Unity Health Toronto ("Network")
Guidelines for Reporting Serious Adverse Events / Unanticipated Problems to the Research Ethics Board (REB)
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1. Introduction

The Unity Health Toronto ("Network") REB has adopted the Canadian Association of Research Ethics Boards (CAREB) guidance document on "*Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*" (July 2010). The following guidance document outlines the requirements for reporting Unanticipated Problems, including serious adverse events, to the Network Board of Record (or "Network REB"). These reporting guidelines apply to clinical intervention trials as well as non-intervention trials. In addition to these guidelines, the researcher should also adhere to the approved study protocol, sponsor requirements, REB study-specific requirements and regulatory requirements regarding the reporting of serious adverse events/unanticipated problems.

2. Definitions

Adverse Event (AE): any unfavourable or unintended occurrence in the health or well-being of a research participant who is administered an investigational product (drug, natural health product, or device) or any other research procedure(s) and which does not necessarily have a causal relationship with the investigational product or any research procedure(s). An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Local (Internal) Adverse event: An adverse event experienced by a research participant enrolled by the investigator(s) at one or more centres under the jurisdiction of the REB of Record. In the context of a single-centre clinical trial, all adverse events would be considered *local adverse events.*

External (Non-Local) Adverse event: From the perspective of the REB overseeing one or more centres engaged in a multi-centre clinical trial, an external adverse event is an adverse event experienced by a research participant enrolled by investigator(s) at centres/institutions outside the REB of Record's jurisdiction.

Adverse Drug Reaction (ADR): all noxious and unintended responses to an investigational product [which includes natural health products and biologics] related to any dose should be considered adverse drug reactions. The phrase *responses to an investigational product* means that a causal relationship between the investigational product and an adverse event is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

Serious Adverse Event/Experience (SAE) or Reaction: any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect

- based upon appropriate medical judgment, is an important medical event that may jeopardize the health of the research participant or may require medical intervention to prevent one of the outcomes listed above.

Unexpected Adverse Drug Reaction (U-ADR): an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the Investigator's Brochure for an unapproved investigational product or the Product Monograph for a marketed drug).

Unanticipated Problem: any incident, experience, or outcome (including an SAE or U-ADR) that meets **all** of the following criteria:

- **Unexpected** (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents (e.g., the REB-approved research protocol and informed consent document, Investigator's Brochure, Product Monograph); and/or 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 event, 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.

Periodic Safety Update Report (PSUR): a summary report prepared by the Market Authorization Holder (MAH) that provides a periodic but comprehensive assessment of the worldwide safety data of a medicinal product. The PSUR can be an important source for the identification of new safety signals, a means of determining changes in the benefit-risk profile, an effective means of risk communication to regulatory authorities and an indicator for the need for risk management initiatives, as well as a tracking mechanism for monitoring the effectiveness of such initiatives.

REB of Record or Board of Record: the REB that has been granted ultimate authority for the ethics review and oversight of a research study.

3. What Unanticipated Events must be reported to the REB?

3.1 In general, the investigator should report to the REB only those serious adverse events that are considered as an unanticipated problem (unexpected, related or possibly related and involving greater risk of harm). Only serious adverse events that occur while the research participant is actively participating in the research study, i.e. receiving an investigational product or study procedure, should be reported to the REB. Serious adverse events/unanticipated problems should be reported to the REB for the duration of the study (i.e. until the study is closed at the REB).

The following adverse events ordinarily should NOT be reported to the REB:

- Serious adverse events that are considered expected
- Serious adverse events that are considered not related to the investigational product or research procedures, whether the event is expected or not
- Non-serious adverse events, whether expected or not

3.2 Network (Local) Serious Adverse Events / Unanticipated Problems

3.2.1 Upon becoming aware of a local adverse event, the investigator (MD) (or delegated qualified [MD] Co-Investigator) should assess the seriousness, the expectedness and the relatedness of the adverse event. A Network (local) serious adverse event (SAE) is required to be reported to the REB if the SAE is unexpected **AND** there is a reasonable possibility that the SAE is related to the research. A reasonable possibility means that a causal relationship cannot be ruled out.

3.2.2 Network (Local) SAE Report Timing and Process

Network (local) serious adverse events (SAEs) that are unexpected **AND** there is a reasonable possibility that the SAE is related to the research shall be reported to the REB **within seven (7) calendar days** of the study team becoming aware of the event. All fatal or life-threatening local SAEs that are unexpected **AND** there is a reasonable possibility that the SAE is related to the research must be reported **within 3 days**. Follow-up reports of the SAE should be submitted to the REB whenever new relevant information regarding the SAE becomes available until the resolution of the SAE.

