a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

# SOP 404

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| **TITLE** | **404: Ongoing REB Review Activities** |
| **SCOPE** | All research submitted to the University of British Columbia's Research Ethics Boards |
| **RESPONSIBILITIES** | The Vice-President Research & Innovation, delegated to the Director, Office of Research Ethics, all Research Ethics Board (REB) Chairs and members, all REB Office Personnel, and Researchers |
| **APPROVAL AUTHORITY** | The Vice-President, Research & Innovation |
| **EFFECTIVE DATE** | May 2018 |
| **Supersedes documents dated** | May 2011, December 2010, March 2010, April 2009, July 2003 |

## 1.0 PURPOSE

The purpose of this standard operating procedure (SOP) is to describe the processes for the ongoing review and monitoring by the REBs of research approved by the University of British Columbia REBs, after approval and prior to review for annual (interval) renewal. The process for follow up reporting of unanticipated problems, reporting of serious and continuous non-compliance (SOP 903), and suspension and termination of research (SOP 409) are described in SOP 408.

## 2.0 DEFINITIONS

See the Glossary of Terms.

## 3.0 RESPONSIBILITIES

The Vice-President, Research & Innovation, all REB members, REB Office Personnel 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 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

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[1], 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[2]. 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.

## 4.1 Amendments to the Approved Research

**4.1.1** The Researcher is responsible for submitting to the REB any changes to the approved research in the form of an amendment[3]. 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 Researcher must indicate his/her recommendation for the provision of the new information to current and/or past research participants;

**4.1.3** Amendments must be submitted via the RISe system, using the "Amendments to Study" form on the Post-Approval Activity page. 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 be re-consented,
- Whether or not the amendment meets minimal risk criteria;

**4.1.4** The Researcher 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;

**4.1.5** The REB Chair or designee reviews the amendment to determine the appropriate level of REB review required (i.e., Full Board or delegated 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** 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;
- Any amendment that requires approval from Health Canada[4];
- 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;
- Amendments to the chemistry and manufacturing information that may affect the safety or quality of the drug;

**4.1.8** For studies that are funded or supported by the U.S. Federal government or that are subject to the regulations of the U.S. Food and Drug administration, only minor changes in previously approved research may be reviewed by the REB under delegated review procedures[5];

**4.1.9** 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;

**4.1.10** 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;

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

**4.1.12** 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 Researcher is responsible for submitting reportable events that meet the criteria outlined in UBC REB SOP 408 (Reporting);

**4.2.2** **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.

**4.2.3** **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;

**4.2.4** **Research Participant Complaint:** The Researcher must report to the REB, and to the University 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 UBC REB Research Participant Complaint Line contact information on all consent forms given to participants.

## 4.3 Review of Reportable Events by the REB

**4.3.1** Reports of unanticipated problems must be submitted using the "Request for Acknowledgment" form via the RISe system.

Reports of Unanticipated problems **other than** those that are adverse events must include:

- A description of the incident, experience or outcome,
- An explanation of the basis for determining that the incident, experience or outcome represents and unanticipated problem (as defined in 3.3.),
- The Investigator's opinion regarding its causality to the study/device procedure,
- The action taken in response to the unanticipated problem,
- The outcome of the unanticipated problem,
- The investigator's opinion regarding the implications for continuation of the study,
- The Investigator's opinion regarding the need for any change to study procedures, protocol or consent documents,

Reports of Unanticipated problems that **are** adverse events must include:

- A detailed description of the event and if the event is local an assessment as to whether the event reaction was mild, moderate or severe,
- An opinion expressed by the investigator (if local) or the sponsor (if a qualifying reportable non-local adverse event) that the event is both serious and unexpected and a justification of that opinion,
- An opinion expressed by the investigator (if local) or the sponsor (if a qualifying reportable non-local adverse event) that the event is related or potentially related to the study drug/procedure/device and an explanation of that opinion,
- An opinion expressed by the investigator (if local) or the sponsor (if a qualifying reportable non-local adverse event) respecting the implications of the event on the continuation of the study and any further actions that may be required such as changes to the study procedure, informed consent or protocol,
- A statement of the response to and the patient outcome of the event;

**4.3.2** The responsible REB Office Personnel will screen the reportable event submission for completeness;

**4.3.3** Privacy breaches are reviewed by the REB Chair or designee, and any recommendations including remedial action are determined in consultation with the Director, Office of Research Ethics and, if necessary, the University's privacy office. The privacy breach report is forwarded to the REB Chair or designee for review and final acknowledgement;

**4.3.4** The REB Office Personnel may route the submission back to the Researcher to request clarifications, missing documents or additional information;

**4.3.5** The REB Office Personnel will forward the submission to the designated REB reviewer(s);

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

**4.3.7** The assigned reviewer(s) may request further information from the Researcher;

**4.3.8** 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),
- Consider whether suspension or termination of the ethics approval of the research is warranted;

**4.3.9** 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;

**4.3.10** 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;

**4.3.11** 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 UBC REB 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 REB chair or designee is responsible for reporting to the Researcher and the University (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.

## 4.4 Site Visits/Audits

**4.4.1** 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 University and site-specific Policies and Procedures as appropriate. Under the direction of the Director, Office of Research Ethics, 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;

**4.4.2** 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 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,

- Any other reason where the REB believes verification should be required.

## 4.5 External Verification

**4.5.1** UBC'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, OHRP and FDA debarment lists and Federal Register notices.);

**4.5.2** The following avenues provide UBC's REBs with information that is supplemental to the information provided by the Researcher:

- UBC's site visit/continuing review procedure,
- UBC's REBs require copies of data monitoring committee reports for review at annual (interval) renewal,
- UBC's Office of Research Ethics (ORE) is in direct contact with UBC officials responsible for handling all allegations of research misconduct. ORE is notified in the event that a Researcher has his or her privileges revoked, or has otherwise been disciplined or investigated by the Institution regarding the conduct of the research,
- UBC's REBs are often directly contacted by research sponsors who notify the Boards of relevant information when appropriate.

## 5.0 REFERENCES


1. *The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, Article 6.14: http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter6-chapitre6/#ch6_en_a6.14

2. *U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46.109(e)):* https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.109
*U.S. Department of Health and Human Services – Title 21 Code of Federal Regulations Part 56 (21 CFR 56.109(f)):* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.109

3. *U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46.103(b)(4)(iii)):* https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.103
*U.S. Department of Health and Human Services – Title 21 Code of Federal Regulations Part 56 (21 CFR 56.108(a)(3)&(4)):* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.108

4. *Health Canada Food and Drug Regulations, Part C, Division 5, C.05.008 Subsection 2*: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/links.html

5. *U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46.110(b)(2)):*
https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.110
*U.S. Department of Health and Human Services – Title 21 Code of Federal Regulations Part 56 (21 CFR 56.110(b)(2)):*
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.110