and will be held accountable for the conduct of the study. There are some steps that investigators can take to prevent or reduce the likelihood of protocol deviations or violations occurring during the conduct of their study. Here are several recommendations:

- It is important for all study personnel to be familiar with the protocol and understand their role in the study. The Principal Investigator should make sure that the delegation of tasks is well understood by the study personnel.
- Researchers should plan that protocol violations might occur during the study, and have an agreed upon procedure for discussing and reporting protocol violations. For example, it is important to understand what type of documentation will be required by the sponsor, determine who will notify the IRB of a violation and determine what course of action might be taken to prevent common protocol violations.
- Prepare study amendments in a timely manner and submit them to OPHS for IRB review before implementing the changes.
- Ensure that Serious Adverse Event (SAE) and DSMB reports are submitted to OPHS in a timely manner.
- Ensure that all key personnel working on a study are IRB approved to do so.
- Ensure that the investigator and research team know the regulations pertaining to research with human subjects, as well as protocol violations.