



Canadian Association of Research Ethics Boards Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada

The Canadian Association of Research Ethics Boards (CAREB) is a grassroots national membership organization intended to represent the interests of all Canadian Research Ethics Boards (REBs) and to reflect REB perspectives and concerns. CAREB has no legal authority over clinical trial regulations or over REBs in Canada. The guidance should only be viewed as a recommendation.

1. INTRODUCTION

This Guidance is intended to assist the research ethics community in Canada in standardizing reporting of unanticipated problems, including certain adverse events, to Research Ethics Boards (REBs) in Canada. Although the sponsor is responsible for the ongoing safety evaluation of the investigational product, and for the prompt reporting of findings that could adversely affect the health of research participants or impact on the conduct of the trial, this Guidance provides recommendations for sponsors and investigators to help them identify those events that must be reported to the REB, and the mechanisms for reporting them.

2. BACKGROUND

Unnecessary reporting to the REB of events or problems that do not potentially affect the rights, welfare or safety of research participants in the study may impair the REB's ability to review and respond in a timely manner to actual situations where research participant rights, welfare or safety are threatened. Single isolated adverse events rarely meet the requirements for reporting to REBs.¹

The Canadian Association of Research Ethics Boards (CAREB) developed this Guidance² in response to concerns raised by the REB community in Canada regarding the over-reporting of adverse events, in particular, the increasingly large volumes of individual external (non-local) adverse event reports. It is these external adverse event reports that represent the majority of adverse event reports submitted by investigators to REBs. As noted by the US Office for Human Research Protections (OHRP), reports of individual external adverse events often lack sufficient information to allow investigators or REBs to make meaningful judgments about whether the adverse events are unexpected, are related to participation in the research, or suggest that the research places research participants or others at a greater risk of physical or psychological

¹ US Department of Health and Human Services. *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting*, January, 2009.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079753.pdf

² Canadian Association of Research Ethics Boards. *History of the Development of the Guidance on Reporting of Unanticipated Problems Including Adverse Events to Research Ethics Boards in Canada* July 2010.

harm.³ In response to this issue, the European Commission (EC), the US Food and Drug Administration (FDA), OHRP and CAREB have developed Guidance documents on reporting unanticipated problems including adverse events.⁴ There is no Health Canada regulation for reporting external adverse events to the REB. ICH requirements will be met if unanticipated problems are reported to the REB as described in this guidance.⁵

3. DEFINITIONS

Unless otherwise specified, the International Conference on Harmonization E-6 Guidelines for Good Clinical Practice (ICH GCP) definitions are used. However, the term “investigational product” is used in place of “medicinal product” and refers to new or new usages of drugs, biologics, medical devices or natural health products; and “research participant” is used in place of “clinical investigation subject”.

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 [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 a investigational product, whether or not related to the investigational product.

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

Local (Internal) 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 REB of Record. In the context of a single-centre clinical trial, all adverse events would be considered *local adverse events*.⁶

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).

³ Office for Human Research Protections (OHRP) and Department of Health and Human Services (HHS) - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*. www.hhs.gov/ohrp/policy/AdvEvtGuid.htm

⁴ The FDA regulations require reporting to **investigators** of IND Safety Reports of serious unexpected events associated with the use of an investigational product. This reporting is relevant to investigators who may encounter subjects with similar experiences in the clinical trial. Not all of these events meet the criteria for reporting to the REB as described in this guidance.

⁵ ICH E2A, II.A.1 indicates that expedited reporting is required for serious unexpected ADRs from clinical trials as well as spontaneous or other sources. ICH E6, 5.17 notes that the sponsor should expedite the reporting of these reports to IRBs [in accordance with ICH E2A] **where required**. There is no Health Canada requirement for this; therefore these reports do not need to be sent to the REB unless they meet the definition of unanticipated problem as described in this guidance.

⁶ Office for Human Research Protections (OHRP) and Department of Health and Human Services (HHS) - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*. www.hhs.gov/ohrp/policy/AdvEvtGuid.htm

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 one of the outcomes listed above.

