



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

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 harm.³ In response to this issue, the European Commission (EC), the US Food and Drug

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 External (Non-Local) Serious Adverse Events to Research Ethics Boards*. February 2010.

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

Administration (FDA), OHRP and CAREB have developed Guidance documents on reporting unanticipated problems including adverse events.

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 treatment. 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*.⁴

Adverse Drug Reaction (ADR): all noxious and unintended responses to an investigational product 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 at any dose:

- 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
- based upon appropriate medical judgement, is an important medical event that may jeopardize the study 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

⁴ 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

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.⁵

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 drugs, devices 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 reactions (SUSARs) 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.⁶

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"⁷.

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

⁵ Minister of Justice Medical Devices Regulation SOR/98-282 Current to January 12, 2010
<http://laws.justice.gc.ca/en/>

⁶ Adapted from the ICH E2F draft consensus guideline "Development Safety Update Report" 5 June 2008.

⁷ 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.

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 be submitted to the REB. The principal investigator must clearly explain why the event represents a “problem” for the study and why it is “unexpected”. 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, whether the event is expected or not.
- Non-serious adverse events, whether expected or not⁸

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. 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 both “unanticipated” and a “problem” for the study. Accordingly, investigators may rely on the sponsor’s assessment and provide to the REB a periodic safety update report prepared by the sponsor. The format used for annual safety reports is acceptable⁹. In general, the sponsor should amend the Investigator’s Brochure as needed so as to keep the description of safety information updated.¹⁰

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**

⁸ ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). 27 October 1994

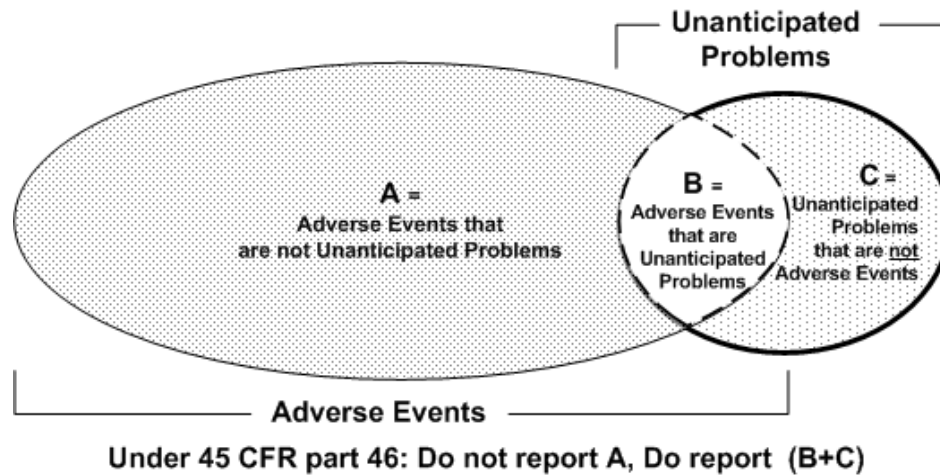
⁹ European Commission. *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use*. April 2006, or the ICH E2F draft consensus guideline “*Development Safety Update Report*” 5 June 2008

¹⁰ US Department of Health and Human Services. *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting*, January, 2009

- 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.

In summary, only adverse events that are *unanticipated problems* should be reported to the REB, as illustrated in the OHRP diagram below¹¹, 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 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 represent an unanticipated problem. If the investigator determines that it is an unanticipated problem, the investigator must report such unanticipated 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 ADR, 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),

¹¹ 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*.

- Recommendations of the Data and Safety Monitoring Committee, where relevant for the safety of the research participants,
- Breaches of privacy and confidentiality,
- Protocol deviations/violations that impact data integrity or the safety of research participants.

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 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

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. There are 11 US DHHS agencies including the National Institutes of Health (NIH). 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 document 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 in 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.¹²

8. REB REVIEW OF UNANTICIPATED EVENTS

If the Chair or other assigned REB member determines that the adverse event, incident, experience, or outcome represents an unanticipated problem, he/she may choose to act on the information immediately; however, unanticipated problems (unexpected, related and involving greater risk – see definition) should be reported to the full Board at the next available meeting.

When reviewing a report of an unanticipated problem, the REB should consider whether the affected research protocol 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.¹¹

¹² 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*.