The local serious adverse event should be reported using the Network REB Local Serious Adverse Event / Unanticipated Problem Reporting Form. The form should include:

- The status of the study and number of participants enrolled to date at the Network site, total number of participants enrolled to date and total target number;
- The name and date of the local serious adverse event/unanticipated problem;
- The unique coded identifier of the research participant (Note: Do not include any personal health information in the report);
- A detailed description of the local serious adverse event (SAE) including an assessment as to whether the event reaction was mild, moderate or severe. Provide all relevant information at the time of the report;
- An opinion expressed by the local investigator that the event is both serious and unexpected and a justification of that opinion;
- An opinion expressed by the local investigator that there is a reasonable possibility that the event is related to the investigational product(s) or procedures involved in the research and an explanation of that opinion;
- A description of the study team's response to the SAE;
- A description of the research participant outcome of the SAE and the impact on their clinical care when the information becomes available;
- An opinion expressed by the local investigator respecting the impact of the SAE on the continuation of the study and any further actions that may be required such as changes to the study protocol and/or informed consent form including the notification of present and/or past research participants;
- If changes to the study are required, the relevant documents should be submitted to the REB using the Network REB Amendment and Administrative Change Request Form.

Two (2) copies of the form (1 copy for the REB and 1 copy for the investigator) should be submitted to the REB. Each local SAE / unanticipated problem report submitted to the REB will be acknowledged, reviewed and signed by the REB Chair, or designee. If the REB determines that further actions in follow-up of the local SAE / unanticipated problem are required, the investigator will be notified.

Note: Local Serious Adverse Events that do not meet the criteria for an unanticipated problem or are incomplete will not be processed and will be returned to the submitter.

3.3 External (Non-Local) Serious Adverse Events / Unanticipated Problems

3.3.1 An external (non-local) serious adverse event (SAE) is an SAE experienced by a research participant enrolled in a multi-centre trial at a participating site which is external to Unity Health Toronto (Network). The investigator shall report individual isolated external (non-local) SAEs to the REB **only** if a determination has been made that the external SAE meets **all** the criteria of an unanticipated problem (i.e., unexpected **AND** related or possibly related to the research study **AND** involving greater risk of harm) **AND** requires a change to the protocol and/or consent form and/or requires immediate notification to research participants for safety reasons.

Note: If the investigator is the Study Sponsor **and/or** the study does not have an Independent Data Safety Monitoring Board (DSMB), the investigator may be required to report **all** external SAEs/unanticipated problems to the REB.

3.3.2 External SAE Report Timing and Process

In the limited circumstances (i.e., multi-centre trial) where an individual external (non-local) SAE constitutes an unanticipated problem (i.e., unexpected **AND** related or possibly related to the research study **AND** involving greater risk of harm) **AND** requires a change to the protocol and/or consent form and/or requires immediate notification to research participants for safety reasons, the report shall be submitted to the Network REB within **seven (7) calendar days** after the study team has received the report.

The individual external serious adverse event should be reported using the Network REB External Serious Adverse Event / Unanticipated Problem Reporting Form. The report should include **all** of the following information:

- Justification of the assessment that the event described is serious **AND** unexpected **AND** related or possibly related to the research;
- Identification of all previous safety reports concerning similar adverse events (if any) and an analysis of the significance of the current SAE in relation to the previous reports;
- A description of the impact of the event on the study as a whole and the impact (if any) at the local site (where the SAE occurred) ; **AND**
- An outline of any proposed changes to the research protocol and/or informed consent form and/or other corrective actions to be taken by the Sponsor and/or site investigator in response to the unanticipated problem;
- If changes to the study are required, the relevant documents should be submitted to the REB using the Network REB Amendment and Administrative Change Request Form.

Two (2) copies of the form (1 copy for the REB and 1 copy for the investigator) should be submitted to the REB. Any sponsor-generated reports that include the items listed above can also be submitted with the report to the REB. Each individual external SAE / unanticipated problem report submitted to the REB will be acknowledged, reviewed and signed by the REB Chair, or designee. If the REB determines that further actions in follow-up of the external SAE / unanticipated problem are required, the investigator will be notified.

Note: Individual External Serious Adverse Events that do not meet the criteria for an unanticipated problem and require a change to the protocol and/or consent form and/or require immediate notification to research participants OR are incomplete will not be processed and will be returned to the submitter.

Note: Regarding any external SAEs / Serious Unexpected Adverse Drug Reactions (SU-ADRs) that are issued *after* the initial ethics submission until *prior to* REB approval, these should be reported to the REB **only** if they meet the criteria of an unanticipated problem **and** require a change to the protocol and/or consent form and/or require immediate notification to research participants for safety reasons. These external SAEs /SU-ADRs should be submitted in summary format using the Network REB Updated Safety Information Reporting Form.

