RR0900 – SAFETY AND ADVERSE EVENTS REPORTING

1.0 PURPOSE

To provide direction for the responsibility of reporting and review of safety information and serious adverse events related to research involving human participants previously approved by the Interior Health (IH) Research Ethics Board (REB).

2.0 DEFINITIONS[1]

TERM	DEFINITION
Adverse Drug Reaction (ADR)	In the pre-approval clinical experience with a new medicinal/natural health product or its new usages, particularly as the therapeutic doses may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug/natural health product reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility; i.e., the relationship cannot be ruled out. Marketed medicinal/natural health products: a response to a drug/natural health product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.
Adverse Event (AE)	Any untoward medical occurrence in a research participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.
Clinical Trial/Study	Any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous. Note: A clinical study may also involve a device, observation, questionnaires, interviews or diagnostic tests.
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.

[1] All definitions in this section have been adapted N2 Network of Networks Glossary of Terms.

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TERM	DEFINITION
Serious Adverse Drug Reaction (SADR)	An adverse drug/natural health product reaction that requires in-patient hospitalization or prolongation of existing hospitalization that causes congenital malformation that results in persistent or significant disability or incapacity, that is life threatening, or that results in death.
Serious Unexpected Adverse Drug Reaction	A serious adverse drug/natural health product reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug/natural health product.
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
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 protocol-related documents, such as the REB approved research protocol and informed consent document, or the Investigator Brochure; and (b) the characteristics of the research participant population being studied; 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. *Unexpected: an event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents such as the REB approved research protocol, the Investigator Brochure, or the current REB approved informed consent document, or other relevant sources of information such as product labelling and package inserts; or when 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. +Related to the research procedures: an event is “related to the research procedures” if in the opinion of the researcher or sponsor, the event was more likely than not to be caused by the research procedures.
Unexpected Adverse Drug Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

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3.0 POLICY

3.1 Safety Reporting

3.1.1 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. Such information may include:

3.1.1.1 Reports of unanticipated problems involving risks to participants or others;

3.1.1.2 Reports of any serious or continuing non-compliance;

3.1.1.3 Reports of any changes significantly affecting the conduct of the research or increasing the risk to research participants;

3.1.1.4 Results of any interim analysis or Data and Safety Monitoring Board (DSMB) assessments;

3.1.1.5 Adverse events that meet the reporting criteria;

3.1.1.6 Summary reports of any audits and inspections; or

3.1.1.7 Any other new information that my affect adversely the safety of the research participants or the conduct of the research.

3.1.2 Local adverse events deemed to be unanticipated problems, and experienced by a research participant enrolled by the researcher at the centre(s) under the jurisdiction of the REB will be reported by the researcher and receive a detailed review.

3.1.3 Non-local adverse events, experienced by research participants enrolled by researchers at other centres/organizations outside the REB's jurisdiction, will be not be regularly reported or receive review by the REB. The REB respects that the sponsor and/or DMSB are responsible to process and analyze safety and adverse event information for multi-centre studies and will accept their reports.

If a non-local adverse event 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 researcher will report it to the REB.

3.1.4 All reviews of safety reports and local adverse events will be reported at the next scheduled REB meeting.

3.1.5 If a safety report represents a significant change to the level of risk to participants it will receive full Board review at the next scheduled REB meeting. The researcher will be contacted to provide any additional information about the event required for the full Board review.

3.1.6 For safety events reviewed at a full Board meeting, the REB will determine whether further action is required. Possible actions that could be taken by the REB include, but are not limited to:

3.1.6.1 Placing a hold on the research pending receipt of further information from the researcher;

3.1.6.2 Requesting modifications to the research;

3.1.6.3 Requesting modifications to the consent form;

3.1.6.4 Providing additional information to past participants;

3.1.6.5 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;

3.1.6.6 Altering the frequency of continuing review;

3.1.6.7 Observing the research or the consent process;

3.1.6.8 Requiring additional training of the researcher and research staff;

3.1.6.9 Termination or suspension of the research;

3.1.6.10 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.

3.1.7 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, the Scientific Director of Research, and has the authority to notify the sponsor and the appropriate regulatory authorities (as applicable). The REB may delegate regulatory authority reporting to a Vice President.

3.2 Researcher Responsibilities

3.2.1 The researcher shall provide the REB with an acceptable plan for monitoring the safety of participants, including a plan for the tabulation, analysis and reporting of safety data, and the sharing of other new information in a form that permits the REB to interpret and respond appropriately.

