TITLE:	Standard Operating Procedure (SOP) Ongoing Review & Reporting	**NUMBER:**	NSHA REB-SOP-4-005
Effective Date:	April 2014	Revision:	September 29, 2017
Applies To:	Executive Chair, Co-Chairs, NSHA REB members and REB Office Personnel		

1. PURPOSE:

The purpose of this standard operating procedure (SOP) is to describe the procedures for ongoing review activities that occur after the initial approval issued by the Nova Scotia Health Authority Research Ethics Board (NSHA REB) and prior to the formally scheduled continuing review of the research project.

2. POLICY:

The Principal Investigator is responsible for reporting to the REB 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 Principal Investigator is responsible for reporting to the REB 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 REB is responsible for reporting to the Principal 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.

3. DEFINITIONS:

1) **Ongoing research**: Research that has received REB approval and has not yet been completed.

2) **Participant:** A person about whom a researcher obtains (1) data through intervention or interaction with the individual or the individual's cadaver, remains,

tissues, biological fluids," embryos or fetuses, or (2) identifiable private information (e.g., health information). The term "subject" may also be used.

3) **Local participant:** A research participant enrolled by the Investigator at one or more centers under the jurisdiction of the Nova Scotia Health Authority Research Ethics Board (NSHA REB).

4) **Adverse event (AE):** any untoward medical occurrence in a research participant, administered investigational product, including an occurrence which does not have a causal relationship with this product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

    - **Local adverse event:** those adverse events experienced by research participants enrolled by the Investigator at the centre(s) under the jurisdiction of the Research Ethics Board (REB).

    - **External (non-local) adverse event:** those adverse events experienced by research participants enrolled by Investigators at other centres/organizations outside the REB's jurisdiction.

5) **Suspected Unexpected Serious Adverse Reaction (SUSAR):** An adverse event that is serious (resulted in death, required hospitalization or prolonged an existing hospitalization, resulted in incapacity or disability, birth defect or jeopardized the participant or required intervention to prevent one of these criteria) and unexpected (not consistent with risks described in the study documents) and related or possibly related to participation in the research.

6) **Data Safety Monitoring Board (DSMB):** a multi-disciplinary, expert advisory group established by a research sponsor, that is responsible for safeguarding the interests of participants by reviewing emerging data**,** assessing the safety and efficacy of research procedures, and monitoring the overall conduct of the research.

7) **Periodic Safety Update Reports (PSURs):** a summary report, created by the sponsor, listing all of the reported unexpected serious adverse events that have occurred in a given reporting period, and which includes any significant areas of concern and the evolving safety profile of the investigational product.

4. 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 my 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 Researcher must notify the REB immediately.

4.1. Amendments to the Approved Research

4.1.1. The Principal 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 Researcher etc.;

4.1.2. When the amendment includes a change to the consent form, the Principal Investigator must indicate his/her recommendation for the provision of the new information to current and/or past research participants;

4.1.3. Supporting correspondence documentation and/or background information may be appended to the amendment submission;

4.1.4. The responsible REB Office Personnel reviews the amendment to determine the appropriate level of REB review required (i.e., Full Board or delegated review);

4.1.5. The REB Chair or designee has the authority to direct any delegated review request to the Full Board for review;

4.1.6. The REB Chair or designee also may use delegated review procedures for review of amendments when the conditions are met;

4.1.7. Full Board review may be required if the proposed change represents more than minimal risk. Amendments that may be classified as more than minimal risk may include, but are not limited to:

- Proposed changes to the scientific intent of the research;
- Reports of any changes that significantly affect the conduct of the research or increasing risk to research participants;
- New information that may adversely affect the safety of the research participants or the conduct of the research;
- Addition of genetic testing, new genetic tests, or tissue banking where genetic testing may or will be performed,
- 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;

4.1.8. 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 Co-Chair;

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

4.1.10. The REB must find that the criteria for approval are still met in order to approve the amendment;

4.1.11. The amended research may not be implemented prior to the REB review and approval, except when necessary to eliminate immediate hazards to participants.

4.2. Reportable Events

4.2.1. The Principal Investigator is responsible for submitting reportable events that meet the REB's reporting criteria according to local NSHA procedures;

4.2.2. Local Suspected Unexpected Serious Adverse Reaction (SUSAR): SUSAR's experienced by local participants are to be reported to the REB within **7 days** of the research team's awareness of the event, even if full details are not yet known,

- If the nature, severity and frequency of the event are consistent with the risks described in the protocol, consent form and applicable product information, the event was 'expected' and should not be reported to the REB;
- Events should only be reported if the PI and/or the sponsor believe that the event was related or possibly related to study participation. If neither the PI nor the sponsor believe that the event may have been caused or exacerbated by study procedures, it was not a 'reaction' and should not be reported to the REB;
- All reports submitted to the REB must have all research participant identifiers removed (i.e. participant research number only),
- Once a local SUSAR is acknowledged by the REB, subsequent follow-up reports related to the SUSAR are expected to be reported to the REB until the event is resolved;
- All initial and subsequent follow-up reports will be retained with the reportable event;

4.2.3. Non-Local (External) Adverse Events: The REB will only accept semi-annual or quarterly reports for external suspected unexpected serious adverse reactions (SUSAR) for clinical trials. Non-Local (External) individual adverse event reports **and** line listings will not be processed and will be returned to the research team;

4.2.4. 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 periodic safety updates or safety summary reports that meet the reporting criteria must be submitted to the REB upon receipt.