3.4 Other Unanticipated Events

3.4.1 There may be other incidents, experiences, or outcomes not considered adverse events but that meet the definition of unanticipated problems (unexpected **AND** possibly related **AND** involving greater risk of harm); such events, in the opinion of the investigator or Sponsor, place research participants or others at a greater risk of physical or psychological harm than was previously anticipated, or have implications for the conduct of the study or the integrity of research data.

Upon becoming aware of any other incident, experience, or outcome that may represent an unanticipated problem, the investigator should assess whether it does constitute an unanticipated problem. If the investigator determines that it is an unanticipated problem, the investigator must report the problem to the REB. 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 of a change in the risk/benefit ratio should be reported to the REB. For example:

- For an "expected," serious adverse reaction, an increase in the rate of occurrence which is judged to be clinically important,
- A significant hazard to the research participant population, such as lack of efficacy with an investigational product used in treating life-threatening disease,
- A major safety finding from a newly completed animal study that suggests a significant risk for human participants (such as carcinogenicity),
- Acts of nature that impact the study conduct or data integrity (e.g., floods, hurricanes, earthquakes, pandemics, etc.)

3.4.2 Other Unanticipated Problems Report Timing and Process

Other unanticipated problems shall be submitted to the REB within **fifteen (15) calendar days** after the study team became aware of the unanticipated problem or after the study team has received the report. These other unanticipated problems should be reported to the REB using the Network REB Reporting Form for local or external serious adverse events / unanticipated problems or updated safety information, as appropriate.

4. Corrective Actions / Substantive Changes

An event, experience, or outcome that meets the three criteria listed in the definition of *unanticipated problem* generally may warrant consideration of changes in the research protocol or informed consent documents or other corrective actions in order to protect the safety, welfare, or rights of research participants or others.

Corrective actions or substantive changes may include:

- Changes to the research protocol initiated by the investigator prior to obtaining REB approval to eliminate apparent immediate hazards to research participants;
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring research participants;
- Suspension of enrollment of new research participants;

- Suspension of research procedures on currently enrolled research participants;
- Modification of informed consent documents to include a description of newly recognized risks; and
- Provision of additional information about newly recognized risks to previously enrolled research participants.

5. Updated Safety Information Reporting Requirements

The investigator is also required to report to the Network REB any new safety information and/or new information that may affect the rights, safety, or well-being of research participants for the duration of the study i.e., until the study is closed at the REB.

Examples of safety information to be submitted to the REB include, but are not limited to the following:

- Data Safety Monitoring Board (DSMB) Meeting Summary
- Periodic Safety Update Report- including a summary list of all suspected unexpected serious adverse events that have occurred in that reporting period and a summary highlighting the main points of concern and evolving safety profile of the investigational product
- Revised Investigator's Brochure with a summary and rationale for the changes highlighted
- Product Safety Information, i.e. Updated Product Monograph with a summary and rationale for the changes highlighted
- Safety Alert
- Audit or Monitoring Report
- Interim Study Results during an active trial
- Notification of Sponsor suspension or termination of the study for safety reasons
- Changes in Health Canada or FDA labeling or withdrawal from marketing of a drug, biologic, natural health product or device used in a research protocol
- Publication in the literature or other findings

New safety information should be submitted to the REB using the Network REB Updated Safety Information Reporting Form within **fifteen (15) calendar days** after the study team has received the information. The investigator should also provide to the REB an analysis of the impact of the new safety information on the entire study and any proposed changes to the research protocol and/or informed consent form, as appropriate. If changes to the study are required, the relevant documents should be submitted to the REB using the Network REB Amendment and Administrative Change Request Form.

Two (2) copies of the form (1 copy for the REB and 1 copy for the investigator) should be submitted to the REB. All new safety information submitted to the REB will be acknowledged, reviewed and signed by the REB Chair, or designee. If the REB determines that further actions in follow-up of the new safety information are required, the investigator will be notified.

6. Reporting Unanticipated Problems Beyond the REB

The investigator is also obligated to report (local) serious adverse events that are unexpected **AND** related or possibly related to the research, as per the study protocol, to the study Sponsor, appropriate institutional officials and to local regulatory authorities, as applicable.

6.1 When the Investigator is the Study Sponsor: Investigator/Sponsor Obligation to Report Serious Unexpected Adverse Drug Reactions (SU-ADRs) to Health Canada

If the investigator is also the sponsor of an investigator- initiated clinical trial approved by Health Canada, the investigator as the study sponsor is required to inform Health Canada, in an expedited manner, of any serious unexpected adverse drug reaction, in respect of the study drug that has occurred inside or outside Canada [C.05.014]:

a) Where it is neither fatal nor life-threatening, within **fifteen (15) days** after becoming aware of the information;
b) Where it is fatal or life-threatening, within **seven (7) days** after becoming aware of the information. Within **eight (8) days** after having initially informed Health Canada of the fatal or life-threatening ADR, submit as complete a report as possible. Follow-up reports of fatal or life-threatening reactions **must** include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

Each ADR which is subject to expedited reporting to Health Canada should be reported individually in accordance with the data element(s) specified in the Health Canada/ICH Guidance Document E2A: *"Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*".

