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THE UNIVERSITY OF BRITISH COLUMBIA

SOP 408

TITLE	**408: Reportable Events and Reporting**
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 (ORE), all Research Ethics Board (REB) Chairs and members and all REB Office Personnel
APPROVAL AUTHORITY	The Vice-President, Research & Innovation
EFFECTIVE DATE	May 2018
Supersedes documents dated	May 2011, March 2010

1.0 PURPOSE

The purpose of this standard operating procedure (SOP) is to build upon the policies described in SOPs 409 and 903, and details the procedures for supplementary reporting of unanticipated problems, serious and continuing non-compliance, and suspension and termination of REB approval.

2.0 DEFINITIONS

See the Glossary of Terms.

3.0 PROCEDURE

It is UBC's policy to require that investigators report as soon as reasonably possible (within 7 days) any unanticipated problems involving risk to participants or others to the relevant UBC REB. Once reported, the REB will make determinations about the reported problems and direct appropriate follow-up with the investigative team.

The REB then has the responsibility to promptly report the unanticipated problems or instances of serious or continuing non-compliance, with the resulting determinations (including suspension or termination of REB approval) to all appropriate study contacts (including the study Sponsor/Contract Research Organization (CRO) and institutional officials, when appropriate), and the appropriate government agencies (OHRP, FDA) when applicable[1].

3.1 Reportable Events

3.1.1 The Researcher is responsible for submitting reportable events that meet the UBC REB's reporting criteria[2];

3.1.2 **Local Adverse Events:** The Researcher must report the following to the REB **as soon as reasonably possible**, but in any case, within seven (7) days of their occurrence using the Request for Acknowledgement Form via the RISe system:

- Any local adverse event that in the opinion of the Researcher meets the definition of an unanticipated problem,
- The completed sponsor's serious adverse event (SAE) form (if applicable) must be appended to the reportable event form,
- 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 available, as SAE update(s). The sponsor's follow-up reporting form(s) signed by the Researcher or medical designee must be appended to the updated reportable event. All initial and subsequent follow-up reports will be retained with the reportable event.

If an Investigator determines that an adverse event is not an unanticipated problem, but the sponsor subsequently determines that it is, the Investigator must report this determination to the REB as soon as reasonably possible after the Investigator becomes aware of the sponsor's determination;

3.1.3 **Non-Local (External) Adverse Events:** In general, Investigators and REBs are not appropriately situated to assess the significance of individual external adverse events. For multi-centre studies, the sponsor and/or data and safety monitoring committee is in a better position to process and analyze adverse event information for the entire study and to determine whether an event is both "unanticipated" and a "problem" for the study. Accordingly, UBCs investigators may rely upon the sponsor's assessment and provide to the REB a **periodic safety update report** prepared by the sponsor. The format used for annual safety reports is acceptable.

Single isolated external adverse events rarely meet the requirements for reporting to REBs. Individual **external** adverse events should only be reported when a determination has been made that the event meets all of the criteria for an unanticipated problem.

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,
- Individual isolated EAEs should only be reported to the REB if they are unanticipated problems and the report includes **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),
- Reports not meeting these requirements will be returned to the submitter with a description of the UBC REB reporting requirements,
- The individual AE reports or periodic safety updates or safety summary reports that meet the reporting criteria must be submitted to the REB as soon as reasonably possible after the receipts of the report or notice of the event by the Investigator;

3.1.4 New Information and Unanticipated Problems that are not Adverse Events and Other Events or Findings:

Regardless of whether a research project is biomedical in nature or behavioural, all UBC 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. In general, only those incidents, experiences or outcomes that require a change to the study procedures, study documents and/or require notifying the research participants should be reported to the REB.

Notification to the applicable REB of events resulting in increased or different risks must be made **as soon as reasonably possible** following the occurrence of the event.

Notification and approval of changes to the research study must be made prior to the changes being implemented, unless it is a change to a protocol taken without prior REB review to eliminate an apparent immediate hazard to a research participant (or a minor logistical change such as a change in monitor or telephone contact number), in which case notification shall be made as soon as reasonably possible after the change has been made.

Notification to the applicable REB of new information that might adversely affect the safety or well-being of the study participants or the conduct of the study must be made as soon as reasonably possible after the Investigator becomes aware of such information.

