

HRH REB UNANTICIPATED PROBLEM REPORTING GUIDANCE

1. INTRODUCTION

The Humber River Hospital (HRH) REB has adopted the Canadian Association of Research Ethics Boards' "Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada" guidance document ⁱ, issued in July 2010. The guidance herein is based on the CAREB document, as well as the OHRP ⁱⁱ and FDA ⁱⁱⁱ guidance documents that CAREB built on.

Together with the new Unanticipated Problem Reporting Form, this guidance document is intended to provide a new, consolidated framework for reporting Unanticipated Problems to the HRH REB. The REB is always available for consultation regarding non-reportable events.

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. [...] 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." ^{iv}

3. SCOPE

This guidance document outlines HRH REB reporting requirements for events that constitute Unanticipated Problems. [For potential additional reporting and documentation requirements, please see supplementary guidance].

Regulators, Sponsors, Funders and Institutions may have different definitions and categorizations for the events covered by this REB 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.

4. DEFINITIONS

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

"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 (e.g., quarterly) and that also includes a concise summary highlighting the main points of concern and the evolving safety profile of the investigational product (e.g., CIOMS reports, Medwatch letters, Dear Investigator letters, etc.) ^v

“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 (e.g. – the REB-approved research protocol and informed consent document[s], Investigator Brochure, Product Monograph, Device Manual, etc.); 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.^{vi}

5. WHAT UNANTICIPATED EVENTS MUST BE REPORTED TO THE HRH REB?

There are 4 different types of unanticipated events that may constitute Unanticipated Problems and require reporting to the HRH REB. This section assists with determining which of these events are reportable to the HRH REB, and which are not.

5.1 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 Investigator-Initiated study (Non-industry funded 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. Further considerations of this nature are outlined in the supplementary guidance.

5.2 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**.

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}

5.2.1 Periodic Safety Update Reports

The HRH REB requires a sponsor generated periodic safety update report (e.g., quarterly) of the external (non-local) adverse events that are not being submitted individually on the HRH REB Unanticipated Problem Reporting Form.

Updated Investigational Product Documentation (e.g., Investigator’s Brochures, Product Monographs, Device Manuals, etc.) need to be reported to the HRH REB.

5.3 Protocol Deviations

Protocol deviations inherently meet the first two criteria of an Unanticipated Problem; that is, they are unexpected and related to the research. Accordingly, protocol deviations need to be reported to the HRH REB.

5.4 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}

6. 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.”^x

7. 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.

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- i Canadian Association of Research Ethics Boards (CAREB). Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada. July, 2010. <http://www.careb-accer.org>
 - 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>
 - iv CAREB. Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada. July, 2010. <http://www.careb-accer.org>
 - v Ibid.
 - vi Adapted from CAREB Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada. July, 2010 <http://www.careb-accer.org>
 - vii CAREB. Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada. July, 2010. <http://www.careb-accer.org>
 - viii Adapted from CAREB Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada. July, 2010. <http://www.careb-accer.org>

ix Adapted from CAREB Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada. July, 2010. <http://www.careb-accer.org>

x Ibid.

This guidance document was adapted from the University Health Network's REB Guidance Document and Form.