Health Sciences North
Horizon Santé-Nord

Unanticipated Problem Guidelines

1. ACKNOWLEDGEMENT

These guidelines have been adapted from the University Health Network Research Ethics Board Guidance Document for Unanticipated Problems.

2. INTRODUCTION

The Health Sciences North Research Ethics Board (HSN REB) has adopted the Canadian Association of Research Ethics Boards (CAREB)'s "Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada" guidance document, issued in July 2010. The guidance herein is adapted from CAREB, as well as the OHRP and FDA guidance documents.

Together with the Unanticipated Problem Reporting Form, this guidance document is intended to provide a consolidated framework for reporting Unanticipated Problems to the HSN REB.

3. SCOPE

This guidance document outlines HSN REB reporting requirements for problems that are considered Unanticipated.

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

4. DEFINITIONS

These terms are adapted from the CAREB guidance document, OHRP guidance document, FDA guidance document and ICH E6 guidelines.

Adverse Drug Reaction (ADR)
Any response to a drug, biologic, or natural health product which is noxious and unintended, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function. A reaction, as opposed to an adverse event, is characterized by the fact that a causal relationship between the product and the occurrence is suspected (i.e. judged to be at least a reasonably possibility).

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 an investigational product, whether or not related to the investigational product.

Local (Internal) Adverse Event
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.

Medical Device Serious Adverse Event (MDSAE)
An adverse event associated with a medical device complaint meets the criteria of a medical device SAE when both of the following are fulfilled:

- The event involves contact with the medical device **and**
- The event results in death or serious deterioration in state of health. This includes:
    - Life-threatening illness or injury
    - Permanent impairment of a body function
    - Permanent damage to a body structure
    - A condition that requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

Non-Local (External) Adverse Event
From the perspective of the REB overseeing one of 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**.**

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.

Privacy Breach
The loss of, unauthorized access to, or disclosure of, personal information, including personal health information.

Serious Adverse Event (SAE)
Any untoward medical occurrence at any dose 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 patient or may require medical intervention to prevent one of the outcomes listed above.

Sponsor
An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical research study.

Unanticipated Problem
Any incident, experience, or outcome that meets <u>all</u> 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 (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
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.

Unexpected Adverse Drug Reaction (UADR)
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 or package insert/summary of product characteristics for an approved product).

5. UNANTICIPATED PROBLEMS THAT MUST BE REPORTED TO THE HSN REB

There are 6 different types of unanticipated problems that require reporting to the HSN REB. This section assists with determining which of these problems are reportable to the HSN REB, and which are not.

1) Internal (Local) Adverse Events

The Principal Investigator should report internal adverse events only if he/she has evaluated the event and determined that it constitutes an Unanticipated Problem.

Reportable local adverse events should be reported to the REB within 15 calendar days of the PI becoming aware of them. Fatal or life-threatening reportable local adverse events should be reported to the REB within 7 calendar days.

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 not.

2) External (Non-Local) Adverse Events

The Principal 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.

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.

3) Periodic Safety Update Reports and Updated Investigational Product Documentation

Periodic Safety Update Reports and Updated Investigational Product Documentation (e.g. – Investigator Brochures, Product Monographs, Device Manuals, etc.) need only be reported as an Unanticipated Problem 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 HSN REB as an amendment (even if events described therein meet the criteria to constitute Unanticipated Problems).

Periodic Safety Update Reports and Updated Investigational Product Documentation that meet the criteria for an Unanticipated Problem 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/report.

4) Protocol Deviations

This guidance document does not differentiate between "protocol deviations" and "protocol violations". All deviations from the protocol or applicable documents constitute a protocol deviation; those deviations range from negligible to significant in their potential impact on research participant safety and the integrity of study data.

Protocol deviations inherently meet the first two criteria of an Unanticipated Problem; that is, they are unexpected and related to the research. Accordingly, for protocol deviations Principal Investigators must determine only whether the protocol deviation suggests that the research places research participants or others at a greater risk of harm than was previously known or recognized. Only protocol deviations that meet this criterion need be reported to the REB as an Unanticipated Problem.

For research conducted in compliance with ICH E6, *Good Clinical Practices* (e.g. externally sponsored drug trials), protocol deviations are required to be documented irrespective of REB reporting requirements (see Important Notes); if it constitutes an Unanticipated Problem, it should be reported to the REB.

Additionally, the Principal Investigator may implement a deviation from the protocol to eliminate an immediate hazard(s) to trial participants without prior REB approval. The deviation, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted as an Unanticipated Problem within 15 days of implementation.

"Waivers"

Sponsors will sometimes prospectively approve protocol deviations (e.g. approve the participation of a research participant who does not meet all inclusion and exclusion criteria). This is also known as a 'limited prospective exception to the protocol'. In these scenarios it is always considered a protocol deviation and should be documented (see Important Notes).
In general, regulatory authorities (e.g. the FDA, OHRP and the European Medicines Agency) have indicated that these planned excursions to the protocol must be reviewed and approved by the REB prior to implementation. Due to the timeliness of the review required for these types of requests, the HSN REB approves waivers if the following conditions are met:
a) The deviation must be documented and approved by the sponsor prior to implementation

b) Both the sponsor and the Principal Investigator must provide a documented assessment that the deviation to the protocol WILL NOT put the potential research participant at increased risk of harm
c) These deviations must be reported with any other protocol deviations during the annual REB renewal.

5) Privacy Breach

In most cases, privacy breaches inherently meet all the criteria of an Unanticipated Problem; that is, they are unexpected, related to the research and put the research participants at increased risk of harm since the confidentiality of their personal information can no longer be assured.

6) Research Participant Complaint

The Researcher must report to the REB, a complaint from a participant when the participant reports concerns about their rights as a research participant or about ethical issues related to the research.

Other Unanticipated Problems

The Principal Investigator should report other unanticipated problems only if he/she has evaluated the problem and determined that it constitutes an Unanticipated Problem.
Examples of other unanticipated problems 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.)

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."

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 PI. In the latter scenario, once the REB and the PI come to an agreement, the REB will accept the Report.

8. IMPORTANT NOTES

It is good practice to log all local adverse events and protocol deviations, due to their potential impact on the data analysis (interim and final) for a study.

9. REFERENCES

Canadian Association of Research Ethics Boards (CAREB). *Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*. July, 2010.

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