17.0 REVIEWING PROTOCOL VIOLATION

17.1 OBJECTIVE

To describe the policies and procedures for reviewing a protocol violation.

17.2 GENERAL DESCRIPTION

Federal regulations require the IRB to review proposed changes in any research activity and to ensure that the investigator does not initiate such changes in approved research without IRB review and approval except when necessary to eliminate apparent immediate hazards/risks to the subject [45CFR46.103(b)(4)(iii) and 21CFR56.108(a)(4)]. Research activity includes all aspects of the conduct of the research study (e.g., recruitment methods, consent process, procedures used to protect privacy and confidentiality, etc.) and all of the information outlined in the IRB application/protocol reviewed and approved by the IRB.

17.3 DEFINITIONS

A *protocol violation* is any exception or deviation involving a single subject that is not approved by the IRB prior to its initiation or implementation. These protocol violations may be major or minor violations (See Modification, Deviation and Exception SOPP for definitions of *exception* and *deviation*).

A *major violation* is one that may impact subjects' safety, make a substantial alteration to risks to subjects, or any factor determined by IRB Chair or IRB member as warranting review of the violation by the convened IRB. Examples of major violations may include, but are not limited to:

- Failure to obtain informed consent, i.e., there is no documentation of informed consent, or informed consent is obtained after initiation of study procedures;
- Enrollment of a subject who did not meet all inclusion/exclusion criteria;
- Performing study procedure not approved by the IRB;
- Failure to report serious unanticipated problems/adverse events involving risks to subjects to the IRB and (if applicable), the sponsor;
- Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity;
- Drug/study medication dispensing or dosing error;

- Study visit conducted outside of required time frame that, in the opinion of the PI or IRB, may affect subject safety;

- Failure to follow safety monitoring plan.

A *minor violation* is a violation that does not impact subject safety or does not substantially alter risks to subjects. Examples of minor violations may include, but are not limited to:

- Implementation of unapproved recruitment procedures;

- Missing original signed and dated consent form (only a photocopy available);

- Missing pages of executed consent form;

- Inappropriate documentation of informed consent, including:
  - Missing subject signature;
  - Missing investigator signature;
  - Copy not given to the person signing the form;
  - Someone other than the subject dated the consent form;
  - Individuals obtaining informed consent not listed on IRB approved study personnel list.

- Use of invalid consent form, i.e., consent form without IRB approval stamp or outdated/expired consent form;

- Failure to follow the approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity;
  - Study procedure conducted out of sequence;
  - Omitting an approved portion of the protocol;
  - Failure to perform a required lab test;
  - Missing lab results;
  - Enrollment of ineligible subject (e.g., subject's age was 6 months above age limit);
  - Study visit conducted outside of required timeframe;

- Over-enrollment;

- Enrollment of subjects after IRB-approval of study expired or lapsed;

- Failure to submit continuing review application to the IRB before study expiration.

17.4 RESPONSIBILITY

Execution of SOPP: Principal Investigator (PI)/Study Personnel, IRB Chair, IRB, Office of Regulatory Research Compliance, Research Compliance Officer, Office of Regulatory Research Compliance Staff

17.5 PROCEDURES

17.5.1 Submission of Protocol Violations

- The PI submits any and all protocol violations that occur during the course of a study to the IRB immediately upon discovering them and within fourteen (14) calendar days of the occurrence. To submit the protocol violation, the PI completes the IRB Protocol Violation Reporting Form and submits the designated number of copies with required attachments to the Office of Regulatory Research Compliance.

- The PI also reports all protocol violations to the sponsor, if applicable, following the sponsor's requirements.

17.5.2 Screening of Submissions

- Office of Regulatory Research Compliance staff screens the IRB Protocol Violation Reporting Form for completeness and accuracy. If the submission is incomplete, Regulatory Research Compliance staff sends incomplete notification to the PI to request additional information, which they forward to the IRB upon receipt.

- Office of Regulatory Research Compliance staff screens to determine whether the violations involve vulnerable populations or require documentation of specific regulatory findings. If either of the above applies, then Office of Regulatory Research Compliance staff advises the IRB of any regulatory requirements the IRB should address in conducting the review. The IRB is responsible for applying the regulatory requirements.

- Office of Regulatory Research Compliance staff screens submitted protocol violations for HIPAA concerns and follow the procedures outlined in the HIPAA in Research SOP concerning noncompliance. Investigators working in a HU covered entity must comply with the HU Hospital's HIPAA policies and procedures.

17.5.3 Determining Mechanism of Review (i.e., Expedited vs. Full)

- Office of Regulatory Research Compliance staff sends the completed IRB Protocol Violation Reporting Form with any applicable attachments to the IRB Chair if available or to a designated voting member of the IRB.

- The IRB Chair or IRB member makes a determination regarding whether the violation is major or minor and whether to review the violation using full

or expedited review procedures, respectively, unless the sponsor/PI requests full review. If the violation is minor, the IRB Chair or IRB member conducts review using expedited procedures.

- If the sponsor or the PI specifically requests full review procedures, Office of Regulatory Research Compliance staff places the protocol report on an agenda for full review following procedures outlined in the Initial Full Review SOPP.

17.5.4 Expedited/Full Review Procedures

- The IRB Chair or a voting IRB member conducts expedited review using standard expedited review procedures (See Expedited Initial Review SOPP)

- If the protocol report undergoes full review, the IRB Chair or IRB member has the option to invite the investigator to attend the meeting to answer any questions or concerns that the IRB may have concerning the protocol violation.

- Office of Regulatory Research Compliance staff notifies the PI in writing if he/she must attend the IRB meeting. Office of Regulatory Research Compliance staff schedules the submission for review and provides IRB members an electronic copy of the IRB Protocol Violation Reporting Form. The full committee reviews the protocol violations using the procedures outlined in the Initial Full Review SOPP.

- If the IRB determines that the violation is reportable to external agencies, Office of Regulatory Research Compliance staff notifies the Research Compliance Officer. The RCO or designee prepares a report to the applicable federal agency and maintains records as outlined in the Mandated Reporting to External Agencies SOPP.

17.5.5 Review Outcome(s)

- The IRB/ORRC staff handles the review and outcomes of review as outlined in the Modification, Deviation and Exceptions--IRB Review of Changes SOPP and/or, if applicable, the Termination or Suspension of Research by the IRB SOPP.

- The IRB may, if appropriate, make a determination that the protocol violation(s) constitute “serious” or “continuing noncompliance”, or an “unanticipated problem involving risks to subjects or others” as defined in the Noncompliance SOPP.

- If the PI has concerns regarding the IRB decision, he/she may submit them to the IRB in a written document that includes justification for changing the IRB decision.

17.6 REFERENCES

21CFR 56.108(a)(4)
45CFR 46.103(b)(4)(iii)