3.1.5 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:
    - 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,
    - Studies which are on hold, or have been re-activated after being on hold,
- 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 as soon as reasonably possible;

3.1.6 Deviations to Previously Approved Research: The Researcher must report to the REB any deviations that meet the following reporting criteria[3]:

- 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,

- Enrolment of participants outside protocol inclusion/exclusion criteria not agreed to by the sponsor,
- Any change in the approved process for obtaining consent (e.g., improper translation, current ICF not implemented),
- Medication/intervention errors (i.e. incorrect drug/intervention, incorrect dosage of the drug),
- Inadvertent deviation in specific research intervention procedures or timing of the research intervention,
- Breach of confidentiality or privacy without a need to know, or by data exposure (computer security breach, documents left unsecured),
- Any deviations that lead to an SAE,

The Researcher should not implement any deviation from, or changes to, the protocol without prior REB approval, except where necessary to eliminate an immediate hazard(s) to participants, or when the change(s) involves only logistical or administrative aspects of the trials (e.g. change in monitor(s), change of telephone number(s)).

Should a Researcher implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to participants without prior REB approval, he/she should submit, as soon as reasonably possible thereafter, a report notifying the REB of the implemented deviation or change, the reasons for it, and, if appropriate, an accompanying proposed protocol amendment(s) for review and approval, using the Request for Acknowledgement form.

Deviations from or changes to the protocol to eliminate immediate hazards to the study participants must be reported to the REB within 7 (seven) days of their discovery. All other deviations must be reported to the applicable REB within 15 (fifteen) days of their discovery. Protocol deviation reports must be completed and signed by the Principal Investigator/designated representative for the study concerned. The report must include at least the following content:

- A description of the deviation that occurred with an explanation of the circumstances that lead to the deviation and the resulting problem,
- An explanation as to whether or not the deviation compromised the scientific integrity of the study,
- An explanation of whether or not the deviation increased the risk or the possibility of risk for the research participant,
- A description of steps taken or that will be taken to correct / address the problem resulting from the deviation, and
- A plan for ensuring that a similar deviation does not occur in the future.

3.2 Reporting Procedures

3.2.1 The REB has the responsibility to report, as soon as reasonably possible, to the Director, Office of Research Ethics (ORE) concerns with regard to research studies in which any of the following have been identified:

- Unanticipated problems involving risk to participants or others,
- Serious or continuing non-compliance,
- Suspension or termination of approved research by the REB;

3.2.2 The Director, Office of Research Ethics will be responsible for promptly notifying external agencies through the completion of incident reports, based on jurisdiction as follows:

- The Office of Human Research Protections (OHRP) if the research is conducted, funded, or overseen by the Department of Health and Human Services (DHHS),
- The U.S. Food and Drug Administration (FDA) if the research is regulated by the FDA,
- Health Canada,
- Other agencies that are signatories to the Common Rule, if the research is conducted, funded, or overseen by DHHS.

3.3 Unanticipated Problems Involving Risk to Participants or Others

3.3.1 REB determinations of unanticipated problems involving risk to participants or others in accordance with section 3.1 of this SOP will be reported to the following entities within 15 days of the REB's determination:

- Principal Investigator (PI),
- Department Head (or equivalent),
- Dean or Unit Director, if appropriate,
- Vice-President, Research & Innovation,
- OHRP (incident report),
- FDA, if applicable,
    - When research is FDA regulated: The REB requires that the PI reports Unanticipated Problems involving risk to participants or others to the Sponsor (as applicable), who must report to the FDA. If the PI is also the Sponsor, then REB requires that the Sponsor-investigator report to the FDA. Regardless of whether such reporting has occurred as indicated by the PI for initial determination or resolution, the REB will report to the FDA[4],
- Sponsor, if appropriate,
- Other administrative personnel as appropriate;

3.3.2 The following information should be included within the incident report:

- Name of the Institution (e.g., university, hospital, foundation, school, etc.) conducting the research,

- Title of the research project and/or grant proposal in which the problem occurred,
- Name of the Principal Investigator on the protocol,
- Number of the research project assigned by the REB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement),
- A detailed description of the problem,
- Actions the Institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend participant enrollment, terminate the research, revise the informed consent document, inform enrolled participants, increase monitoring of participants, etc.);

3.3.3 The Director, Office of Research Ethics, in consultation with the REB Chair, approves the incident report which the Director, Office of Research Ethics sends through the office of the Vice-President, Research & Innovation to the appropriate federal agency(ies) and copied to the PI and the Chair of the applicable REB.

