

SOP 407: PROTOCOL DEVIATIONS AND UNANTICIPATED PROBLEMS

1. POLICY

Protocol deviations and unanticipated problems may be discovered in a variety of ways, including but not limited to discovery by research staff, IRB Staff or IRB Reviewers; Quality Improvement (QI)/Evaluation processes; communications with research participants; or communications from related University administrative units.

Despite the method of discovery, investigators are required to promptly report to the IRB any event that may represent a major protocol deviation and/or unanticipated problem as described below.

The time of Continuing Review Investigators are required to report to the IRB minor protocol deviations and other harm caused to research participants that do not constitute an unanticipated problem.

Specific Policies

1.1 PROTOCOL DEVIATIONS

1.1.1 Protocol Deviation: A protocol deviation is any change, divergence, or departure from the research study approved by the IRB.

Upon discovery, the Principal Investigator is responsible for reporting protocol deviations as described in Section 1.1.3 below to the IRB within five (5) days using the Protocol Deviation form available on the electronic information system.

1.1.2 Minor Protocol Deviation: A minor protocol deviation is any change, divergence, or departure from the research protocol that has not been approved by the IRB and that DOES NOT have a major impact on the participant's rights, safety, or well-being or on the completeness, accuracy, and reliability of the research project data. (Examples include, but are not limited to: study procedure or participant visit conducted out of time frame, or blood samples obtained at times close to but not at the time specified in the IRB approved protocol, or having participants sign a non-stamped consent document, not providing the participant with copies of the consent documents.)

Changes or alterations in the conduct of the research project that do not have a major impact on the participant's rights, safety, or well-being, or on the completeness, accuracy, and reliability of the research project data are considered minor protocol deviations. Minor protocol deviations are reported to the IRB by the Investigator at the time of Continuing Review.

1.1.3 Major Protocol Deviation: Examples of major protocol deviations are described below. There may be other examples. Investigators are encouraged to contact the IRB to determine on a case-by-case basis whether a protocol violation has occurred. Major protocol deviations falling into the following categories shall be

considered an Unanticipated Problem that will require IRB review as determined by the IRB Chair, IRB designee or Board:

I. The deviation has harmed or posed a significant or substantive risk of harm to a research participant (this is also an unanticipated problem)

Examples:

- A research participant received the wrong treatment or incorrect dose.
- A research participant met withdrawal criteria during the research project but was not withdrawn.
- A research participant received an excluded concomitant medication.

II. The deviation compromises the scientific integrity of the data collected for the research project.

Examples:

- A research participant was enrolled but does not meet the protocol's eligibility criteria.
- Failure to treat research participants per protocol procedures that specifically relate to primary efficacy outcomes (if it involves patient safety, it meets the first category above).
- Changing the protocol without prior IRB approval (except where necessary to eliminate an apparent immediate hazard to the participant).
- Inadvertent loss of samples or data.

III. The deviation is a willful or knowing breach of human subjects research protection regulations, policies, or procedures on the part of the investigator(s).

Examples:

- Failure to obtain informed consent prior to initiation of research project-related procedures.
- Falsifying research or medical records.
- Performing tests or procedures beyond the individual's professional scope or privilege status (credentialing).

IV. The deviation involves a serious or continuing noncompliance with federal, state, local, or University human subjects research protection regulations, policies, or procedures.

Examples:

- Working under an expired professional license or certification.
- Failure to follow federal and/or local regulations and intramural research or University policies.
- Repeated minor deviations.

V. The deviation is inconsistent with the HRPP's research, medical, or ethical principles.

Examples:

- A breach of confidentiality.
- Inadequate or improper informed consent procedure.

1.2 Review of Protocol Deviations

If, in the opinion of the Investigator, the deviation represents a minor protocol deviation, the investigator will track this deviation in the Protocol Deviation Summary Report and submit this and all deviations that have occurred since the last IRB review at the time of Continuing Review.

When a deviation occurs and if, in the investigator's opinion, the deviation meets the criteria for an unanticipated problem involving risks to participants or others or is a major protocol deviation involving risks to participants or others, the investigator shall complete the Protocol Deviation Report and submit this to the IRB within five (5) University business days.

Whether the Protocol Deviation Report or the Protocol Deviation Summary Report is submitted, the IRB Chair or IRB designee shall also determine whether any of the protocol deviations meet the definition of an unanticipated problem involving risks to participants or others.

If the IRB Chair or IRB designee determines that the deviation may represent an unanticipated problem involving risks to participants or others or that the deviation resulted from serious or continuing noncompliance, the IRB Administrator shall place the deviation on the agenda of the next available IRB meeting for review.

If the IRB Chair or IRB designee determines that the deviation is NOT an unanticipated problem involving risks to participants or others, the IRB Chair or IRB designee shall note this determination in the IRB's electronic information system. The investigator must log this event in the Protocol Deviation Summary Report and submit this report at the time of Continuing Review.

