Western Research

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| **Guidance Document** | Unanticipated Problem Reporting – Adverse Event (Serious, External, & Internal) |
| **Effective Review** | HSREB/NMREB |
| **Version Date** | July 10, 2018 |

## General Information

This guidance document outlines the REB's reporting requirements for events that constitute Unanticipated Problems. Please note that Protocol Deviations/Violations are addressed in a separate Guidance Document: *REB Unanticipated Problem Reporting – Protocol Deviation/Violation*.

Western University's Research Ethics Board has streamlined the process for the reporting of unanticipated problems, by implementing the 'Canadian Association of Research Ethics Boards' (CAREB) "Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada" (CAREB AE Guidelines, July 2010)[i]. The guidance herein is based on the CAREB document, as well as the OHRP[ii] and FDA[iii] guidance documents that CAREB built on.

Regulators, Sponsors, Funders and Institutions may have different definitions and categorizations for the events covered by this guidance document, as well as documentation and reporting requirements. It is the responsibility of the Investigator to familiarize himself/herself with, and follow the requirements applicable to his/her study.

**Unanticipated Problem:** Any incident, experience, or outcome 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[s], Investigator Brochure, Product Monograph, Device Manual, etc.); and 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.[vi]

***If your event does not constitute an Unanticipated Problem, it need not be reported to the REB.***

## Unanticipated Events That Should Be Reported To The REB

The following are types of unanticipated events that may constitute Unanticipated Problems and require reporting to the REB. This section assists with determining which of these events are reportable to the REB, and which are not.

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**Internal (Local) Adverse Events**
The Investigator should report internal adverse events **only if** he/she has evaluated the event and determined that **it constitutes an Unanticipated Problem**.

In the case of a Sponsor-Investigator study (sometimes known as an "Investigator-Initiated study") the Investigator may have different obligations as Sponsor to report the event to other participating sites, and to regulatory authorities, irrespective of whether or not the event constitutes an Unanticipated Problem under this guidance document.

**External (Non-Local) Adverse Events**
"Individual isolated external adverse events should only be reported to the REB if they are unanticipated problems"[vii]. As such, the Investigator should report external adverse events **only if** the Sponsor has evaluated the event and determined that **it constitutes an Unanticipated Problem AND requires a change to the research and/or informed consent form and/or requires immediate notification to participants for safety reasons**.

In the case of Sponsor-Investigator studies, the Investigator should provide separate documentation (as Sponsor) confirming that – as Sponsor – he/she has evaluated the event and determined that it constitutes an Unanticipated Problem.
In either case, the documentation supplied by the sponsor should include all of the following:

- 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 changes to the protocol and/or informed consent documents and/or other corrective actions to be taken by the sponsor in response to the unanticipated problem"[viii].

**Periodic Safety Update Reports**
Periodic Safety Update Reports require reporting only if the event(s) meet all 3 of the criteria to constitute an Unanticipated Problem and are accompanied by the required information from the Sponsor as outlined in the REB guidance document. If all three are not applicable, do not report to the REB, but retain documentation of the event for your study file.

**Updated Investigational Product Documentation**
Updated Investigational Product Documentation (e.g. – Investigator Brochures, Product Monographs, Device Manuals, etc.) need only be reported to the REB if they represent a change to the risk/benefit ratio for research participants. Practically speaking, if the updated safety information requires a change to the informed consent document(s) and/or protocol, it should be submitted to the REB as an amendment (even if events described therein meet the criteria to constitute Unanticipated Problems).

**All other Periodic Safety Update Reports and Updated Investigational Product Documentation do NOT need to be submitted to the REB**. The REB reserves the right to request these documents if it deems necessary.

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**Protocol Deviations/Violations**
Please see the Protocol Deviation/Violation guidance document for instructions on what is important to report the REB.

**Other Unanticipated Events**
The Investigator should report other unanticipated events **only if** he/she has evaluated the event and determined that **it constitutes an Unanticipated Problem**.
Examples of other unanticipated events include but are not limited to:

- 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),
- Breaches of privacy and confidentiality (*despite following security and confidentiality measures outlined in the protocol and standard operating procedures*),
- Acts of nature that impact the study conduct or data integrity (e.g. – floods, hurricanes, earthquakes, pandemics, etc.)"[ix]

## Definitions

For the sake of brevity, with the exception of a few key terms, terms that are defined identically to the CAREB AE guidance document, OHRP guidance document, FDA guidance document or ICH GCP E6 are omitted in this section.

**Adverse Event (AE):** Any untoward medical occurrence experienced by 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 unfavorable 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 (CAREB AE Guidelines, July 2010).

**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.

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**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[v].

## 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;

Provision of additional information about newly recognized risks to previously enrolled research participants."[x]

## REB REVIEW OF UNANTICIPATED PROBLEM REPORTS

Upon receipt of an Unanticipated Problem Report, the REB will review the Report and may either accept the Report without modifications to the proposed corrective/preventative actions, or may propose modifications to the Investigator. In the latter scenario, once the REB and the Investigator come to an agreement, the REB will accept the Report.

## REFERENCES

i Canadian Association of Research Ethics Boards (CAREB). *Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*. July, 2010. http://careb-accer.ca/?q=node/240

ii 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*. January 15, 2007. http://www.hhs.gov/ohrp/policy/advevntguid.html

iii U.S. Department of Health and Human Services. *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting*. January, 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079753.pdf

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iv CAREB. *Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*. July, 2010. http://careb-accer.ca/?q=node/240
v Ibid.
vi Adapted from CAREB *Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*. July, 2010. http://careb-accer.ca/?q=node/240
vii CAREB. *Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*. July, 2010. http://careb-accer.ca/?q=node/240
viii Adapted from CAREB *Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*. July, 2010. http://careb-accer.ca/?q=node/240
ix Adapted from CAREB *Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*. July, 2010. http://careb-accer.ca/?q=node/240
x Ibid.