William Osler Health System

Title	Guidelines for Reporting Serious Adverse Events/ Unanticipated Problems
Original Issue Date:	22-November 2016
Revised:	16-January 2026
Approved By:	REB Chair

1.0 PURPOSE

The purpose of this guideline is to describe the reporting requirements of unanticipated problems, including serious adverse events, to the Osler Research Ethics Board. These reporting guidelines apply to clinical intervention trials as well as non-intervention trials. Teams are encouraged to also read the Osler Policy on Ethical Conduct for Research Involving Humans and the Osler Responsible Conduct of Research.

2.0 POLICY STATEMENT

In addition to scheduled (usually annual) renewal of the REB approval, the REB must receive and review unanticipated problems that may affect the safety, rights, and well-being of research participants.

3.0 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a research participant, administered investigational product, including an occurrence which does not have a causal relationship with this product. 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.

Serious Adverse Event (SAE): 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
- is a congenital anomaly/birth defect

An important medical event that may not be immediately life-threatening or result in death or hospitalization, that may jeopardize the participant or that may require intervention to prevent serious outcomes (see ICH E2A and E19) should generally be considered as serious.

Adverse Drug Reaction (ADR): In the pre-approval clinical experience with a new investigational product or its new usages (particularly as the therapeutic dose(s) may not be established): unfavourable and unintended responses, such as a sign (e.g., laboratory results), symptom or disease related to any dose of a medicinal product where a causal relationship between a medicinal product and an adverse event is a reasonable possibility. The level of certainty about the relatedness of the adverse drug reaction to an investigational product will vary. If the ADR is suspected to be medicinal product-related with a high level of certainty, it should be included in the reference safety information (RSI) and/or the Investigator's Brochure (IB).

For marketed medicinal products: a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.

(See ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

External (Non-Local) adverse event: From the perspective of the REB overseeing one or more centres engaged in a multicentre clinical trial, external adverse events are those adverse events experienced by research participants enrolled by investigator(s) at other centres/institutions outside the Osler REB's jurisdiction.

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

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.

Unanticipated Problem: any incident, experience, or outcome (including an adverse event) that meets all of the following criteria:

1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the Research Ethics Board (REB) approved research protocol and informed consent document, or the Investigator Brochure; and (b) the characteristics of the research participant population being studied; **and**
2) 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**

3) 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.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

Unexpected: an event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents such as the Research Ethics Board (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.

As soon as reasonably possible: The term "as soon as reasonably possible" means that the timing of reporting will vary in accordance with the severity/seriousness of the information being reported, including the nature of the research associated with the problem. Unless, however, the event is a routine safety letter, DSMB report, summary report or changes to the Investigator's Brochure that are minor and/or routine in nature, all new information and unanticipated problems must be reported within seven days of the incident, occurrence, outcome event, or the Investigator's receipt of the notice of the event or the new information.

4.0 PROCEDURES

4.1 Unanticipated Problem Reporting and Timelines

The Principal Investigator (PI) is responsible for submitting adverse events that meet the reporting criteria. In general, the PI should report to the Osler REB only those serious adverse events that are considered as an unanticipated problem *(unexpected, related or possibly related and involving greater risk of harm).*

Internal (local) serious adverse events/unanticipated problems:
Upon becoming aware of a local adverse event, the principal investigator should assess the seriousness, the expectedness and relatedness of the adverse event. An internal (local) serious adverse event (SAE) must be reported to the Osler REB if the SAE is *unexpected* AND there is a reasonable possibility that the SAE is *related* to the research study AND involves *greater risk of harm*.

A reasonable possibility means that a causal relationship cannot be ruled out. If the investigator determines that a serious adverse event is not an unanticipated problem, but

the sponsor subsequently determines that it is, the sponsor must report this determination to the PI, and such reports must then be submitted to the REB.