4.2.5. Other Reportable Events: The PI 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 PI is also responsible for submitting to the REB other types of reportable events, such as:
  - DSMB reports, to be submitted to the REB as soon as possible and no later than **one month** following receipt from the sponsor,
  - Periodic Safety Update Reports (PSUR), to be submitted to the REB within **two months** of receipt from the sponsor,
  - 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).

4.2.6. Deviations to Previously Approved Research: The PI must report to the REB any deviations that meet the following reporting criteria:

- Major study violations are deviations from applicable regulatory requirements or REB-approved documents, policies, and/or processes that impact data integrity or participant safety, privacy / confidentiality, or willingness to continue in the study, examples include:
  - Obtaining informed consent with an outdated or unapproved version of the consent form; beginning study procedures before consent was obtained; enrolling participants who didn't meet eligibility criteria; omitting key protocol-required tests or procedures; medication errors, including prescribing a contraindicated medication; using the wrong survey instrument; or using or releasing personal information without the participant's consent,
- Major study violations that affect, or have the potential to affect, the safety or wellbeing (including the privacy) of NSHA patients are considered "patient safety events" and as per policy CH 30-035 must be entered in NSHA's Patient Safety Reporting System before they are reported to the REB,
- Major study violations must be reported to the REB upon discovery if they were initiated (accidentally or intentionally) by the research team or the sponsor. Participant-initiated violations need not be reported;

Clinical trials: Study deviations that do not affect data integrity or participant safety, privacy / confidentiality, or willingness to continue in the study are to be submitted to the REB using the Minor Study Deviation Reporting Form when annual approval or study closure is requested.

4.2.7. Privacy Breaches: The PI must report to the REB any unauthorized collection, use, or disclosure of personal information including, but not limited to:

- The collection, use and disclosure of personal health information that is not in compliance with the Personal Health Information Act (PHIA),
- Circumstances where personal information is stolen, lost or subject to unauthorized use or disclosure or where records of personal information are subjected to unauthorized copying, modifications or disposal,
- In the Principal Investigator context, any unauthorized collection, use or disclosure of personal information 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 (i.e. NSHA Privacy Officer, IT services, legal counsel as applicable) as soon as the PI becomes aware of the breach;

4.2.8. Audit or Inspection Findings: The PI 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;

4.2.9. Research Participant Complaint: The PI 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.

4.3. Review of Reportable Events

4.3.1. The responsible REB Office Personnel will screen the reportable event submission for completeness;

4.3.2. The REB Office Personnel may route the submission back to the PI to request clarifications, missing documents or additional information;

4.3.3. The REB Office Personnel will send a notification via Romeo of the submission to the designated Co-Chair;

4.3.4. The designated Co-Chair will conduct a review of the report and determine if any action or follow-up is required;

4.3.5. Privacy breaches are reviewed by the REB Chair/Co-Chair or designee, and any recommendations including remedial action are determined in consultation with the organization's privacy office.

4.3.6. The privacy breach report is forwarded to the REB Chair or designee for review and final acknowledgement;

4.3.7. When reviewing a reportable event, the REB should:

- 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;

4.3.8. If the event does not raise concerns and does not appear to involve risks to research participants or others, the REB Chair/Co-Chair or designee acknowledges the report, and no further action is required;

4.3.9. If the REB Chair/Co-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 REB Executive Committee, providing the justification for such action is documented;

4.3.10. 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 Executive Committee meeting;

4.3.11. For reportable events reviewed at the Executive Committee, meeting, the Executive Committee, 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;

4.3.12. 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.

4.4. Documentation and Communication

4.4.1. NSHA REB review activities will be documented, filed and retained per the operational procedures of the research ethics office;

4.4.2. Notice of approval or changes required to obtain continuing approval will be distributed to investigators from the research ethics office in a timely manner.

5 REFERENCES

I. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 2014 (TCPS2 2014), Chapter 1 Section C; Chapter 2 Section B;
II. The International Conference on Harmonization Good Clinical Practices, Sections 3, 4.4, 4.5, 4.10, 4.11, 4.12;
III. US Office for Human Research Protections (OHRP) Code of Federal Regulations (CFR) Title 45 Part 46.109, 46.111, 46.113, 46.115;
IV. US Food and Drug Administration (FDA) CFR Title 21 Part 56.108, 56.109, 56.110, 56.111, 56.115

6 RELATED DOCUMENTS:

I. CDHA RS 01-012 Changes in Principal Investigators and Supervising Investigators

II. CDHA RS 01-016 Changes in Study Personnel
III. CDHA CH 30-035 Patient Safety Reporting
IV. NSHA REB-SOP-4-003-Delegated Review Procedure
V. Privacy Breach Protocol Guidelines document, May 19, 2011

Version History

Effective Date	Major Revisions (e.g. Standard 4 year review)	Minor Revisions (e.g. spelling correction, wording changes, etc.)
June 3, 2016		Reflect the change from nine DHA's to one
September 29, 2017		Harmonize with CAREB/N2 SOP's