Human Research Protection Program
Policies & Procedures

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, research management or to make determinations of serious or continuing non-compliance.

Scope:

This policy defines the three levels of protocol deviations, the reporting and review process for deviations and the hearing process for major protocol 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 protocols that meet the definition of serious and/or continuing non-compliance will be reported to the appropriate agencies per the policy on serious and continuing non-compliance.

Process

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/Co-Chair will review reported deviation. The IRB Chair/Co-Chair 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 Chair/Co-Chair.

4. The protocol deviation will only be noted if the IRB Chair/Co-Chair determines that no deviation occurred.

B. Moderate Protocol Deviations:

1. All moderate protocol deviations must be reported.

2. If a moderate protocol deviation is reported, an IRB Chair/Co-Chair will review reported deviation, seek consultation from 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 IRB Chair/Co-Chair.

4. The report will be considered a minor protocol deviation if it is determined that deviation meets one of those definitions.

5. The protocol deviation will only be noted if the IRB Chair/Co-Chair determines that no deviation occurred.

C. Major Protocol Deviations:

1. All major protocol deviations must be reported.

2. Reporting Timeline - A direct harm/risk of harm major protocol deviation 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 two IRB Chairs who will make a preliminary determination regarding whether the reported action meets the definition of major deviation. When two Chairs disagree on the categorization, it is reviewed by the IRB Leadership Team (Chair, Co-Chairs, ORIO Director and ORIO Associate Director) and a determination is made.

4. Instances of major protocol deviations that come 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) will be processed in the same way and the PI will be notified of the determination.

5. The report will be considered a minor or moderate protocol deviation if it is determined that deviation meets one of those definitions.

6. The protocol deviation will only be noted if it is determined that no deviation occurred.

II. Major Protocol Deviation Hearing

A. Following a preliminary determination of a major protocol deviation, the Chair or a designee will collect and assess all information related to the protocol deviation and contrast the deviation with

the approved protocol. The IRB Chair or a designee will assemble a small team to discuss the matter with the P.I. and give the P.I. an opportunity for inquiry and to provide information. The protocol deviation process will be reviewed with the P.I., including the deviation definitions and potential outcomes for final determinations. At this time, the P.I. may be offered the opportunity to decline the hearing and let the determination stand. Additionally, the Chair or designee may alter the preliminary determination based on new information gained. Further corrective actions may be required, but any substantive protocol changes must receive IRB review. Consultation with experts in the particular area of research may be obtained as needed.

B. If, after meeting with the P.I,if it is determined that a hearing is necessary, the IRB Chair or designee will convene a hearing committee to consider all facts in the case and to meet with the PI and any other necessary investigator(s). The hearing committee will consist of:

1. IRB Chair
2. ORIO Director or Associate Director
3. Two or more representatives from the PI's department or discipline
4. One IRB community member
5. The chair of the VAMC IRB (or his/her designee) if the protocol is being conducted at both OHSU and the VAMC*
6. A quorum of a Board of the IRB
7. Others as determined by the IRB Chair to be appropriate and useful for the particular case.

C. Hearing Process

1. The P.I. will be provided with notice of the protocol deviation determination and a meaningful opportunity to be heard by the hearing committee. Any additional information that the PI wishes to include for consideration may be submitted. As well, if the fact finding team has information to be considered, it shall be shared with the Committee and the PI.
2. The hearing process, including the charge to the committee, shall be established and conducted according to guidance provided by the OHSU Legal Counsel.
3. The hearing committee will convene with an already scheduled meeting of the IRB. The Board shall be determined by a Chair/Co-Chair and efforts shall be made to assign the review to a reviewer who has experience reviewing the study.
4. The hearing committee shall consider all the information submitted to it and conclude whether a major, moderate, or minor protocol deviation or no protocol deviation has occurred. The hearing committee may also make the determination that the protocol deviation meets the definition of serious or continuing non-compliance. The hearing committee shall also submit recommended corrective actions or sanctions to the Principal Investigator for any major protocol deviation.
5. Recommended sanctions 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.
6. Depending on the nature and seriousness of the deviation, the hearing committee may recommend an audit of some or all studies for which the investigator in question serves as PI.
7. If it appears to the IRB chair 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) along with pertinent information collected by the hearing committee.
8. If the committee concludes that a major protocol deviation did not occur, the matter will be dismissed and the PI will be so notified by the IRB Chair.

III. Reporting the IRB Determinations

A. Internal reports

1. Major and Moderate determinations will be reported through a protocol deviation report to the PI.
2. For those deviations requiring a hearing, a written summary will be forwarded to the PI with copies sent to the Vice President for Research (VPR), the PI's department chair, and the appropriate dean or director. A copy will be retained in the IRB study file
3. If interruption of the protocol and/or study procedures would result in harm to enrolled research participants, the Board will request that the PI's department Chair or unit director assign PI duties to another qualified person and submit a modification request explaining this substitution.
4. 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 handled by the IRB chair/co-chair, 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 modification or other appropriate action.

B. Reporting to Outside Agencies

1. If a study is suspended pursuant to 45CFR46.109(d) this action will be reported to OHRP and/or the FDA, to any federal Agency funding the research, and to other appropriate agencies or parties within 10 working days of the action. This reporting procedure will be followed whether the suspension or termination is the result of IRB, IRB Chair/Co-Chair, or protocol deviation hearing action. Any subsequent actions, such as changing a suspension to a termination or lifting a suspension will also be reported to the appropriate Agencies or parties within 10 working days.
2. The ORIO is the office responsible for reporting instances of serious or continuing noncompliance or other serious determinations or sanctions by the IRB to the OHRP and appropriate Departments or Agencies.

IV. Investigator's Right to Appeal the Hearing Committee's Decision

A. If an investigator disagrees with the findings and/or requirements arising from a protocol deviation hearing, the P.I. may appeal the decision to the VPR. The IRB Chair will forward all information gathered by the inquiry and/or hearing process to the VPR who will consider it along with any additional information the investigator provides.

B. The VPR may not reverse a decision by the IRB to terminate or modify a protocol but may reconsider recommendations of the committee and actions taken based upon an assertion that there was a failure to follow process, procedural error, or substantial evidence was not considered.

C. The VPR will either uphold the decision or refer the matter back to the IRB Chair for further review by the hearing committee.

V. 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. A hearing under this procedure will be convened as soon as is possible if the emergency action taken is to suspend the protocol or if it appears a major protocol deviation has occurred.

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 directly 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. Direct Harm/Risk of Harm

- The deviation resulted in no substantive direct 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. Direct Harm/Risk of Harm

- The deviation resulted in a direct harm or risk of harm that is not greater than the minimal risk levels defined in 45CFR46.110 and 21CFR56.110; 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. **Direct 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 harmed or posed a significant risk of substantive 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 section of this policy.

D. **Substantive Action** - A substantive action is one that is required to prevent an adverse physical or psychological risk or outcome that requires follow-up treatment or monitoring and that is greater than minimal risk.

E. **Protocol Exception**: Any temporary protocol deviation that is approved by the IRB prior to its initiation, e.g., enrollment of a subject who does 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)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)94) 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.