

# Human Research Protection Program Investigator Guidance



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## Protocol Deviations

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### Background:

The term “protocol deviation” is not defined by either the HHS human subjects regulations (45 CFR 46) or the FDA human subjects regulations (21 CFR 50). The federal regulations require that modifications to research occur only when prospectively approved by the IRB. Additionally, they require that all serious and continuing non-compliance is reported promptly to the IRB. Protocol deviations are a reality of the conduct of research and it is vital that they are reported to the IRB in order to assess problems in the protocol or with research management, and to make determinations of serious or continuing non-compliance.

### Scope:

This policy defines the three levels of protocol deviations and the reporting and review process for deviations.

### Policy:

- I. It is the responsibility of the Principal Investigator not to deviate from the protocol approved by the IRB, except to avoid an immediate hazard to the subject.
- II. Planned changes to the IRB-approved protocol, i.e., protocol deviations and protocol exceptions, must be submitted as formal protocol amendments (may be termed protocol exceptions if there is no change in protocol) to the IRB and must be approved prior to initiation or implementation of the change.
- III. The PI will report all protocol deviations per the required reporting procedures.
- IV. Any protocol deviations that meet the definition of serious and/or continuing non-compliance or unanticipated problems involving risks to subjects or others will be reported to the appropriate agencies per the policies on serious and continuing non-compliance, unanticipated problems, and institutional reporting requirements.

### Procedure:

- I. Reporting and Review
  - A. Minor Protocol Deviations:
    1. Minor protocol deviations do not need to be reported.
    2. If a minor protocol deviation is reported, an IRB Chair or designated IRB member will review the reported deviation. The reviewer may require corrective action to be taken when there is a pattern of repeated minor protocol deviations.
    3. Minor protocol deviations that are reported to the IRB may be reviewed and resolved by one reviewer. The reviewer will generate a memo describing the resolution.
    4. If the reviewer determines that no deviation occurred, the reviewer will generate a memo to that effect.

**B. Moderate Protocol Deviations:**

1. All moderate protocol deviations must be reported.
2. If a moderate protocol deviation is reported, an IRB Chair or designated IRB member will review reported deviation, seek consultation from other IRB members with necessary expertise when appropriate, and confirm that the protocol deviation meets the definition of moderate. The IRB Chair/Co-Chair may require corrective action to be taken for moderate protocol deviations.
3. Moderate protocol deviations may be reviewed and resolved by one reviewer.
4. The report will be considered a minor protocol deviation if it is determined that deviation meets one of those definitions.
5. If the reviewer determines that no deviation occurred, the reviewer will generate a memo to that effect.

**C. Major Protocol Deviations:**

1. All major protocol deviations must be reported.
2. Reporting Timeline - A major protocol deviation involving significant harm or risk of significant harm to a subject must be reported to the OHSU IRB within 24 hours of discovery of the deviation. All other major protocol deviations must be reported within 10 working days of discovery of the deviation.
3. If a major protocol deviation is reported, it will be reviewed initially by an IRB Chair or designated IRB member, who will make a preliminary determination regarding whether the reported action meets the definition of major deviation. If the deviation is major but no corrective action is warranted, the deviation may be resolved by one reviewer.
4. For a major deviation where corrective action is needed, two reviewers are required.
5. When two reviewers disagree on the categorization, it is reviewed by the IRB leadership team, including the IRB Chair, Vice-Chairs, and other IRB/ORIO staff as appropriate. The leadership team may also refer the matter to the convened IRB.
6. The IRB Chair may take emergency corrective action (including an order to temporarily stop research activities) if, in the IRB Chair's assessment, it appears that research subjects may be at risk of harm due to the reported protocol deviation.
7. When a major protocol deviation comes to the attention of the IRB via mechanisms other than PI reports (e.g., continuing reviews, adverse experience reports, protocol modification requests or other compliance reports), the PI will be asked to submit a protocol deviation report, which will be reviewed as above..
8. The report will be considered a minor or moderate protocol deviation if it is determined that deviation meets one of those definitions.
9. If the reviewer determines that no deviation occurred, the reviewer will generate a memo to that effect.

**II. Major Protocol Deviation Resolution**

**A.** Following a determination of a major protocol deviation, the IRB Chair or a designated IRB member will contact the PI to:

1. Explain the rationale for the determination;
2. Confirm the IRB's understanding of the facts and allow the PI to provide additional relevant information; and
3. Establish and/or confirm the corrective action plan.

**B.** Actions the IRB and/or institutional leadership may take in response to a major protocol deviation may include but are not limited to termination of the study, suspension of the study until corrective action is taken, increased reporting or monitoring requirements for the study or

the investigator, mandatory compliance education, additional oversight, or reassignment of some or all of the PI duties to another person.