The internal (local) serious adverse event should be reported to the Osler REB using the eREB Reportable Events Form. The REB will not accept serious adverse events reports submitted through the eREB Reportable Events Form unless the PI has provided an e-signature in the eREB system. Any supporting documents (i.e., discharge reports) can also be uploaded in the eREB Reportable Events Form. Each individual internal (local) SAE/unanticipated problem report submitted will be acknowledged and reviewed by the Osler REB. The Osler REB may require further actions in follow-up of the internal (local) SAE/unanticipated problem.

The eREB Reportable Events Form directs the Principal Investigator to provide detail on:

- 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 form);
- A detailed description of the internal (local) SAE/unanticipated problem 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 internal (local) SAE/unanticipated problem;
- A description of the research participant outcome of the internal (local) SAE/unanticipated problem and the impact on their clinical care when the information becomes available;
- An opinion expressed by the local investigator respecting the impact of the internal (local) SAE/unanticipated problem 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 through the eREB system using the Osler Amendment form.

Internal (local) unanticipated problems must be reported to the REB within 7 calendar days of the PI becoming aware of them. Fatal or life-threatening local unanticipated problems must be reported to the REB with 3 calendar days. Follow-up reports of the internal (local) SAE/unanticipated problem should be submitted to the Osler REB whenever relevant information regarding the SAE becomes available until the resolution of the SAE.

The Principal Investigator must continue to report unanticipated problems to the Osler REB for the duration of the study (i.e., until the study is closed at the principal investigator's institution).

External (non-local) adverse events/unanticipated problems:

Single isolated external (non-local) serious adverse events (SAEs) rarely meet the requirements for reporting to REBs. Individual external (non-local) SAEs should only be reported to the REB when a determination has been made that the event meets ALL of the criteria for 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 and/or requires immediate notification to research participants for safety reasons.

The individual external (non-local) SAE/unanticipated problem should be reported to the Osler REB using the eREB Reportable Events Form. The REB will not accept external (non-local) SAE/unanticipated problem reports submitted through the eREB Reportable Events Form unless the PI has provided an e-signature in the eREB system. Any supporting documents (i.e., reports) can also be uploaded in the eREB Reportable Events Form. Each individual external (non-local) SAE/unanticipated problem report submitted will be acknowledged and reviewed by the Osler REB. The Osler REB may require further actions in follow-up of the external (non-local) SAE/unanticipated problem.

The eREB Reportable Events Form directs the PI to provide detail on:

- Justification of the assessment that the event described is serious AND unexpected AND related or possibly related to the research
- The report identifies all previous safety reports concerning similar adverse experiences
- The report analyzes the significance of the current adverse experience in light of the previous reports and
- The report outlines any proposed protocol changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the unanticipated problems.
- If changes to the study are required, the relevant documents should be submitted to the REB through the eREB system using the Osler Amendment form.

External serious adverse events assessed to be unanticipated problems must be reported to the REB within **3 calendar days** of the sponsor (i.e., Health Canada Clinical Trial Application holder) becoming aware of or receiving the event/the report. Reports not meeting these requirements will be returned in the eREB to the submitter with a description of the REB reporting requirements.

Other Unanticipated Problems Not Considered Adverse Events

There may be other incidents, experiences, or outcomes not considered adverse events but that meet the definition of unanticipated problems; such events, in the opinion of the PI or sponsor, place research participants or others at a greater risk of physical or psychological harm. This may include:

- A significant hazard to the research participant population, such as lack of efficacy with an investigational product used in treating life-threatening disease.
- Breaches of privacy and confidentiality (ex. Records accessed for patients who have not consented to the study, or researcher abstract data not approved for collection from patients enrolled in a study, Physician referral form containing PHI and study information accidentally faxed to an incorrect number)
- Acts of nature that impact the study conduct or data integrity (e.g. – floods, hurricanes, earthquakes, pandemics, etc.).

Other unanticipated problems shall be submitted to the Osler REB within **15 calendar days** after the PI becomes aware of the unanticipated problem or after PI has received the report. These other unanticipated problem(s) should be reported to the Osler REB using the eREB Reportable Events Form. These unanticipated problems submitted will be acknowledged and reviewed by Osler REB. The Osler REB may require further actions in follow-up of the new safety information.

