

<b>Title</b>	Ongoing REB Review Activities
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### Site Approvals

Status	Title	Date
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<i>Acknowledge of receipt</i>	MUHC Board of Directors	

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## 1. PURPOSE

This SOP describes the procedures for the ongoing review activities that occur after the initial Research Ethics Board (REB) approval of a research project and prior to the next formally scheduled continuing review of the research project.

## 2. SCOPE

This SOP pertains to REBs that review human participant research in compliance with applicable regulations and guidelines.



### 3. RESPONSIBILITIES

All REB members, CAE Staff and Researchers are responsible for ensuring that the requirements of this 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 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 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 (i.e., delegated or Full Board) or action required. The REB must find that the criteria for approval are met before providing approval.

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.

### 4. DEFINITIONS

**Reportable event:** includes anything that could significantly impact the conduct of the research or alter the Research Ethics Board's (REB) approval or favourable opinion to continue the research.

**Unanticipated problem:** any incident, experience, or outcome (including an adverse event) that meets **all** of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the REB approved documents, such as the research protocol and informed consent document, the Investigator Brochure or other relevant sources of information such as product labelling and package inserts; and (b) the event is not associated with the expected natural progression of any underlying disease, disorder, predisposing risk factor, or condition of the participant(s) experiencing the adverse event; and
- Related or possibly related to participation in the research, (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the [investigational product(s)] or procedures involved 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.

## 5. PROCEDURES

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 and/or for which a preventative or corrective action is possible.

Such information may include: amendments, reportable events, relevant reports, or any other new information that may adversely affect 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.

### 5.1. Amendments to the Approved Research

- 5.1.1. The Researcher is responsible for submitting, via NAGANO Form F1, to the REB any changes to the approved research in the form of an amendment. Changes to the approved research may 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.;
- 5.1.2. When the amendment is the result of a sponsor safety notice or action letter, this document must be appended to the amendment request.
- 5.1.3. When the amendment includes a change to the consent form, the Researcher must indicate his/her recommendation for the provision of the new information to current and/or past research participants;
- 5.1.4. The REB Chair or designee pre-reviews the amendment to determine the appropriate level of REB review required (i.e., Full Board or delegated review) in accordance with MUHC-REB SOP Delegated Review. 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:
    - A change in drug dosing/duration of exposure,
    - A change in recruitment that may affect confidentiality or the perception of coercion,

- A change in experimental procedure or research population;
- 5.1.5.** For amendments requiring Full Board review, the responsible CAE Personnel assigns the amendment to the next available Full Board meeting. For amendments that meet the criteria for delegated review, the responsible CAE Personnel will forward the amendment to the designated reviewer(s);
- 5.1.6.** 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;
- 5.1.7.** The amended research may not be implemented prior to the REB review and approval, except when necessary to eliminate immediate hazards to participants. A change to the research that was initiated without prior REB review to eliminate an apparent immediate hazard to a research participant must be reported to the REB immediately;
- 5.1.8.** Amendments considered to be administrative in nature (for example, change of address) that have no impact on participants or their well-being, may be submitted at time of annual renewal of the project using Nagano Form F1;
- 5.1.9.** The REB must find that the criteria for approval are still met in order to approve the amendment.

## **5.2. Reportable Events**

The Researcher is responsible for submitting reportable events or findings that meet the REB's reporting criteria in accordance with this SOP and within the time frame specified in section 5.4. All reports submitted to the REB must have all research participant identifiers removed (i.e., participant research number only); The Researcher must determine if an event meets the REB reporting criteria:

As a general rule, any new information that would require modification to 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 unanticipated problems, events or reports that could significantly impact the overall conduct of the research or alter the participants' willingness to participate or the REB's approval or favorable opinion to continue the research, must be reported to the REB.