3.4 Serious or Continuing Non-Compliance

3.4.1 REB determinations of serious or continuing non-compliance in accordance with SOP 903 will be reported to the following entities within 15 days of the REB's determination[5]:

- Principal Investigator,
- Person(s) involved in the non-compliance,
- Department Head (or equivalent),
- Dean or Unit Director, if appropriate,
- Vice-President, Research & Innovation,
- OHRP (incident report),
- FDA, if applicable,
- Sponsor, if appropriate,
- Other administrative personnel as appropriate,
- Person raising the allegation (if the identity of the person is known and the feedback deemed appropriate);

3.4.2 The following information should be included within the incident report:

- Name of the Institution (e.g., university, hospital, foundation, school, etc.) conducting the research,
- Title of the research project and/or grant proposal in which the non-compliance occurred,
- Name of the Principal Investigator on the protocol,
- Number of the research project assigned by the REB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement),
- A detailed description of the non-compliance, and

- Actions the Institution is taking or plans to take to address the non-compliance (e.g., educate the Investigator, educate all research staff, suspend the protocol, suspend the Investigator, conduct random audits of the Investigator or all investigators, etc.);

3.4.3 The Director, Office of Research Ethics, in consultation with the REB Chair, approves the incident report which the Director, Office of Research Ethics sends through the office of the Vice-President, Research & Innovation to the appropriate federal agency(ies), and copied to the PI and the Chair of the applicable REB.

3.5 Suspension or Termination of Approved Research by the REB

3.5.1 REB decisions to suspend research in accordance with SOP 407 will be reported to the following entities within 15 days of the REB's determination:

- Principal Investigator,
- Department Head (or equivalent),
- Dean or Unit Director, if appropriate,
- Vice-President, Research & Innovation,
- OHRP (incident report),
- FDA, if applicable,
- Sponsor, if appropriate,
- Other administrative personnel as appropriate,

3.5.2 The following information should be included within the incident report:

- Name of the Institution (e.g., university, hospital, foundation, school, etc.) conducting the research,
- Title of the research project and/or grant proposal that was suspended or terminated,
- Name of the Principal Investigator on the protocol,
- Number of the research project assigned by the REB that was suspended or terminated and the number of any applicable federal award(s) (grant, contract, or cooperative agreement),
- A detailed description of the reason for the suspension or termination, and
- Actions the Institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged noncompliance, educate the investigator, educate all research staff, require monitoring of the investigator or the research project, etc.);

3.5.3 The Director, Office of Research Ethics, in consultation with the REB Chair, approves the incident report which the Director, Office of Research Ethics sends through the office of the Vice-President, Research & Innovation to the appropriate federal agency(ies), and copied to the PI and the Chair of the applicable REB.

4.0 REFERENCES

1. *U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46.103(b)(5)):*
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(b)):
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.108

2. *The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, Article 6.15:
http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter6-chapitre6/#ch6_en_a6.15
U.S. Department of Health and Human Services - Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection:
https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126572.pdf

3. *International Conference on Harmonization – Good Clinical Practice (ICH-GCP 3.3.7)*:
https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/efficacy/guidance-document-good-clinical-practice-integrated-addendum-e6-r1-topic-e6-r2.html#a3.3
International Conference on Harmonization – Good Clinical Practice (ICH-GCP 4.5.2):
https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/efficacy/guidance-document-good-clinical-practice-integrated-addendum-e6-r1-topic-e6-r2.html#a4.5

4. *Office for Human Research Protections: Guidance on Reporting Incidents to OHRP (2011):*
https://www.hhs.gov/ohrp/compliance-and-reporting/guidance-on-reporting-incident/index.html

5. *U.S. Department of Health and Human Services – Title 45 Code of Federal Regulations Part 46 (45 CFR 46.108(a)):*
https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.108