Expedited reports are required for events that meet **all** of these three criteria: serious, unexpected and a suspected causal relationship.

1) Serious:
   Any untoward medical occurrence that at any dose:
   - results in death,
   - is life-threatening,
   - requires inpatient hospitalisation or prolongation of existing hospitalisation,
   - results in persistent or significant disability/incapacity, or
   - is a congenital anomaly/birth defect.

2) Expectedness:
   An "unexpected" adverse reaction is one in which the nature or severity is not consistent with information in the relevant source document(s), such as the IB or Product Monograph. Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.
   Reports which add significant information on specificity or severity of a known, already documented serious ADRs constitute unexpected events. For example, an event more specific or more severe than described in the IB would be considered "unexpected" and should be reported (i.e., hepatitis with a first report of fulminant hepatitis).

3) Causality:
   Causality assessment is required for clinical investigation cases:
   - All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs and should be reported.
   - Concomitantly, adverse reactions that are considered to be unrelated to the study drug by both the investigator and the sponsor should not be reported.

Further clarifications on ADR reporting requirements can be found on Health Canada's website: *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting - Reminder for Sponsors*, https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/clinical-safety-data-management-definitions-standards-expedited-reporting-reminder-sponsors.html

When submitting an ADR report to Health Canada, a complete ADR Expedited Reporting Summary Form (Form 01-03) and the CIOMS Form should be attached and as applicable be mailed or faxed to:

Biologics and Genetic Therapies Directorate
Biologics and Radiopharmaceuticals **Fax: 613-957-0364**

Therapeutic Products Directorate
Pharmaceuticals **Fax: 613-941-2121**

Health Canada may request a sponsor, at any time during an ongoing clinical trial, to submit information or records kept under C.05.012 in order to assess the safety of the drug. The safety report could include a line listing of all serious events and/or other expected and unexpected ADRs.

When a fatal or other serious outcome is the **primary efficacy endpoint** in a clinical trial, the protocol should clearly indicate the serious event(s) that will be treated as disease-related and not subject to expedited reporting.

There are situations in addition to the above that may necessitate rapid communication to Health Canada, and appropriate scientific and medical judgment should be applied to each situation. For example, information that might influence the risk-benefit assessment of a drug, or that would be sufficient to consider changes in drug administration, or in the overall conduct of a clinical trial, represent such situations; including:

a) For an "expected" serious ADR, an increase in the rate of occurrence which is judged clinically important;
b) A significant hazard to the patient population, such as lack of efficacy with a drug used in treating a life-threatening disease; and
c) A major safety finding from a newly completed animal study.

Summary of Reporting Timelines

Type of Event	**Reporting Timeline* to the REB** ***within study team awareness of event / report**
Network (Local) SAE / Unanticipated problem	7 days
Network (Local) SAE / Unanticipated problem that is fatal or life-threatening	3 days
External SAE / Unanticipated problem / requires change(s) and/or notification to participants	7 days
Other Unanticipated Problem	15 days
Updated Safety Information e.g. Periodic Safety Update Report, revised Investigator's Brochure	15 days
If Investigator is Study Sponsor, Health Canada approved drug trial	**Reporting Timeline* to Health Canada** ***within study team awareness of event / report**
Serious Unexpected–Adverse Drug Reaction (SU-ADR)	15 days
SU-ADR that is fatal or life threatening	7 days with follow-up within 8 days

Note: The REB guidelines for reporting serious adverse events / unanticipated problems apply when the Network REB is the Board of Record for the research study. If the Network REB is **not** the Board of Record for the research study, the researcher will defer to the serious adverse event /unanticipated problem reporting requirements as stated in the Board of Record Agreement for the research study.

REFERENCES

Canadian Association of Research Ethics Boards (CAREB): Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada, July 2010.

Health Canada, Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications, Effective Date: May 29, 2013.

Health Canada, Guidance for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Topic E2A, 1995.

University of British Columbia (UBC) Clinical Research Ethics Boards: Guidance Notes for Reporting Unanticipated Problems to the REB, November 14, 2011.

Sunnybrook Health Sciences Centre Research Ethics Board (REB): Guidelines for Reporting an Internal Serious Adverse Event (SAE), February 06, 2012.

University of Manitoba Bannatyne Campus Research Ethics Boards: Adverse Event Reporting and Safety Information, January 2014.