1.3 Unanticipated Problems Involving Risks to Participants or Others

Investigators are required to submit to the IRB within five (5) University business days of discovery any unanticipated problems (both internal and external) involving risks to participants or others. This is accomplished by answering the questions within the Unanticipated Problem Report form. If all three criteria are answered "YES", the event may constitute an unanticipated problem; however, only the convened IRB can make this determination. To receive the IRB determination, the investigator must submit the Unanticipated Problem form to the IRB for further review.

If any of the three criteria in the form are not answered "YES", the investigator should log this event in the Summary of Participant Harms and submit the Summary of Participant Harms to the IRB at Continuing Review.

There is a high probability that the following problems/events represent some of the types of unanticipated problems involving risks to participants or others:

- Any harm experienced by a participant that in the opinion of the Investigator, is both unexpected and related to the research, regardless of whether the harm was an on-site or off-site adverse event and regardless of whether the harm was a serious or non-serious adverse event.
- Information that indicates a change to the risks or potential benefits of the research. For example:
 - An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different from that initially presented to the IRB.
 - A paper is published from another study that shows that the risks or potential benefits of the research may be different from that initially presented to the IRB.
- A breach of confidentiality of the research project data than was previously known or recognized.
- A change to the protocol made without prior IRB review to eliminate an apparent immediate hazard to a research participant.
- Incarceration of a participant who is enrolled in a protocol not approved to enroll prisoners.
- A sponsor-imposed study suspension due to risk to participants.
- A complaint by a participant when the complaint indicates unexpected risks or when it cannot be resolved by the research team.
- A change in FDA labeling or FDA withdrawal from marketing of a drug, device, or biologic used in the research protocol.
- An unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application [including a supplementary plan or application], or any other unanticipated serious problem associated with a device that relates to the rights and welfare of participants).

It is within the authority of the IRB to initiate a For-Cause Evaluation or to require IRB Education or QI/Evaluation visits to promote research integrity if the IRB receives an excessive number of reported protocol deviations or unanticipated problems involving risks to participants or others or if the IRB independently suspects investigator noncompliance or improprieties on the part of the investigator and/or research personnel.

1.4 Determination of an Unanticipated Problem Involving Risks to Participants or Others

If the IRB Chair or IRB designee determines on the Unanticipated Problem Report form that the problem/event may represent an unanticipated problem involving risks to participants or others or the problem/event resulted from serious or continuing noncompliance, the IRB Administrator shall place the event on the agenda of the next available IRB meeting for review.

If the IRB Chair or IRB designee determines on the Unanticipated Problem Report form the problem/event is NOT an unanticipated problem involving risks to participants or others and did not result from serious or continuing noncompliance, the IRB will administratively withdraw the submission and will request the Investigator log this event in the Summary of Participant Harms and submit it to the IRB at Continuing Review.

1.5 Review of an Unanticipated Problem Involving Risks to Participants or Others by the Convened IRB

In reviewing events that may represent unanticipated problems, the convened IRB shall use the primary and secondary reviewer system, as described in SOP 403, Initial Review - Criteria for IRB Approval. The Unanticipated Problem Report form will be provided to all Board members, per SOP 302: Administrative Review and Distribution of Materials. The IRB submission materials will be available at the Board meeting for review.

The possible actions that could be taken by the IRB at the meeting include, but are not limited to:

- Requiring the investigator to modify the protocol.
- Modifying the information disclosed during the consent process.
- Providing additional information to past participants.
- Notifying current participants when such information might relate to participants' willingness to continue to take part in the research.
- Requiring that the current participants re-consent to participation.
- Modifying the continuing review schedule.
- Monitoring the research.
- Monitoring the consent process and documentation.
- Suspending the research.
- Terminating the research.
- Referring to other organizational entities (e.g., VA Research and Development Committee, Radiation Safety Committee).
- Obtaining additional information.

The IRB shall report Unanticipated Problems in accordance with SOP 308: Reporting to Regulatory Agencies and Institutional Officials.

Following the convened IRB review of the unanticipated problem, more than minor modifications to the approved protocol or research documentation shall be submitted by the Investigator as described in SOP 405: Modification for review by the convened IRB.

During QI/Evaluation or Continuing Review, the IRB staff or IRB reviewer may have questions about unanticipated problems involving risks to participants or others that were not submitted to the IRB. These shall be submitted to the IRB by the Investigator. In this case, if the IRB agrees, the IRB may determine an Unanticipated Problem occurred even though the investigator did not submit the form for determination.

