Guidelines for Reporting Serious Adverse/Unanticipated Problems to
The Joint Group Health Centre/Sault Area Hospital Research Ethics Board

1. Introduction

The Joint Group Health Centre (GHC)/Sault Area Hospital (SAH) Research Ethics Board (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 (UPs), including serious adverse events (SAEs), to the REB. These reporting guidelines apply to clinical intervention trials, as well as non-intervention trials. In addition to these guidelines, the research should also adhere to the approved study protocol, sponsor requirements, REB study-specific requirements, and regulatory requirements regarding the reporting of SAEs/UPs.

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 (IP) or any research procedure(s). An AE, therefore, can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

Local (Internal) Adverse Event: an AE 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 AEs would be considered *local AEs*.

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 AE is an AE 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 IP [which includes natural health products and biologics] related to any dose should be considered ADRs. The phrase "responses to an IP" means that a causal relationship between the IP and an AE 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 judgement, is an important medical event that may jeopardize the health of the research participant or may require medical intervention to prevent 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 [IB] for an unapproved IP or the Product Monograph [PM] for a marketed drug).

Unanticipated Problem (UP): any incident, experience, or outcome (including a 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, IB, PM); and/or the characteristics of the research participant population being studied; **and**
- **Related or possibly related** to participation in the research ("possibly related" means that there is a reasonable possibility that the event, experience, or outcome may have been caused by the IP[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 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 principal investigator (PI) should report to the REB only those SAEs that are considered as an UP (unexpected, related, or possibly related, and involving greater risk of harm). Only SAEs that occur while the research participant is actively participating in the research study (i.e. receiving an IP or study procedure) should be reported to the REB. SAEs/UPs should be reported to the REB for the duration of the study (i.e. until the study is closed at the REB).

The following AEs ordinarily should NOT be reported to the REB:

- SAEs that are considered expected
- SAEs that are considered not related to the IP or research procedures, whether the event is expected or not
- Non-SAEs, whether expected or not

3.2 Local (Internal) SAEs/UPs

3.2.1 Upon becoming aware of a local AE, the local (MD) PI (or delegated qualified [MD] Co-Investigator) should assess the seriousness, the expectedness, and the relatedness of the adverse event. A local 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 Local SAE Report Timing and Process

Local 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 GHC/SAH 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 three (3) calendar 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 SAE should be reported using the REB Notification Report Form. The following information should be included:

- The status of the study and number of participants enrolled to date at GHC and/or SAH, the total number of participants enrolled to date, and the total target number;
- The name and date of the local SAE/UP;
- 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 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 PI that the event is both serious and unexpected, and a justification 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 his/her clinical care when the information becomes available; *and*
- An opinion expressed by the local PI 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 REB Amendment Application Form. Each local SAE/UP report submitted to the REB will be reviewed by the REB; a copy will be maintained in the REB files and the original Sponsor SAE reporting form will be returned to the PI.

3.3 External (Non-Local) SAEs/UPs

3.3.1 An external (non-local) SAE is a SAE experienced by a research participant enrolled at an external site in a multi-centre trial in which SAH and/or GHC is participating. The PI 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 UP (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 PI is the Study Sponsor **and/or** the study does not have Independent Data Safety Monitoring Board (DSMB), the PI may be required to report **all** external SAEs/UPs 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 UP (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 REB within **seven (7) calendar days** after the SAH/GHC study team has received the report.

These other UPs should be reported to the REB using the REB Notification Report Form. The following information 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 AEs (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 PI in response to the UP.

If changes to the study are required, the relevant documents should be submitted to the REB using the REB Amendment Application Form. Each external SAE/UP report submitted to the REB will be reviewed by the REB; a copy will be maintained in the REB files and the original Sponsor SAE reporting form will be returned to the PI.

Note: Individual External SAEs that do no meet the criteria for an UP 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: Any external SAEs/Serious U-ADRs that are issued *after* the initial ethics submission until *prior to* REB approval should be reported to the REB **only** if they meet the criteria of an UP **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/Serious U-ADRs should be reported to the REB using the REB Notification Report Form.

