TITLE	**404: Ongoing HREB Review Activities**
SCOPE	All health research submitted to the Health Research Ethics Board (HREB) operating under the direct authority of the Health Research Ethics Authority (HREA)
APPROVAL AUTHORITY	Ethics Director
EFFECTIVE DATE	April 2021

1.0 PURPOSE

This standard operating procedure (SOP) describes the procedures for the ongoing review activities that occur after the initial REB approval of a research project until completion of the project.

2.0 DEFINITIONS

See the Glossary of Terms

3.0 RESPONSIBILITIES:

HREB members, Research Ethics Office (REO) Personnel and Researchers are responsible for ensuring that the requirements of this SOP are met.

The Researcher is responsible for reporting to the HREB any new information generated throughout the course of the research that might affect the rights, safety and well-being of research participants, including reportable events that meet the reporting criteria as per this SOP.

The Researcher is responsible for reporting to the HREB any information about the conduct of the research that could affect the rights, safety and well-being of research participants, including information about any serious or continuing non-compliance.

When action is taken to ensure the protection of the rights, safety, and well-being of participants (e.g., for an unanticipated problem involving risks to participants or others) the HREB is responsible for reporting to the Researcher and to the appropriate officials at the Researcher's organization, as applicable. The HREB also has the authority to notify the sponsor and/or the appropriate regulatory authorities of any events that meet the reporting criteria. The HREB may delegate reporting to the Researcher's organization, if applicable.

The HREB Chairperson or designee is responsible for reviewing all reportable events submitted to the HREB, as well as any proposed amendments to the research, and for determining the type of review (i.e., delegated or Full Board) and any action required.

HREB members are responsible for reviewing any new information, reportable events or proposed amendments that are assigned to them or that are assigned to a Full Board meeting, and for recommending the appropriate course of action.

4.0 PROCEDURE

The HREB must receive and review any new information generated throughout the course of the research that might affect the rights, safety and well-being of research participants, in addition to the formally scheduled continuing review.

Information reviewed by the HREB will include:

- modifications or changes to the previously approved research;
- reports of unanticipated problems involving risks to participants or others;
- reports of any serious or continuing non-compliance;
- reports of any changes significantly affecting the conduct of the research or increasing the risk to research participants;
- results of any interim analysis or Data and Safety Monitoring Board (DSMB) assessments;
- deviations to the previously approved research;
- adverse events that meet the reporting criteria;
- reports of any privacy breaches;
- summary reports of any audits and inspections; and
- any other new information that my affect adversely the safety of the research participants or the conduct of the research.

Modifications to approved research will not be initiated without HREB review and approval except where necessary to eliminate apparent immediate hazards to human participants. If changes are made to eliminate immediate hazards, the Researcher must notify the HREB immediately.

4.1 Amendments to Approved Research

4.1.1 The Researcher is responsible for submitting an amendment to the HREB outlining any changes to the approved research. Changes to the approved research include, but are not limited to, addition or removal of Researcher or modifications to the research application, consent forms, Investigator Brochure and participant materials (e.g., wallet cards, diary cards, and recruitment materials). Researchers are responsible for disclosing any conflicts of interest to the HREB that may arise from changes to the approved research.

4.1.2 When the amendment includes a change to a consent form, the Researcher will indicate their recommendation for the provision of the new information to current and/or past research participants.

4.1.3 The Researcher may indicate the type of review being requested (i.e., Full Board, delegated review or acknowledgement for a minor correction). Supporting correspondence documentation and/or background information may be appended to the amendment submission.

4.1.4 The HREB Chairperson or designee will review the amendment to determine the appropriate level of REB review required (i.e., Full Board or Delegated review).

4.1.5 If the proposed change represents more than minimal risk, it will be reviewed by the HREB at a Full Board meeting. Amendments that may be classified as more than minimal risk may include:

- addition of genetic testing, new genetic tests, or tissue banking where genetic testing may or will be performed;
- addition of an open label extension phase following a randomized trial;
- emergency amendments that arise because of participant safety and may include, but are not limited to:
    1. a change in drug dosing/duration of exposure;
    2. a change in recruitment that may affect confidentiality or the perception of coercion; and/or
    3. a change in experimental procedure or research population;
- any amendment that requires approval from Health Canada;
- amendments to the protocol that affect the evaluation of the clinical efficacy of the drug;
- amendments to the protocol that alter the risk to the health of a clinical trial participant;
- amendments to the protocol that affect the safety evaluation of the drug;
- amendments to the protocol that extend the duration of the clinical trial; and
- amendments to the chemistry and manufacturing information that may affect the safety or quality of the drug.

4.1.6 For amendments requiring Full Board review, the responsible REO Personnel will assign the amendment to the next available Full Board meeting. For amendments that meet the criteria for delegated review, the responsible REO Personnel will forward the amendment to the designated reviewer.