The Researcher must report the following to the REB, via NAGANO, within the time frame specified by the REB (5.4):

### **5.2.1. Local Serious Adverse Events (SAE)**

- The Researcher must report to the REB, any local incident, experience, or outcome (including an adverse event) that, in the opinion of the Researcher, meets the definition of an unanticipated problem:
  - a. Unexpected and;
  - b. Related or possibly related to participation in the research and;
  - c. Suggests that the research places research participants or others at a greater risk of harm than previously identified at time of review and approval.



- Any applicable forms completed/required by the sponsor (ex. SAE form), must be appended to the Nagano Form F3a (Reportable Local SAE);
- Once a local SAE is reported to the REB, subsequent important follow-up reports related to the SAE should be submitted when available, as update(s). The sponsor's follow-up reporting form(s) must be appended to the updated reportable event. All initial and subsequent follow-up reports will be retained with the reportable event.

#### **5.2.2. Non-Local (External) Serious Adverse Events (SAE)**

- The Researcher must report to the REB, any non-local incident, experience, or outcome (including an adverse event) that, in the opinion of the Researcher, meets the definition of an unanticipated problem:
  - a. Unexpected and;
  - b. Related or possibly related to participation in the research and;
  - c. Suggests that the research places research participants or others at a greater risk of harm than previously identified at time of review and approval;

**and**

  - d. 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, via Nagano Form F3a (Local Reportable SAE), must include all of the following information:
  - The description of the unanticipated problem,
  - Previous safety reports concerning similar events, if available,
  - An analysis of the significance of the current unanticipated problem, 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),
  - A copy of the sponsor's report, if available.

#### **5.2.3. Deviations to Previously Approved Research**

- The Researcher must report to the REB, in Nagano Form F3b (Other Reportable events: Deviations, Privacy Breaches, Complaints), any local deviations that meet the following reporting criteria:
  - Deviations that in the opinion of the Researcher: jeopardize the safety of research participants, the research efficacy, data integrity, or otherwise could impact participant rights, safety or well-being;
  - 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 leads to an SAE.

#### **5.2.4. Privacy Breaches**



- The Researcher must report to the REB, using Nagano Form F3b (Other Reportable events: Deviations, Privacy Breaches, Complaints), 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 and, if applicable, to the appropriate Organizational Official as soon as the Researcher becomes aware of the breach.

#### **5.2.5. Research Participant Complaint**

- The Researcher must report to the REB, using Nagano Form F3b (Other reportable events: deviation, privacy breaches, complaints, 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 as per SOP 406.001.

#### **5.2.6. Other Reportable Events or Findings**

The Researcher is responsible for reporting to the REB, using the appropriate Nagano form for Amendments F1, Other Correspondence F2, Reportable events F3, Change of Status F6, etc., other events or findings, including:

- 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, approval status or withdrawal from marketing of a drug, device, health product, genetic therapy or biologic used in research;
- Any unanticipated problems or other events that could significantly impact the conduct of the research at the site (e.g., concerns of non-compliance, institutional feasibility issues etc.);
- Any relevant findings of an inspection or audit: 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.



### 5.3. Reports

The Researcher is responsible for submitting to the REB, using Nagano form F2, reports related to the research in accordance with 5.4:

Reports that are generated in accordance with the research protocol or are routine or random and that do **not** require action to protect the safety and well-being of research participants may be submitted, if required by the sponsor, at the time of annual renewal. The REB will acknowledge receipt of these reports.

### 5.4. Time frames for reporting events to the REB

The REB must be notified of reportable events as described in this SOP in accordance with the following timelines:

REB notification of...	Time delay (calendar days)	Follow up required
<b>5.1 Amendments</b>		
a. Undertaken immediately to protect participants	Immediately	REB review and approval of amendments
b. All other amendments	Report prior to introducing any change	REB review and approval are required prior to initiation of amendment.
<b>5.2 All Reportable events as described herein</b>		
a. Reportable events in context of death and/or life-threatening reactions:	Within 7 days of researcher becoming aware of the event.	A detailed report containing an analysis of the event, its consequences and corrective measures taken must be submitted within 8 days of the first report
b. All other reportable events	Within 15 days of researcher becoming aware of the event	
<b>5.3 Reports</b>		
Scheduled, routine or random reports without identified impact on participant safety or well-being or required changes	Submit at time of annual renewal	REB acknowledgement letter will be sent.
<b>Any new information that may adversely affect the safety of the research participants or the conduct of the research</b>	Within 15 days of researcher becoming aware of this info	



