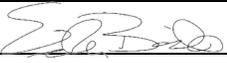


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| SOP Title | HSREB Ongoing Review |
| Number.Version | 405.008 |
| Effective Date | 02/21/2020 |

Approvals

| Name and Title of Signatories | Signature | Date mm/dd/yyyy |
|--|---|----------------------------|
| Erika Basile Director, Research Ethics and Compliance |  | Oct 1, 2021 |
| Dr. Philip Jones Chair, Health Sciences Research Ethics Board |  | Oct 1, 2021 |

1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for the ongoing review activities that occur after the initial HSREB approval of a research proposal and prior to the scheduled continuing review.

2. GENERAL POLICY STATEMENT

It may be that the real risk/benefit ratio can be evaluated only after research has begun; therefore, in addition to the formally scheduled continuing review, the HSREB 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. Such review may include:

- 5.1. Revisions to the previously approved research,
- 5.2. Review of significant new findings or new information that may affect adversely the safety of the research participants or the conduct of the trial,
- 5.3. Review of serious and unexpected adverse events and unanticipated problems posing risks to participants or others,
- 5.4. Protocol deviations,
- 5.5. Results of any interim analyses or data and safety monitoring board assessments,
- 5.6. Reports of any privacy breaches,
- 5.7. Summary reports of any audits and inspections,
- 5.8. Revisions to the approved research proposal may not be initiated without prior HSREB review and approval except where necessary to eliminate apparent immediate hazards to human participants. If revisions are made to eliminate immediate hazards, the Investigator must notify the HSREB immediately.

3. RESPONSIBILITY

This SOP is applicable to the Office of Human Research Ethics (OHRE), HSREB Chair, Vice-Chair(s), HSREB members and the Investigator.

The Investigator is responsible for reporting to the HSREB 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 Investigator is responsible for reporting to the HSREB 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 HSREB is responsible for reporting to the Investigator and the Organizational Official(s) and has the authority to notify the sponsor and/or the appropriate regulatory authorities of any events that meet the reporting criteria. The REB may delegate regulatory authority reporting (as applicable) to the organization.

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

The HSREB 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. DEFINITIONS

See Glossary of Terms

5. SPECIFIC POLICIES AND PROCEDURES.

It may be that the real risk/benefit ratio can be evaluated only after the research has begun; therefore, in addition to the formally scheduled continuing review, the REB 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. Such information may 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,
- Any other new information that may affect adversely the safety of the research participants or the conduct of the research,

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

5.1. Amendments to the Approved Research

- 5.1. Investigator is responsible for submitting to the REB any changes to the approved research in the form of an amendment. Changes to the approved research include modifications including (for example) modifications to the research, to the consent form, to the Investigator Brochure (IB) or product monograph (PM), changes in participant materials (e.g., wallet cards, diary cards, recruitment materials), a change in the Investigator etc.;

- 5.2. When the amendment includes a change to the consent form, the Investigator must indicate his/her recommendation for the provision of the new information to current and/or past research participants;
- 5.3. The Investigator must 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;
- 5.4. The REB Chair or designee reviews the amendment to determine the appropriate level of REB review required (i.e., Full Board or delegated review);
- 5.5. The REB Chair or designee also may use delegated review procedures for review of amendments when the conditions are met:
- 5.6. If the proposed change represents more than minimal risk, it must be reviewed by the REB 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,
 3. A change in experimental procedure or research population
- 5.7. For amendments requiring Full Board review, the responsible REB Office Personnel assigns the amendment to the next available Full Board meeting. For amendments that meet the criteria for delegated review, the responsible REB Office Personnel will forward the amendment to the designated reviewer;
- 5.8. When an amendment involves a revised consent, the REB will consider the recommendations of the Investigator in determining if, how and when the new information should be provided to the research participants and whether re-consent is required.
- 5.9. The REB must find that the criteria for approval are still met in order to approve the amendment;
- 5.10. The amended research may not be implemented prior to the REB review and approval, except when necessary to eliminate immediate hazards to participants.

5.2. Reportable Events

- 5.1. The Investigator is responsible for submitting reportable events that meet the HSREB's reporting criteria according to the local procedures;

5.2. Local AE's: The Researcher must report the following to the REB in a timely manner:

- Any local adverse event that in the opinion of the Researcher meets the definition of an unanticipated problem,
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- All reports submitted to the REB must have all research participant identifiers removed (i.e., participant research number only),
- The sponsor's SAE report (if applicable) must be signed by the Researcher or medical designee,
- Once a local SAE is acknowledged by the REB, subsequent important follow-up reports related to the SAE should be submitted when relevant information is available, as SAE update(s). All initial and subsequent follow-up reports will be retained with the reportable event;

5.3. 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 REB reporting criteria:

- Non-local adverse event reports are reportable to the REB, if in the opinion of the Researcher, it 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,
- The report submitted to the REB 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 AE reports or periodic safety updates or safety summary reports that meet the reporting criteria must be submitted to the REB within a time frame specified by the REB;

5.4. Other Reportable Events: The Investigator is responsible for reporting to the REB other events or findings, 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 REB 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,
 - Information is 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,

- The Researcher is also responsible for submitting to the REB 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 REB's approval or favorable opinion to continue the research,
- A change to the research that was initiated without prior REB review to eliminate an apparent immediate hazard to a research participant,
- Any unanticipated problems or other events that could significantly impact the conduct of the research at the site (e.g., concerns of non-compliance),
- Other reportable events must be submitted to the REB within a time frame specified by the REB;