4.1.7 When an amendment involves a revised consent, the HREB will consider the recommendations of the Researcher in determining if, how and when the new information should be provided to the research participants and whether re-consent is required.

4.1.8 The HREB must find that the criteria for approval are still met in order to approve the amendment.

4.1.9 The amended research must not be implemented prior to the HREB review and approval, except when necessary to eliminate immediate hazards to participants.

4.2 Reportable Events

4.2.1 The Researcher is responsible for submitting reportable events that meet the HREB's reporting criteria according to the local procedures.

4.2.2 **Local Adverse Events:** The Researcher must report to the HREB in a timely manner, any local adverse event that in the opinion of the Researcher meets the definition of an unanticipated problem (i.e. is unexpected AND related or possibly related to participation in the research AND suggests that the research places research participants or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

The local Serious Adverse Event (SAE) form submitted to the HREB, must have all research

participant identifiers removed (i.e., participant research number only). Once a local SAE is acknowledged by the HREB, subsequent important follow-up reports related to the SAE must be submitted when relevant information is available, as a SAE update(s). All initial and subsequent follow-up reports will be retained with the reportable event.

If a Researcher determines that an adverse event is not an unanticipated problem, but the sponsor subsequently determines that it is, the Researcher must report this determination to the HREB as soon as reasonably possible after they become aware of the sponsor's determination.

4.2.3 Non-Local (External) Adverse Events: Upon receipt of an external adverse event (EAE) or a periodic safety update or safety summary report, the Researcher must determine if it meets the HREB reporting criteria. Non-local adverse event reports are reportable to the HREB, if in the opinion of the Researcher, they meets the definition of an unanticipated problem AND requires a change to the research and/or informed consent form and/or requires immediate notification to participants for safety reasons.

Individual isolated EAEs should only be reported to the HREB if they are unanticipated problems and the report submitted to the HREB must include **all** of the following information:

- the description of the serious and unexpected event(s);
- all previous safety reports concerning similar adverse events;
- an analysis of the significance of the current adverse event(s) in light of the previous reports; and
- the proposed research changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the event(s).

The individual adverse event reports or periodic safety updates or safety summary reports that meet the reporting criteria must be submitted to the HREB in a timely manner.

4.2.4 Other Reportable Events: The Researcher is responsible for reporting to the HREB other events or findings in a timely manner, such as:

- any new information (e.g., sponsor's safety notice or action letter) that would cause the sponsor to modify the Investigator's Brochure, the research or the consent form, or would prompt other action by the HREB to ensure protection of research participants;
- any changes to the risks or potential benefits of the research, such as:
  - an interim analysis indicates that participants have a lower rate of response to treatment than initially expected;
  - safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected; and
  - information published from another research project that shows that an arm of the research is of no therapeutic value;
- a change in Health Canada or FDA safety labeling or withdrawal from marketing of a drug, device, health product, genetic therapy or biologic used in research;
- other types of reportable events, such as:
  - DSMB reports;
  - interim analysis results;

  - any unanticipated problems or other events that could significantly impact the overall conduct of the research or alter the HREB's approval or favorable opinion to continue the research; and
  - studies which are on hold, or have been re-activated after being on hold;
- a change to the research that was initiated without prior HREB review to eliminate an apparent immediate hazard to a research participant; and
- any unanticipated problems or other events that could significantly impact the conduct of the research at the site (e.g., concerns of non-compliance).

4.2.5 Deviations to Previously Approved Research: The Researcher must report to the HREB, in a timely manner, any deviations that meet the following reporting criteria:

- deviations that in the opinion of the Researcher jeopardize the safety of research participants, or that jeopardize the research efficacy or data integrity;
- any sponsor-approved waivers to the participant eligibility criteria;
- enrolment of participants outside protocol inclusion/exclusion;
- any change in the approved process for obtaining consent (e.g., improper translation, current consent form not implemented);
- medication/intervention errors (i.e. incorrect drug/intervention, incorrect dosage of the drug);
- inadvertent deviation in specific research intervention procedures or timing of the research intervention; and
- any deviations that lead to an SAE.

4.2.6 Privacy Breaches: The Researcher must report to the HREB any unauthorized collection, use, or disclosure of personal information (PI) including, but not limited to:

- the collection, use and disclosure of PI that is not in compliance with the jurisdictional legislation or its regulation;
- circumstances where PI is stolen, lost or subject to unauthorized use or disclosure or where records of PI are subjected to unauthorized exposure, copying, modifications or disposal; and
- in the Researcher context, any unauthorized collection, use or disclosure of PI, including personal health information, that was not authorized under the research and approved in the plan that was submitted to the HREB.