3.4 Other Unanticipated Events

3.4.1 There may be other incidents, experiences, or outcomes not considered AEs but that meet the definition of UPs (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 UP, the PI should assess whether it does constitute an UP. If the PI determines that it is an UP, the PI 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" SAE, 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 IP used in treating life-threatening disease
- A major safety finding from a newly-completed animal study that suggests a significant risk for human participants
- Acts of nature that impact the study conduct or data integrity (e.g. floods, hurricanes, pandemics, etc.)

3.4.2 Other UPs Report Timing and Process

Other UPs shall be submitted to the REB within **fifteen (15) calendar days** after the GHC/SAH study team becomes aware of the UP or after the study team has received the report. These other UPs should be reported to the REB using the REB Notification Report Form.

4. Corrective Actions/Substantive Changes

An event, experience, or outcome that meets the three criteria listed in the definition of *UP* 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 PI 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*
- Provisions of additional information about newly-recognized risks to previously-enrolled research participants.

5. Updated Safety Information Reporting Requirements

The PI is also required to report to the REB any new safety information and/or information that may affect the well-being, rights, or safety 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:

- DSMB Meeting Summary
- PSUR – including a summary list of all suspected unexpected SAEs that have occurred in that reporting period and a summary highlighting the main points of concern and evolving safety profile of the IP
- Revised IB with a summary and rationale for the changes highlighted
- Product Safety Information, i.e. updated PM 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 labelling 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 REB Notification Report Form within **fifteen (15) calendar days** after the GHC/SAH study team has received the information. The PI 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 REB Notification Report Form.

All new safety information submitted to the REB will be reviewed by the REB and a copy will be maintained in the REB files; the REB may require further action(s) in follow-up of the new safety information.

6. Reporting UPs Beyond the REB

The PI is also obligated to report local (internal) SAEs 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 GHC/SAH PI is the Study Sponsor: PI/Sponsor Obligation to Report Serious U-ADRs to Health Canada

If the GHC/SAH PI is also the sponsor of a PI-initiated clinical trial approved by Health Canada, the GHC/SAH PI as the study sponsor is required to inform Health Canada, in an expedited manner, of any serious U-ADRs, 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) calendar days** after becoming aware of the information;
b) Where it is fatal or life-threatening, within **seven (7) calendar days** after becoming aware of the information. Within **eight (8) calendar 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 ADRs **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/International Conference on Harmonisation 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 hospitalization or prolongation of existing hospitalization,
   - 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 PM. 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 ADR 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, ARs that are considered to be unrelated to the study drug by both the PI and the sponsor should not be reported

Further clarification of 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, (*http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e2a_pre_notice_avis-eng.php).

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.

There are situations in addition to the above that may necessitate rapid communication to Health Canada, and appropriate scientific and medical judgement 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 SAH/GHC study team awareness of the event***
Local SAE/UP	7 days
Local SAE/UP that is fatal or life-threatening	3 days
External SAE/UP/requires change(s) and/or notification to participants	7 days
Other UPs	15 days
Updated Safety Information (e.g. PSUR, revised IB, etc.)	15 days
If GHC/SAH PI is Study Sponsor of a Health Canada-Approved Drug Trial	**Reporting Timeline* to the REB** ***within SAH/GHC study team awareness of the event***
Serious U-ADRs	15 days
Serious U-ADRs that are fatal or life-threatening	7 days with follow-up within 8 days

References

Canadian Association of Research Ethics Boards: 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 Clinical Research Ethics Boards: Guidance Notes for Reporting Unanticipated Problems to the REB, November 14, 2011.

St. Michael's Hospital (SMH) Research Ethics Board, Guidelines for Reporting Serious Adverse Events/Unanticipated Problems to the SMH Research Ethics Board, July 9, 2014.

Sunnybrook Health Sciences Centre Research Ethics Board: Guidelines for Reporting an Internal Serious Adverse Event, February 6, 2012.

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