Medical Device Serious Adverse Event: An adverse event associated with a medical device complaint meets the criteria of a medical device SAE when the event involves a medical device **and** results in death or serious deterioration in state of health. “Serious deterioration in the state of health” means: a life-threatening disease, disorder or abnormal physical state; the permanent impairment of a body function or permanent damage to a body structure; or a condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage.⁷

Unexpected Adverse Drug Reaction: 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). *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 Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.*

Unanticipated Problem: any incident, experience, or outcome 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 IRB-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.

Periodic Safety Update Report: a summary report, created by the sponsor, listing all of the suspected unexpected serious adverse events that have occurred in that reporting period and that also includes a concise summary highlighting the main points of concern and the evolving safety profile of the investigational product.⁸

⁷ Minister of Justice Medical Devices Regulation SOR/98-282 Current to January 12, 2010
<http://laws.justice.gc.ca/en/>

⁸ Adapted from the ICH E2F draft consensus guideline “Development Safety Update Report” 5 June 2008.

REB of Record or Board of Record: the REB that has been granted ultimate authority by an institution for the ethics review and oversight of research conducted at that institution. Throughout this document “REB” refers to “REB of Record”⁹.

4. WHAT EVENTS MUST BE REPORTED TO THE REB?

4.1. Criteria for Reporting

4.1.1. Local (internal) adverse events

The principal investigator is required to report to the REB only those local adverse events that are deemed to be *unanticipated problems* (unexpected, related and involving greater risk – see definition). Upon becoming aware of a local adverse event, the investigator should assess whether the adverse event represents an unanticipated problem. If the investigator determines that the adverse event represents an unanticipated problem, the investigator must report it to the REB. If the investigator determines that an adverse event is not an unanticipated problem, but the sponsor subsequently determines that it is, the sponsor should report this determination to the principal investigator, and such reports must then be submitted to the REB. The principal investigator must clearly explain how the event represents an “unanticipated problem”. A description of any proposed protocol changes or other corrective actions to be taken by the principal investigator or sponsor in response to the event must also be described in the report.

The following local 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 not¹⁰

4.1.2. External (Non-Local) Adverse Events

The FDA and OHRP note that it is neither useful nor necessary for reports of individual adverse events occurring in research participants enrolled in multi-centre studies to be distributed routinely to investigators at all centres conducting the research or to the REB overseeing those centres. There is no Health Canada regulation for reporting external adverse events to the REB. ICH requirements will be met if unanticipated problems are reported to the REB as described in this guidance.¹¹ In general, the 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 assess whether an event is an “unanticipated problem”. Accordingly, investigators may rely on the sponsor's assessment and provide to the REB a

⁹ A term that is being widely adopted in the Canadian research ethics environment. It can refer to a local REB or to an external REB (including a central REB) providing ethics review and oversight for multiple institutions.

¹⁰ ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). 27 October 1994

¹¹ ICH E2A, II.A.1 indicates that expedited reporting is required for serious unexpected ADRs from clinical trials as well as spontaneous or other sources. ICH E6, 5.17 notes that the sponsor should expedite the reporting of these reports to IRBs [in accordance with ICH E2A] **where required**. There is no Health Canada requirement for this; therefore these reports do not need to be sent to the REB unless they meet the definition of unanticipated problem as described in this guidance.

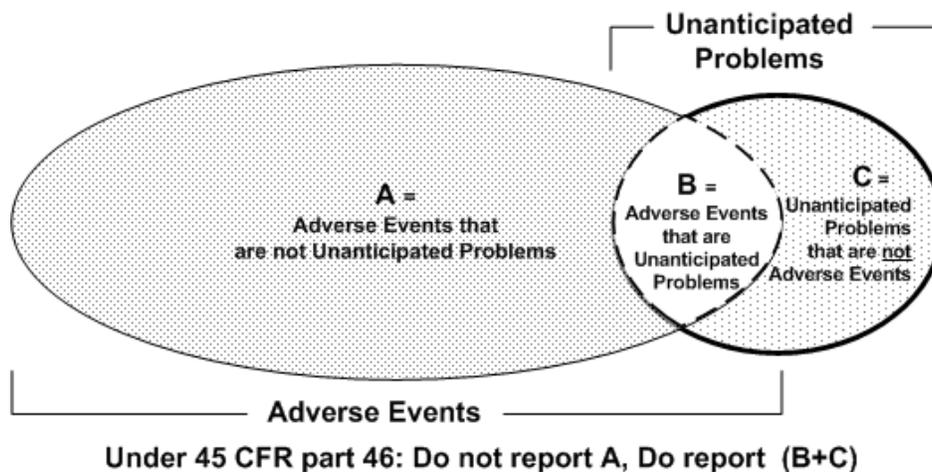
periodic safety update report prepared by the sponsor. The format used for annual safety reports is acceptable¹². In general, the sponsor should amend the Investigator's Brochure as needed so as to keep the description of safety information updated.¹³