- C. Depending on the nature and seriousness of the deviation, the IRB and/or institutional leadership may require an audit of some or all studies for which the investigator in question serves as PI.
- D. If it appears to the reviewers that academic misconduct (plagiarism, falsification, fabrication) has also occurred (OHSU Policy 04-15-005 through -035), the matter will be referred to the Chair of the Scientific Integrity Committee (SIC).

### III. Reporting the IRB Determinations

#### A. Internal reports

- 1. Major and Moderate determinations will be reported through a protocol deviation report to the PI, generated via the eIRB system. If appropriate per the Institutional Reporting policy, a copy may be sent to the PI's department chair or unit director and/or the Institutional Official.
- 2. Major protocol deviations and their administrative resolutions must also be tabulated and reported to the IRB on the Continuing Review Questionnaire (CRQ) at the time of continuing review. Even though major protocol deviations that may have occurred during the period of approval will have been reviewed and resolved by the IRB as above, the continuing review process will include discussion and assessment of the protocol deviation or of any unanticipated problems involving risks to subjects or others. Thus, the continuing review may prescribe additional protocol modifications or other appropriate action.

#### B. Reporting to Outside Agencies

- 1. The ORIO is responsible for determining whether a protocol deviation or actions taken as a result thereof constitute suspension or termination of IRB approval, serious or continuing noncompliance, or unanticipated problems involving risks to subjects or others.
- 2. When a deviation or action meets the definition of one of the above, the ORIO will report the incident to the appropriate federal agencies per the Institutional Reporting policy.

IV. Investigator's Right to Appeal: If an investigator disagrees with the IRB's findings and/or requirements relating to a protocol deviation, the investigator may appeal the decision.

### Definitions

- A. Protocol Deviation: A protocol deviation occurs when there is an inconsistency in a research study between the protocol that has been reviewed and approved by the Institutional Review Board (IRB) and the actual activities being done. Protocol deviations may cause harm or present the risk of harm to human subjects or may be administrative in nature, such as those related to data or records-keeping. Protocol deviations may be minor, moderate, or major as defined below.
- B. Minor Protocol Deviation
  - 1. Harm/Risk of Harm
    - The deviation resulted in no harm or risk of harm to research participants; or

- The deviation did not result in or require any substantive action to be taken or result in a substantive change to the subject's condition or status (i.e., did not affect the subject's participation in a substantive way, did not result in a change to the subject's emotional or clinical condition, did not cause an adverse experience or require a change to the clinical care of the subject, etc.)
2. Administrative
    - The deviation had no substantive effect on the value of the data collected (i.e., the deviation does not confound the scientific analysis of the results); or
    - The deviation did not result from willful or knowing misconduct on the part of the investigator(s); or
    - The deviation is easily corrected (e.g., consenting a subject with an old version of an ICF, recording data on an expired/incorrect form, forgetting to record data that may be acceptably recorded at the next visit, etc.)
- C. Moderate Protocol Deviation
1. Harm/Risk of Harm
    - The deviation resulted in a harm or risk of harm that is not significant; or
    - The deviation resulted in the need for minimal risk interventions, such as those defined in 45CFR46.110 and 21CFR56.110;
  2. Administrative
    - The deviation resulted in the loss or improper collection or recording of some data for one or more subjects, but did not invalidate the entire data set for the study; or
    - The deviation resulted in a regulatory violation that can be acceptably resolved; or
    - Repeated minor protocol deviations from the same laboratory, site or research team; or
    - There has been a failure to follow action ordered to correct minor or moderate protocol deviations
- D. Major Protocol Deviation
1. Harm/Risk of Harm
    - The deviation resulted in or required a substantive action to be taken or resulted in a change to the subject's condition or status;
    - The deviation has significantly harmed or posed a risk of significant harm to research participants;
  2. Administrative
    - The deviation has substantially damaged the scientific integrity of the data collected for the entire study;
    - The deviation is evidence of willful or knowing misconduct on the part of the investigator(s);
    - The deviation involves serious or continuing noncompliance with federal, state, or local research regulations;
    - There have been repeated minor and/or moderate protocol deviations from the same laboratory, site or research team;
    - There has been a failure to follow action ordered to correct minor and/or moderate protocol deviations; or

- There has been a failure to follow action ordered in accordance with the emergency action provision of this policy.
- F. Protocol Exception: Any temporary protocol deviation that is approved by the IRB prior to its initiation, e.g., enrollment of a subject who does not meet the eligibility criteria. Note: Any permanent change to the protocol constitutes an amendment that must be submitted to the IRB for approval prior to initiation.

### **Authority**

**45 CFR 46.113(b)(5) and 21 CFR 56.113** provide that an IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

**45 CFR 46.103(b) and 21 CFR 56.108(b)(2)** requires the IRB to have written procedures for reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB.

**45 CFR 46.103b (4)(iii) and 21 CFR 56.108(a)(4)** require adherence to written procedures for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.