The unfounded classification of a Serious Adverse Event constitutes serious non-compliance

1.6 Unanticipated Problems Involving Risks to Participants or Others and Unanticipated Serious Adverse Events in VA Research Projects

For reporting, review, and determination of unanticipated problems involving risks to participants or others and unanticipated serious adverse events in VA research projects involving serious unanticipated adverse, see SOP 603A: Veterans Affairs Medical Center.

2. SCOPE

This SOP applies to all research submitted to the IRB.

3. RESPONSIBILITY

It is the responsibility of the HRPP Director and IRB Chair to review all events submitted as unanticipated problems involving risks to participants or others to determine if the event should be reported in accordance with SOP 308: Reporting to Regulatory Agencies and Institutional Officials.

The IRB Chairs are responsible to review reports of unanticipated problems involving risks to participants and others and protocol deviations and forward them to the convened IRB when appropriate.

The IRB Chair or IRB designee is responsible for selecting one Primary and one Secondary reviewer with the relevant expertise to review protocol deviations and/or unanticipated problems. If the IRB Chair or IRB designee cannot select Primary and Secondary reviewers with the relevant expertise, the IRB Chair or IRB designee shall defer the review to another IRB with Primary and Secondary reviewers with the relevant expertise or obtain consultation to obtain that expertise.

Investigators involved in human participant research shall report all protocol deviations, per Section 1.1 of this policy. Investigators involved in human participant research shall report all suspected unanticipated problems involving risks to participants or others to the IRB, per Section 1.3 of this policy.

4. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46.103,109

21 CFR 56.108,109

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects and Others and Adverse Events (Jan. 2007)

5. REFERENCES TO OTHER APPLICABLE SOPS

SOP 301: Research Submission Requirements
SOP 302: Administrative Review and Distribution of Materials
SOP 308: Reporting to Regulatory Agencies and Institutional Officials
SOP 403: Initial Review – Criteria for IRB Approval
SOP 405: Modifications
SOP 603D: Communication with Research Participants
SOP 901: Quality Improvement Program
SOP 903: Noncompliance/Scholarly Misconduct

6. ATTACHMENTS

407-A Unanticipated Problem Report
407-B Protocol Deviation/Violation Report
407-C Summary of Participant Harms
407-D Protocol Deviation Summary Report

7. PROCESS OVERVIEW

The IRB Staff confirms that all documents are reviewed for submission per SOP 301: Research Submission Requirements.

7.1 Review Procedures for Protocol Deviations

If the IRB Chair or IRB designee determines and documents on the Protocol Deviation Report form that the deviation is NOT an unanticipated problem involving risks to participants or others and the deviation was not a result of serious or continuing noncompliance, the IRB Chair or IRB designee shall withdraw the event in the IRB's electronic information system.

If the IRB Chair or IRB designee determines and documents on the Protocol Deviation Report form that the deviation may represent an unanticipated problem involving risks to participants or others or that the deviation resulted from serious or continuing noncompliance, the IRB Administrator shall place the deviation report on the agenda of the next available IRB meeting for review.

The IRB Reviewer will present the protocol deviation to the convened IRB for discussion and possible action(s). See Section 1.5 of this policy for possible actions.

Following review, the IRB Administrator will update the IRB's electronic information system and notifies the investigator of the IRB's action.

7.2 Review Procedures for Unanticipated Problems Involving Risks to Participants or Others:

If the IRB Chair or IRB designee determines and documents on the Unanticipated Problems Report form that the event is NOT an unanticipated problem involving risks to participants or others and the event is not a result of serious or continuing noncompliance, the IRB Chair or IRB designee shall indicate withdrawal of the event and request the Investigator log this event in the Summary of Participant Harms which shall be submitted by the Investigator at Continuing Review. The IRB Administrator will update the IRB's electronic submission system and sends a withdrawal letter to the investigator

If the IRB Chair or IRB designee determines and documents on the Unanticipated Problem Report Form that the problem/event may represent an unanticipated problem involving risks to participants or others or the problem/event resulted from serious or continuing noncompliance, the IRB Administrator will place the event on the agenda of the next available convened IRB meeting for review.

The IRB Reviewer will present the unanticipated problem to the convened IRB for discussion and IRB action(s). See Section 1.3 of this policy for possible actions.

Following review, the IRB Administrator will update the IRB's electronic information system and notify the investigator of the IRB's action.

7.3 Reporting Requirements for Unanticipated Problems Involving Risks to Participants or Others, and Protocol Deviations

If the convened IRB determines that an event is an unanticipated problem involving risks to participants or others, the IRB staff will forward a copy of the report and the IRB letter to the Director of HRPP for reporting to regulatory agencies and Institutional Officials per SOP 308: Reporting to Regulatory Agencies and Institutional Officials.

APPROVED BY: _____ **DATE:** 08/31/2014

NEXT ESTABLISHED REVIEW DATE: AUGUST 2016