Please also refer to the Osler REB Guidelines for Reporting Protocol Deviations for additional information and for the privacy breach in research reporting information.

4.2 Updated Safety Information Reporting Requirements

Any new safety information and/or new information which may affect the rights, safety, or well-being of research participants should be reported to the Osler REB. Examples of safety information 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
- 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 Osler REB using the Reportable Events form or the Osler Amendment form. Periodic safety update reports and other local unanticipated problems must be reported to the REB within **15 calendar days** of the sponsor (i.e., Health Canada Clinical Trial Application holder) becoming aware of or receiving the event/the report or within **3 days** if the new safety information and/or new information may affect the rights, safety, or well-being of research participants.

All new safety information submitted will be reviewed and acknowledged by the Osler REB. The Osler REB may require further actions in follow-up of the new safety information.

4.3 REB Review of Unanticipated Problems Reporting

Unanticipated problems will be reviewed by the REB Chair or a delegated REB member. The Chair or other assigned REB member may choose to act on the information immediately (e.g., suspend enrolment).

When reviewing a report of an unanticipated problems, the REB will assess the appropriateness of any proposed corrective or preventative measures by the sponsor and/or PI, consider any additional appropriate measures that may or may not have been identified or proposed by the sponsor and/or PI, and consider whether the affected research still satisfies the requirements for REB approval.

In particular, the REB will consider 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.

Corrective actions or substantive changes required by the REB may include:

- 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.

Local unanticipated problems occurring in research covered by a US Office for Human Research Protections (OHRP) approved assurance also must be reported by the institution

to the supporting US Department of Human Health Services agency head (or designee) and OHRP.

4.4 Reporting Unanticipated Problems beyond the REB

The PI is also obligated to report internal (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.

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

If the Osler PI is *also* the sponsor of a PI-initiated clinical trial approved by Health Canada, the Osler PI as the study sponsor is required to inform Health Canada, in an expedited manner, of any serious unexpected adverse drug reaction (SU-ADR), 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 hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- or is a congenital anomaly/birth defect.

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

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.*

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 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.

5.0 Table for Reporting Timelines

Type of Event	Reporting Timelines to the Osler REB *within Osler PI awareness of event/report
Local SAE/Unanticipated Problem that is fatal or life threatening	3 Days
Local SAE/Unanticipated Problem	7 Days
External SAE/ Unanticipated Problem that requires change(s) and/or notification to participants	3 Days
Updated Safety Information that may affect the rights, safety or well-being of participants, e.g. Periodic Safety Update Report, Revised Investigator's Brochure	3 Days
Other Unanticipated Problems	15 Days
Updated Safety Information e.g. Periodic Safety Update Report, Revised Investigator's Brochure	15 Days
If Osler PI is Study Sponsor, Health Canada approved drug trial	**Reporting Timelines to Health Canada *within Osler PI 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

6.0 REFERENCES

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

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 2022. https://ethics.gc.ca/eng/documents/tcps2-2022-en.pdf

Government of Canada, Food and Drug Regulations: Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects, August 2022. https://lawslois.justice.gc.ca/PDF/C.R.C.,_c._870.pdf

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A.* October 1994. https://www.ich.org/page/efficacy-guidelines

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). *ICH Harmonised Guideline: Good Clinical Practice E6(R3).* Final version, adopted on 06 January 2025. https://www.ich.org/page/efficacy-guidelines

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).*E19 Guideline on Optimisation of Safety Data Collection.* November 2022. https://www.ich.org/page/efficacy-guidelines

Office for Human Research Protections (OHRP). Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. January 15, 2007. http://www.hhs.gov/ohrp/policy/advevntguid.html#Q5

U.S. Department of Health and Human Services. Protection of Human Subjects, 45 CFR Part 46. eCFR :: 45 CFR Part 46 -- Protection of Human Subjects

7.0 REVISION HISTORY

Effective Date	Summary of Changes
18-Oct-2019	Original version
16-Jan-2026	Revised to include eREB updates and updated ICH GCP E6 (R3)