# Dealing with Protocol Deviations (Exceptions and Violations)

## Objective

The objective of this standard operating procedure (SOP) is to describe procedures for documenting protocol deviations (exceptions and violations) and their submission to the appropriate bodies.

## Persons/Areas Affected

This SOP concerns the MUHC research community (employees, investigators, physicians, management, consultants, students, volunteers or other persons) involved in conducting research with human subjects.

## Definitions

I. **Protocol Deviation**: Divergence or departure from the expected conduct of an approved study not consistent with the current REB approved version of the research protocol, consent document or addenda that had not been anticipated by the Principal Investigator/Qualified Investigator.

II. **Protocol Exception**: Minor protocol deviation for which the REB may grant acceptance.

III. **Protocol Violation**: Major protocol deviation for which an REB decision on corrective action is required.

IV. **Sponsor**: An individual, company, institution or organization which takes responsibility for the initiation, management or financing of a human research study (modified from ICH, E6 1.53).

V. **Sponsor-Investigator**: An individual who both initiates and conducts alone or with others a research study. The term does not include any person other than an individual (it does not include a corporation or an agency). The obligations of a Sponsor-Investigator include both those of a Sponsor and those of a Principal Investigator/Qualified Investigator (ICH, E6 1.54).

VI. **Principal Investigator (PI)**: A person responsible for the conduct of the research study at a study site. If a study is conducted by a team of investigators at the same study site, the Principal Investigator is the responsible leader of the team (ICH, E6 1.34).
VII. **Qualified Investigator**: The person responsible to the Sponsor/Sponsor-Investigator for the conduct of a clinical research study with an experimental drug at the study site, who is entitled to provide health care under the laws of the province where that study is located, and who is (HC, C.05.001):

a. In the case of a clinical research study with an experimental drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association;

b. In any other case, a physician and a member in good standing of a professional medical association.

**Procedures**

1. **Generalities**

   1.1.1. To ensure adherence to ICH 4.5.1 (for clinical research studies) and to other similar guidelines (for other types of research studies), the Principal Investigator/Qualified Investigator should conduct the study in compliance with the protocol approved by the Sponsor/Sponsor-Investigator or peer-reviewed Granting Agency and, if applicable, Regulatory Authorities to which the Research Ethics Board (REB) has given its approval/favourable opinion. The Principal Investigator/Qualified Investigator and Sponsor/Sponsor-Investigator should sign the protocol or other contract to confirm the agreement.

   1.1.2. Subjects should be informed of the importance of complying with the protocol as explained.

2. **Protocol Deviations**

   2.1.1. The Principal Investigator/Qualified Investigator should accurately and regularly document all protocol deviations in the source documents and case report forms (CRFs) or any other documents stipulated in the protocol.

   2.1.2. The Sponsor/Sponsor-Investigator should be informed immediately of any protocol deviation and receive relevant explanation. The deviations, as well as actions taken as a result of these deviations should be documented in the source documents.

   2.1.3. If eligibility criteria are regularly overridden, the protocol will have to be reviewed and if necessary, amended. Amendments should take into account the statistical consequences of protocol deviations as well as blinding methodology (if appropriate).

   2.1.4. The Statistical Analysis Section should be prepared at the beginning of the research study and should indicate how protocol deviations will be analyzed.

   2.1.5. The final study report should state the frequency and type of protocol deviations and explain their effect on the results.

   2.1.6. All documentation related to non-compliance with the protocol should be available for inspection by Health Canada, FDA, or an independent inspector designated by the Sponsor/Sponsor-Investigator.
2.2. Protocol Exceptions

2.2.1. The protocol deviation is considered a “protocol exception” when the action:

- has no substantive effect on the risk posed to a research subject or others; and
- has no substantive effect on the value of the data collected; and
- does not confound the scientific analysis of the study results; and
- did not result from wilful or voluntary misconduct on the part of an Investigator or a member of the Investigator’s study team.

2.2.2. Protocol exceptions do not need to be reported to the REB. However, with a written rationale a Principal Investigator/Qualified Investigator may collect all protocol exceptions occurring since the previous REB review and submit the information in a summary document only at the time of continuing review.

2.2.3. The form to submit a Protocol Exception to the REB is available on the RI MUHC website.

2.3. Protocol Violations

2.3.1. The protocol deviation is considered a “protocol violation” when the action:

- constitutes a change in the conduct of the research that should have received prospective REB review and approval prior to implementing the change; or
- has harmed or posed a significant risk of harm to a research subject or others; or
- has damaged the scientific integrity of the data collected or confounded the scientific analysis of the study results; or
- resulted from wilful or voluntary misconduct on the part of an Principal Investigator/Qualified Investigator or a member of the research team.

2.3.2. Protocol violations are reported to the REB without delay along with corrective action proposed by the Principal Investigator/Qualified Investigator to avoid repetition of the event.

2.3.3. The REB’s view on the adequacy of the corrective measures will result in a decision to accept or reject the action taken, and will be communicated in writing to the Principal Investigator/Qualified Investigator.

2.3.4. If a similar protocol violation has occurred previously in the study, the Principal Investigator/Qualified Investigator will provide an amendment to the protocol designed to avoid repetition of the event.

2.3.5. If the protocol violation introduces new information that may affect a subject’s willingness to continue in the study, all study subjects must be informed, and the REB may require the subjects to renew their consent in writing.

2.3.6. The only protocol violation permitted without prior REB approval is one where urgent action is required to eliminate an apparent or immediate hazard to a study subject or others. The
Principal Investigator/Qualified Investigator must still forward without delay to the Sponsor/Sponsor-Investigator, and to the REB, a written explanation of the protocol violation describing the action taken, the outcome of the action and the corrective measures proposed to avoid repetition of the event.

2.3.7. Protocol violations will be discussed at a convened meeting of the Full Board to permit the REB to maintain surveillance over the event.

2.3.8. The form to submit a Protocol Violation to the REB is available on the RI MUHC website.

References