## **5.5. Review of Reportable Events by the REB**

- 5.5.1.** The responsible CAE Personnel will screen for completeness and that the MUHC REB reportable event form is used if applicable;
- 5.5.2.** The CAE Personnel may route the submission back to the Researcher to request clarifications, missing documents or additional information;
- 5.5.3.** The CAE Personnel will forward the submission to the designated REB reviewer(s);
- 5.5.4.** The assigned REB reviewer(s) will conduct a review of the report and determine if any action or follow-up is required. The assigned reviewer(s) may request further information from the Researcher;
- 5.5.5.** 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;
- 5.5.6.** 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;
- 5.5.7.** 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;
- 5.5.8.** 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 (put study on Hold) pending review by the Full Board, providing the justification for such action is documented;
- 5.5.9.** If the event raises concerns or involves risk to research participants such that REB action may be required, the item is reviewed by a Full Board;
- 5.5.10.** For reportable events reviewed at by a Full Board, 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;
- 5.5.11.** 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 MUHC/RI 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

## **5.6. Amendments and Reportable Events in the Context of Multi-centered Research:**

- 5.6.1.** The MUHC REB will apply this SOP to studies for which it acts as the Evaluating REB for multi-centered research within the Québec public health care system.
- 5.6.2.** In a multi-center study conducted by a different researcher at participating institutions with the same sponsor, each investigator is responsible for submissions of reportable events in their institution and to the Evaluating REB. The local MUHC researcher must submit in accordance with this SOP.
- 5.6.3.** A Quebec investigator who submits an amendment for approval to the Evaluating REB, must forward the approved amended documents as well as a copy of the original document with approved changes highlighted to the mandated person in each public institution where the research is taking place.
- 5.6.4.** For multi-centre trials in Québec for which the MUHC is the evaluating REB, all participating site within the Québec public health care system covered by the MUHC REB approval will be considered local.
- 5.6.5.** Adding a site that transforms your project into a multicentre project, or that adds a site to a multi-centre study, must use Nagano Form F1MP.

## 6. REFERENCES

- Canadian Association of Research Ethics Boards. History of the Development of the Guidance on Reporting of Unanticipated Problems Including Adverse Events to Research Ethics Boards in Canada July 2010.
- ICH E2A, II.A.1
- ICH E6: Good Clinical Practice (GCP), 5.17
- MUHC, RI SOP-007
- MUHC, RI SOP-012
- N2 CAREB REB SOPs September 15, 2014, <https://www.careb-accr.org/n2careb-accr-reb-sops>
- Office for Human Research Protections (OHRP) and Department of Health and Human Services (HHS) – Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, <http://www.hhs.gov/ohrp/policy/advevntguid.pdf>
- Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, December 2014 (TCPS2)
- USA Food and Drug Administration Code of Federal Regulations Title 21 Part 56.108 (b)
- US Department of Health and Human Services. Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting, January, 2009. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079753.pdf>
- See References

## 7. REVISION HISTORY

SOP Code	Effective Date	Summary of Changes
SOP-REB-404.001	2016-02-22	First issue
MUHC-REB-SOP-405.002	2017-02-24	MUHC SOP Code and minor page layout changes
MUHC-REB-SOP-405.002_1	2017-07-07	5.1.4. Change to reference to MUHC-REB SOP 402.001. 5.2.2. Change of Form reference (From F1 to F3a) 5.2.5. Change of Form reference (From F8 to F3b) 5.4. Time delay changed from 14 to 15 days. 6. Corrected references: harmonized with RI-SOPs.