5.5. Deviations to Previously Approved Research: The Researcher must report to the REB 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,
- Any change in the approved process for obtaining consent (e.g., improper translation, current ICF not implemented),
- Any deviations that lead to an SAE,
- Deviations must be reported within a time frame specified by the REB; deviations that lead to an SAE should be reported within a time frame specified by the REB;

5.6. Privacy Breaches: The Researcher must report to the REB 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 copying, modifications or disposal,
- In the Researcher context, any unauthorized collection, use or disclosure of PI that was not authorized under the research and approved in the plan that was submitted to the REB,

The breach must be reported to the REB and, if applicable, to the appropriate Organizational Official as soon as the Researcher becomes aware of the breach;

5.7. Audit or Inspection Findings: The Researcher must report to the REB a summary of any relevant audit or inspection findings following a Health Canada inspection, an FDA or other regulatory audit, an internal QA audit or other audits at the site;

5.8. Research Participant Complaint: The Researcher must report to the REB, and to the organization if required by local 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.

5.3. Review of Reportable Events by the REB

- 5.1. The responsible REB Office Personnel will screen the reportable event submission for completeness;
- 5.2. Privacy breaches are reviewed by the REB Chair or designee, and any recommendations including remedial action are determined in consultation with the organization's privacy office. The privacy breach report is forwarded to the REB Chair or designee for review and final acknowledgement;
- 5.3. The REB Office Personnel may route the submission back to the Researcher to request clarifications, missing documents or additional information;
- 5.4. The REB Office Personnel will forward the submission to the designated REB reviewer(s);
- 5.5. The assigned REB reviewer(s) will conduct a review of the report and determine if any action or follow-up is required;
- 5.6. The assigned reviewer(s) may request further information from the Researcher;
- 5.7. When reviewing a reportable event, the REB should: If the event does not raise concerns and does not appear to involve risks to research participants or others, the REB Chair or designee acknowledges the report, and no further action is required;
 - 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 termination of the ethics approval of the research is warranted;
- 5.8. If the event does not raise concerns and does not appear to involve risks to research participants or others, the REB Chair or designee acknowledges the report, and no further action is required;
- 5.9. If the REB Chair 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;
- 5.10. If the event raises concerns or involves risk to research participants such that REB action may be required, the item is added to the agenda of the next Full Board meeting;

5.11. For reportable events reviewed at a Full Board meeting, the REB determines whether further action is required. Possible actions that could be taken by the REB 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,
- Termination or suspension of the research,
- If the REB determines that the event does not raise concerns about risks to research participants, the REB may decide that no further action needs to be taken;

5.12. 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 REB chair or designee is responsible for reporting to the Researcher and the Organizational Official(s) and has the authority to notify the sponsor and the appropriate regulatory authorities (as applicable). The REB may delegate regulatory authority reporting (as applicable) to the organization.

6. REFERENCES

- 6.1. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 2010 (TCPS2), Chapter 1 Section C; Chapter 2 Section B;
- 6.2. The International Conference on Harmonization Good Clinical Practices, Sections 3, 4.4, 4.5, 4.10, 4.11, 4.12;
- 6.3. US Office for Human Research Protections (OHRP) Code of Federal Regulations (CFR) Title 45 Part 46.109, 46.111, 46.113, 46.115;
- 6.4. OHRP Guidance on Continuing Review;
- 6.5. US Food and Drug Administration (FDA) CFR Title 21 Part 56.108, 56.109, 56.110, 56.111, 56.115;
- 6.6. FDA Information Sheets: FAQ Section IV ;
- 6.7. ISO 14155 Clinical investigation of medical devices for human subjects – Good Clinical Practice.

7. SOP HISTORY

| SOP Number.Version | Key Changes | Effective Date mm/dd/yyyy |
|--------------------|--|------------------------------|
| 205.001 | Original | 01/20/2014 |
| 405.002 | Erika Basile's position was updated Administrative revisions for clarity | 05/22/2014 |
| 405.003 | Revised entire SOP to be consistent with N2 SOP | 10/24/2014 |
| 405.004 | Minor administrative corrections for clarity | 05/10/2016 |
| 405.005 | 1. Remove 5.1.2 As it was redundant with 5.1.1 | 12/01/2017 |

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| | <p>2. Addition of the following:</p> <p>5.7. For amendments requiring Full Board review, the responsible REB Office Personnel assigns the amendment to the next available Full Board meeting. For amendments that meet the criteria for delegated review, the responsible REB Office Personnel will forward the amendment to the designated reviewer;</p> <p>5.8. When an amendment involves a revised consent, the REB will consider the recommendations of the Investigator in determining if, how and when the new information should be provided to the research participants and whether re-consent is required.</p> <p>5.9. The REB must find that the criteria for approval are still met in order to approve the amendment;</p> <p>5.10. The amended research may not be implemented prior to the REB review and approval, except when necessary to eliminate immediate hazards to participants.</p> <p>3. Formatting corrections</p> | |
| 405.006 | Minor administrative corrections | 08/10/2018 |
| 405.007 | Minor Administrative Changes | 09/06/2018 |
| 405.008 | 5.2. Clarification on timing of reportable events; Clarification on SAE documents | 02/21/2020 |