ONGOING RESEARCH ETHICS BOARD REVIEW ACTIVITIES 508

Procedures are a series of required steps to complete a task, activity or action

Purpose:	To provide Island Health Research Ethics Boards (REBs) a standardized approach for describing the processes for ongoing review and monitoring by the REBs of research approved by the REBs, after approval and prior to review for annual (interval) renewal. The process for follow up reporting of unanticipated problems (SOP 511), reporting of serious and continuous non-compliance (SOP 514), and suspension and termination of research SOP 516
Context	Island Health offers programs and services on the unceded and traditional territories of the Coast Salish, Nuu-chah-nulth, and Kwakwaka'wakw Peoples. As a signatory to the 2015 Declaration of Commitment to Cultural Safety and Cultural Humility, Island Health is committed to addressing the ongoing impacts of colonialism and Indigenous-specific racism in order to provide a culturally safe, inclusive, healthy and respectful environment. The organization is committed to strengthening diversity, equity and inclusion to enable excellence in health and care for everyone, everywhere, every time. Through these commitments, Island Health strives to deliver the highest possible standard of care and to promote safe workplaces.

Scope:	• Affected Roles
	  o Researchers
	  o REB Chairs
	  o REB Members
	  o All REB Office Personnel
	• Environment
	  o Research Environment

Outcomes:	• Procedures for the ongoing review activities that occur after the initial REB approval of a research project and prior to the formally scheduled continuing review of the research project.

1 Responsibility

All REB Members, REB Office Personnel, and Researchers are responsible for ensuring that the requirements of this Standard Operating Procedure (SOP) are met.

The Researcher 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 Researcher 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 Researcher and the organizational Leadership 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 REB 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 (e.g., delegated or Full Board) or action required.

The REB 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.

2 Procedure

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 review may include:

- Review of significant new findings or new information that may affect adversely the safety of the research participants or the conduct of the trial;
- Review of serious and unexpected adverse events and unanticipated problems posing risks to participants or others;
- Review of amendments or changes to research, including protocol deviations;
- Site visits; and
- Third party verification.

Information reviewed by the REB 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.

2.1 Amendments to Approved Research

2.2 The Researcher 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's Brochure (IB) or product monograph (PM), changes in participant materials (e.g., wallet cards, diary cards, recruitment materials), a change in the Researcher etc.

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

2.4 Amendments must be submitted via the online database system where the study is held, using the appropriate Amendment Application Form. Amendments must clearly explain the following:

- What aspects of the protocol, consent form, information sheet and/or recruitment materials are affected. The revised documents must be highlighted on an attached, revised document;
- The nature of the proposed change;
- The reason for the proposed change;
- Any increase in risk or discomfort for study participants and why it is required;
- Any need for a change in the consent process;
- Whether previously or currently enrolled study participants need to re-consent;
- Whether or not the amendment meets minimal risk criteria;
- Other relevant supporting correspondence and/or background information.

2.5 The Researcher must indicate the type of review being requested (e.g., Full Board, delegated review or acknowledgement for a minor correction). Supporting correspondence documentation and/or background information may be appended to the amendment submission. The REB Chair or designee reviews the amendment to determine the appropriate level of REB review required (e.g., Full Board or delegated review).

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

2.7 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 above 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:
  a) A change in drug dosing/duration of exposure,
  b) A change in recruitment that may affect confidentiality or the perception of coercion,
  c) 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.

2.8 For studies that are funded or supported by the United States (U.S.) Federal government or that are subject to the regulations of the U.S. Food and Drug Administration (FDA), only minor changes in previously approved research may be reviewed by the REB under delegated review procedures.

2.9 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.

2.10 When an amendment involves a revised consent, the REB 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.

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

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

3 Reportable Events

3.1 The Researcher is responsible for submitting reportable events that meet the criteria outlined in Island Health REB SOP 511 Reporting. Regardless of whether a research project is biomedical in nature or behavioural, Researchers must promptly notify the applicable REB of any information about a study that could affect the rights, safety and well-being of research participants.

3.2 SOP 503 Safety Information and Unanticipated Problems Reporting defines the requirements for reporting unanticipated problems including serious adverse events (SAEs) and how the REB will process the information.

3.3 Periodic summary reports of unanticipated problems and SAEs reported will be provided by the Research Ethics Coordinator to the Manager, Research Ethics & Compliance to help inform the risk-based compliance auditing program.

3.4 **Local Adverse Events (AEs):** 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;
- All reports submitted to the REB must have all research participant identifiers removed (i.e., participant research number only);
- 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 a SAE update(s). All initial and subsequent follow-up reports will be retained with the reportable event.

3.5 **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:
  a) The description of the serious and unexpected event(s);
  b) All previous safety reports concerning similar adverse events;
  c) An analysis of the significance of the current adverse event(s) in light of the previous reports; and
  d) 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 in a timely manner.

3.6 **Other Reportable Events:** The Researcher 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:
  a) An interim analysis indicates that participants have a lower rate of response to treatment than initially expected;
  b) Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected;
  c) 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:
  a) DSMB reports;
  b) Interim analysis results;
  c) 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 timely manner.

3.7 **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 consent form 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 with a timely manner;

3.7.1 Minor deviations (e.g. typographical corrects of consent form, changes to wording on questionnaires) from the research that do not impact risk or have ethical implications may be summarized in annual status reports (e.g. annual renewals).

3.8 **Privacy Breaches**: The Researcher 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 information that is not in compliance with the jurisdictional legislation or its regulation;
- 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 Researcher 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 as soon as the Researcher becomes aware of the breach and the REB and Office Personnel will report to the Information Stewardship, Access & Privacy (ISAP) office and Research Privacy Specialist and Research leadership.