Single isolated external adverse events rarely meet the requirements for reporting to REBs.⁹ 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. Individual isolated external adverse events should only be reported to the REB if they are unanticipated problems and the report includes **all** of the following information:

- the event described is both serious and unexpected,
- 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 problem

Reports not meeting these requirements should be returned to the submitter with a description of the REB reporting requirements (e.g., a copy of the relevant REB policy).

In summary, only adverse events that are *unanticipated problems* should be reported to the REB, as illustrated in the OHRP diagram below¹⁴, and with the required accompanying documentation:



4.1.3. Other unanticipated problems

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 investigator or sponsor, place research participants or others at a greater risk of physical or psychological harm

¹² European Commission. *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use*. April 2006, or the ICH E2F draft consensus guideline "Development Safety Update Report" 5 June 2008

¹³ US Department of Health and Human Services. *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting*, January, 2009

¹⁴ Office for Human Research Protections (OHRP) and Department of Health and Human Services (HHS) - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*.

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. This may include:

- 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 a 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),
- Breaches of privacy and confidentiality,
- Acts of nature that impact the study conduct or data integrity (e.g. – floods, hurricanes, earthquakes, pandemics, etc.)

5. WHEN TO REPORT UNANTICIPATED PROBLEMS TO THE REB

Reportable local adverse events (i.e., those that represent unanticipated problems) should be reported to the REB within 15 calendar days of the principal investigator becoming aware of them. Fatal or life-threatening reportable local adverse events should be reported to the REB with 7 calendar days.

Periodic safety update reports, individual reportable external adverse events (i.e., those that represent unanticipated problems), and other unanticipated problems should 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.

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

If arrangements have been made for the sponsor to report the unanticipated problem directly to the REB, the principal investigator should not provide the REB with a duplicate copy of the report(s) received from the sponsor.

6. REPORTING UNANTICIPATED PROBLEMS BEYOND THE REB

REBs must have written procedures for ensuring the prompt reporting (by the PI and/or sponsor) to the REB, appropriate institutional officials and the FDA of any unanticipated problems involving risks to research participants or others.¹⁵

¹⁵ USA Food and Drug Administration Code of Federal Regulations Title 21 Part 56.108 (b)

Institutions must have written procedures for reporting unanticipated problems to appropriate institutional officials. Unanticipated problems occurring in research covered by an 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. For multi-centre research projects, only the institution where the unanticipated problem occurred must report the event to the supporting agency head (or designee) and OHRP. Alternatively, the sponsor may be designated to submit reports of unanticipated problems to the supporting agency head and OHRP.

7. CORRECTIVE ACTIONS / SUBSTANTIVE CHANGES

An incident, experience, or outcome that meets the three criteria listed in the definition of *unanticipated problem* generally will warrant consideration of substantive 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 might include:

- Changes to the research protocol initiated by the principal 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.¹⁶

8. REB REVIEW OF UNANTICIPATED EVENTS

The Chair or other assigned REB member may choose to act on the information immediately (e.g., suspend enrolment); however, unanticipated problems (unexpected, related and involving greater risk – see definition) should be reported to the full REB at the next available meeting(s).

When reviewing a report of an unanticipated problem, the REB should 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 should 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.¹³ The REB should consider whether some or all of the research participants should be notified of the unanticipated problem (i.e., if it may affect the participant's willingness to continue participation in the research). The REB should also consider whether suspension or termination of the research or the research site is warranted.

¹⁶ Office for Human Research Protections (OHRP) and Department of Health and Human Services (HHS) - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*.