3.2.2 The researcher is responsible and accountable for the safety of participants for the duration of the research project including ongoing evaluation of risk of harm related to adverse events. The researcher will evaluate all adverse events during the study and determine whether the events are considered serious against the following criteria:

3.2.2.1 Results in death;

3.2.2.2 Is life-threatening;

3.2.2.3 Requires hospitalization or prolongation of existing hospitalization;

3.2.2.4 Results in persistent or significant disability/incapacity;

3.2.2.5 Results in a congenital anomaly/birth defect; or

3.2.2.6 Jeopardizes the participant or requires intervention to prevent one of the outcomes listed above.

3.2.3 The researcher shall promptly report any new information that may affect the welfare or consent of participants, to the REB, and to other appropriate regulatory or advisory bodies. Events that may increase the level of risk to participants, or have other ethical implications that may affect participants' welfare must be reported within **14 calendar days.** Local serious events, where there is real harm to participants will be reported

to the REB at the earliest opportunity and no later than **7 calendar days** from the time of the event.

3.2.4 For local adverse events, drug reactions, and unanticipated problems the researcher should include the following information in the report of the event:

3.2.4.1 A description of the event including severity, with participant identifiers removed (use participant research ID only);

3.2.4.2 Attached copy of the completed sponsor's serious adverse event form (if applicable) and signed by the researcher or medical designee;

3.2.4.3 All previous safety reports concerning similar adverse events;

3.2.4.4 An analysis of the significance of the current adverse event(s) in light of the previous reports; and

3.2.4.5 The proposed research changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the event(s);

3.2.4.6 Once a local serious event is acknowledged by the REB, subsequent important follow-up reports related to the event should be submitted when available, as 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.

3.2.5 When new information is relevant to the participants' welfare, the researchers shall promptly inform all participants to whom the information applies (including former participants). The researcher will work with the REB to determine which participants must be informed, and how the information should be conveyed.

4.0 PROCEDURES

4.1 Research Ethics Office

4.1.1 Receives all safety information and reports and responds as follows:

4.1.1.1 For reports that present no risk to participants, sends an Acknowledgement of Receipt e.g. CIOMS reports, Dear Investigator Letters, periodic line listings, DSMB reports

4.1.1.2 For local events that are serious but expected, are not related to the investigational product or research procedures, or are not serious, forward to the Chair for review

4.1.1.3 For local, Serious and Unexpected Adverse Events, notify the Chair and add to the REB agenda for full board review.

4.1.2 Adds all safety reports and related documents to the project file.

4.1.3 Maintains tracking tool on all safety events and reports these to the REB at the next scheduled meeting.

4.2 REB

4.2.1 Reviews all safety events that require full Board review.

4.2.2 Reviews the Safety Report and discusses safety events as required.

4.3 REB Chair

4.3.1 Reviews all safety information and reports and determines the level of risk. This may be delegated to the Research Ethics Board Coordinator.

4.3.2 Sends acknowledgment to the researcher indicating;

4.3.2.1 The event has been reviewed and acknowledged; or

4.3.2.2 Further action is required by the researcher; or

4.3.2.3 The event requires review by the full Board.

4.3.3 After full Board review, the Chair will inform the researcher of the decision in writing.

4.3.4 Any serious events posing immediate potential or real harm to participants will be directly reported to the Scientific Director of Research, who will then report to the Vice President responsible for research for consideration of referral to the IH Board.

5.0 REFERENCES

- Canadian Association of Research Ethics Boards. (2010). *Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada.*
- Canadian Association of Research Ethics Boards and N2 Network of Networks. (2016). Standard Operating Procedure 404.002: *Ongoing REB Review Activities.*
- Canadian General Standards Board. (2013). *Research Ethics Oversight of Biomedical Clinical Trials.* Gatineau.
- 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.
- Health Canada, Food and Drug Regulations, Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects, (Schedule 1024), June 20, 2001.
- Interior Health. (2018). Research Policy Manual: *RR1200 Suspensions and Terminations of REB Approval.*
- International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Harmonized Guideline, Integrated Addendum to ICH E6(R1); Guideline for Good Clinical Practice, E6(R2), November 9, 2016.
- Island Health Authority. (2013). Research Ethics. Standard Operating Procedure 503: *Safety Information and Unanticipated Problems Reporting*, version 1.

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- UBC Office of Research Ethics. (2011). Standard Operating Procedure 405: *Ongoing Review and Reporting*.

- US Department of Health and Human Services, Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects (45CFR46).

- US Food and Drug Administration Code of Federal Regulations, Title 21, Volume 1:
  - Part 50, Protection of Human Subjects, (21CFR50).
  - Part 56, Institutional Review Boards, (21CFR56).

**This policy replaces the following policies which are no longer active:
IH REB Policy: *Serious and Unexpected Adverse Events, Management Of* approved March 6, 2008
IH REB Policy: *Safety Monitoring Log* approved December 6, 2007