3.9 **Audit or Inspection Findings**: The Researcher must report within a reasonable amount of time to the REB a summary of any relevant findings following a regulatory inspection (e.g. Health Canada or FDA), an internal Quality Assurance (QA) audit, Sponsor audit or other audits at the site.

3.10 **Research Participant Complaint**: The Researcher must report to the REB, as soon as possible, and to the health authority if required by the REB, 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. Researchers are required to include the Island Health REBs Research Participant Complaint Line contact information on all consent forms given to participants.

4 Review of Reportable Events by the REB

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

4.2 Privacy breaches are reviewed by the REB Chair or designee, the REB Coordinator, and any recommendations including remedial action are determined in consultation with the Manager, Research Ethics & Compliance in consultation with ISAP and the Research Privacy Specialist. The privacy breach report is forwarded to the REB Chair or designee for review and final acknowledgement.

4.3 The REB Office Personnel may route the submission back to the Researcher to request clarifications, missing documents or additional information.

4.4 The REB Office Personnel will forward the submission to the designated REB reviewer(s).

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

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

4.7 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.

4.8 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.

4.9 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, they may suspend ethics approval of the research pending review by the Full Board, providing the justification for such action is documented.

4.10 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.

4.11 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.

If the research study is funded by the U.S. Federal government, or regulated by the U.S. FDA, the REB will notify the appropriate institutional officials in accordance with Island Health REB SOP 511 Reporting.

4.12 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 health authority (as necessary) 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.

5 Site Visits/Audits

5.1 The REBs have the authority to observe, or have a third party observe, the consent process of research it has approved, and to verify that the study is being conducted as required by the REB and within Island Health and site-specific Policies and Procedures as appropriate. Under the direction of the Manager, Research Ethics & Compliance, REB Office Personnel, including but not limited to, third parties not affiliated with the institution, may perform site visits to verify information in the initial study application or in any continuing review submissions. Where appropriate, as determined by the REB and Manager, Research Ethics & Compliance, research leadership should be made aware.

5.2 The REB will consider the following criteria to determine if a site visit is required:

- The research involves vulnerable populations or high risk procedures;
- The Researcher has a history of serious or continuing non-compliance related to continuing review in the past three (3) years;
- The REB has reason to doubt the veracity of the information provided by the Researcher;
- The information provided by the Researcher is inconsistent with other information known to the REB and the inconsistency cannot be resolved through communication with the Researcher;
- A regulatory audit report indicating issues of concern with compliance to Tri Council Policy Statement (TCPS 2);
- Any other reason where the REB believes verification should be required.

6 External Verification

6.1 Island Health's REBs routinely utilize sources other than the Researcher to identify information that may affect projects currently under their oversight. Those sources include but are not limited to the Institution, including the Researcher's supervisor, FDA or Health Canada Inspection reports, media reports, participant complaints, research staff informants, site visit reports and the Internet (FDA warning letters, Office for Human Research Protections (OHRP) and FDA debarment lists and Federal Register notices.).

6.2 The following avenues provide Island Health's REBs with information that is supplemental to the information provided by the Researcher:

- Island Health's site visit/continuing review procedure;

- Island Health's REBs require copies of data monitoring committee reports for review at annual (interval) renewal;
- Island Health's Research Ethics & Compliance office (RECO) is in direct contact with Island Health officials responsible for handling all allegations of research misconduct. RECO is notified in the event that a Researcher has their privileges revoked, or has otherwise been disciplined or investigated by the Institution regarding the conduct of the research;
- Island Health's REBs may also be directly contacted by research Sponsors who notify the Boards of relevant information when appropriate.

7 Training

7.1 Review of the SOP.

8 Compliance Monitoring

8.1 The Island Health Manager, Research Ethics & Compliance or their delegate is responsible for ongoing monitoring of Island Health operations to verify compliance with this.

8.2 The Island Health Manager, Research Ethics & Compliance or their delegate is responsible for communicating any changes to this SOP to all relevant personnel.

8.3 Deviations from this SOP will be addressed through corrective and preventative action implementation.

9 Definitions

See the Glossary of Terms – Research Ethics

10 Related Island Health Policy Documents

- SOP 503 Safety Information and Unanticipated Problems Reporting
- SOP 511 Research Ethics Boards - Reportable Events and Reporting
- SOP 514 Non-Compliance
- SOP 516 Research Ethics Boards – Administrative Holds, Terminations and Suspensions Approval

11 References

- The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Article 6.14
- U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46.109(e))
- U.S. Department of Health and Human Services – Title 21 Code of Federal Regulations Part 56 (21 CFR 56.109(f)
- U.S. Department of Health and Human Services – Title 21 Code of Federal Regulations Part 56 (21 CFR 56.109(g)
- U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46.103(b)(4)(iii)

- U.S. Department of Health and Human Services – Title 21 Code of Federal Regulations Part 56 (21 CFR 56.108(a)(3)&(4))
- Health Canada Food and Drug Regulations, Part C, Division 5, C.05.008 Subsection 2
- U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46.110(b)(2)
- U.S. Department of Health and Human Services – Title 21 Code of Federal Regulations Part 56 (21 CFR 56.110(b)(2)

12 Summary of Changes

Version	Effective Date	Change Description
1.0	15 JUL 2013	New procedure
2.0	01 JAN 2015	Amendment to provide clarity on Minor and Major amendments.
3.0	23 MAR 2023	Changed Issuing Authority from Research & Capacity Building to Vice President, Quality, Research and Chief Nursing & Allied Health Officer. Updated based on current Network of Network (N2) SOP 404.003 Ongoing REB Review Activities.