The breach must be reported to the HREB, to the data custodian (if applicable), and to the appropriate Organizational Official, if applicable, as soon as the Researcher becomes aware of the breach.

4.2.7 Audit or Inspection Findings: The Researcher must report to the HREB a summary of any relevant audit or inspection findings following a Health Canada inspection, a U.S. Food and Drug Administration (FDA) or other regulatory audit, an internal Quality Assurance audit or other audits at the site.

4.2.8 Research Participant Complaint: The Researcher must report to the HREB, and to their Organization, if applicable and required by organizational procedures, a complaint from a participant when the participant reports concerns about their rights as a research

participant or about ethical issues related to the research.

4.3 Review of Reportable Events by the HREB

4.3.1 The responsible REO Personnel will screen the reportable event submission for completeness.

4.3.2 Privacy breaches will be reviewed by the HREB Chairperson or designee, and any recommendations including remedial action will be determined in consultation with the applicable Organization's privacy office, if applicable. The privacy breach report will be forwarded to the HREB Chairperson or designee for review and final acknowledgement.

4.3.3 The REO Personnel may route the submission back to the Researcher to request clarifications, missing documents or additional information.

4.3.4 The REO Personnel will forward the submission to the designated HREB reviewer(s).

4.3.5 The assigned HREB reviewer(s) will conduct a review of the report and determine if any action or follow-up is required.

4.3.6 The assigned reviewer(s) may request further information from the Researcher.

4.3.7 When reviewing a reportable event, the HREB will:

- assess the appropriateness of any proposed corrective or preventative measures by the sponsor and/or Researcher;
- consider any additional appropriate measures that may or may not have been identified or proposed by the sponsor and/or Researcher;
- consider whether the affected research still satisfies the requirements for REB approval; in particular whether risks to research participants are still minimized and reasonable in relation to the anticipated benefits, if any, to the research participants and the importance of the knowledge that may reasonably be expected to result;
- consider whether some or all of the research participants should be notified of the events (i.e., if it may affect the participant's willingness to continue participation in the research); and
- consider whether suspension or cancellation of the ethics approval of the research is warranted.

4.3.8 If the event does not raise concerns and does not appear to involve risks to research participants or others, the HREB Chairperson or designee will acknowledge the report, and no further action is required.

4.3.9 If the HREB Chairperson or designee determines that the event meets the criteria for an unanticipated problem, and if immediate action is required to protect the safety of research participants, he/she may suspend ethics approval of the research pending review by the Full Board, providing the justification for such action is documented and is in compliance with subsection 11(5) of the HREA Act.

4.3.10 If the event raises concerns or involves risk to research participants such that HREB action may be required, the item will be added to the agenda of the next Full Board meeting.

4.3.11 For reportable events reviewed at a Full Board meeting, the HREB will determine whether further action is required. Possible actions that could be taken by the HREB include, but are not limited to:

- placing a hold on the research pending receipt of further information from the Researcher;
- requesting modifications to the research;
- requesting modifications to the consent form;
- providing additional information to past participants;
- notifying current participants when such information might affect the participants' willingness to continue to take part in the research and requiring that current participants re-consent for ongoing participation;
- altering the frequency of continuing review;
- observing the research or the consent process;
- requiring additional training of the Researcher and research staff; and
- suspension or cancellation of the research in compliance with subsection 11(5) of the HREA Act.

If the HREB determines that the event does not raise concerns about risks to research participants, the HREB may decide that no further action needs to be taken. If the research study is funded by the U.S. Federal government, or regulated by the U.S. FDA, the HREB will notify the appropriate institutional officials in accordance SOP 408.

4.3.12 When action is taken to ensure the protection of the rights, safety, and wellbeing of participants (e.g., for an unanticipated problem involving risks to participants or others) the HREB Chairperson or designee is responsible for reporting to the Researcher and the Organizational Officials, as applicable. The HREB Chairperson or designee has the authority to notify the sponsor, the official(s) at the Researcher's organization, as applicable, and the appropriate regulatory authorities, as per section 26 of the HREA Act.

The HREB may delegate regulatory authority reporting (as applicable) to the organization.

5.0 REFERENCES

Health Research Ethics Authority Act: An act to establish a health research ethics authority for the province. (2011). Retrieved from: SNL2006 CHAPTER H-1.2 - HEALTH RESEARCH ETHICS AUTHORITY ACT (assembly.nl.ca)

The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Chapter 6: tcps2-2018-en-interactive-final.pdf (ethics.gc.ca)

U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46): Electronic Code of Federal Regulations (eCFR)

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56): Electronic Code of Federal Regulations (eCFR)

Health Canada Food and Drug Regulations, Part C, Division 5, C.05.008 Subsection 2: Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects" (GUI-0100) - Canada.ca