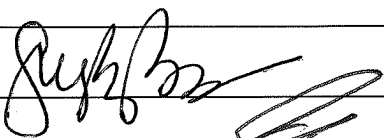



RESEARCH ETHICS OFFICE
STANDARD OPERATING PROCEDURE

Title:	Reporting of Unanticipated Problems that are Non-Local (External) Adverse Events for studies involving drugs, new usages of drugs, biologics, medical devices or natural health products.
Number:	REB – SOP- AE 2.0
Version Date:	26 September 2017
Applicable REB:	REB – Biomedical Panel

APPROVALS:

Name and Title of Signatories	Signature	Date (yyyy/mm/dd)
Director, Research Ethics Office		2017/09/28
Chair, REB 4, Biomedical Panel		2017/10/27

1.0 Purpose

The purpose of this standard operating procedure (SOP) is to describe the procedure for submitting reports of unanticipated problems that are non-local (external), and the local Research Ethics Board's review of these reports.

2.0 Background

This SOP was written in response to the problem of over-reporting of non-local (external) serious adverse events which in and of themselves provide little or no information/explanation of the impact of the event on the study for which it was being reported to Research Ethics Boards. In response to this issue, the European Commission, the U.S. Food and Drug Administration and the Canadian Association of Research Ethics Boards have all developed Guidances endorsing summary reporting of non-local (external) SAE's, with some accompanying form of analysis of the events. The Guidances also confirm that single, isolated adverse events rarely meet the requirements for reporting to the REB's.

3.0 Definitions

Adverse Event (AE): Any untoward medical occurrence in a research participant including any abnormal sign, symptom, or disease temporally associated with the subject's participation in research, whether or not related to their participation in the research.

Non-local (external) adverse event: From the perspective of the REB overseeing one or more centres engaged in a multi-centre clinical trial, non-local adverse events are those adverse events

experienced by research participants enrolled by investigators at other centres/institutions outside the REB's jurisdiction.

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 REB 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 reported unexpected serious adverse events that have occurred in a given reporting period, and which includes any significant areas of concern and the evolving safety profile of the investigational product. *Adverse events that are considered to be unanticipated problems should be reported immediately and not be buried in a periodic report.*

4.0 Responsibility

Each Investigator is responsible for reviewing and retaining copies of all non-local AE reports received from the sponsor. The Investigator is responsible for reporting to the REB only those non-local AE's that might affect the rights, safety and well-being of research participants. AE reports not meeting REB's submission criteria are to be kept on file at the study site and made available for review by REB upon request.

5.0 Procedures

5.1 Criteria for Reporting Non-Local Adverse Events

5.1.1 Non-local (external) adverse events should be reported to the REB in the form of **periodic summary reports**, accompanied by information that is meaningful and of use to the REB. The contents of the summary report(s) should ordinarily, at a minimum, include a sponsor analysis of the significance of the adverse event or perhaps such an analysis from an independent Data Safety Monitoring Board (DSMB), with (where appropriate) a discussion of previous similar events. Such summary reports should be submitted as **an email within the respective REMO file to the REB Administrator responsible for that file.**

5.1.2 Upon becoming aware of an individual case report of a non-local adverse event that **may represent an unanticipated problem** (per the definition in 5.1.3 below), the Investigator must report it to the REB. The Investigator may rely on the sponsor's assessment and provide the REB with a report prepared by the sponsor;

5.1.3 The Investigator should only submit the non-local adverse event report (unanticipated problem) to the REB if it is:

- Unexpected, **AND**
- Related or possibly related, **AND**
- Suggests that the research places research participants or others at a greater risk of harm, **AND**
- Requires a change to the protocol and/or informed consent form and/or requires immediate notification to participants for safety reasons;

- 5.1.4 The non-local adverse event report must include **all** of the following information:
- The description of the unanticipated event
 - All previous safety reports concerning similar adverse events (as provided by the sponsor)
 - An analysis of the significance of the current adverse event in light of previous reports, **and**
 - The proposed protocol changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the event;
- 5.1.5 Individual non-local adverse event reports that meet ALL of the above criteria must be reported to the REB within 30 calendar days of the Investigator receiving the report;
- 5.1.6 The Investigator should continue to report unanticipated problems to the REB until the study is closed even if no local participants are currently enrolled in the study.

5.2 Review of Non-local Adverse Events by the REB

- 5.2.1 Upon receipt of non-local adverse event report, the REB will review the submission and request any clarifications, missing documents or information;
- 5.2.2 If a non-local adverse event report does not meet the submission requirements, an email will be sent back to the Investigator (or delegate) with a description of the reporting requirements;
- 5.2.3 The Chair or delegate will conduct an initial review of the report and determine any action or follow-up required;
- 5.2.4 The Chair may choose to act on the information immediately (e.g., suspend enrolment); however, if the Chair determines that immediate action is required, the adverse event should be reported to the Full Board at the next available committee meeting;
- 5.2.5 When reviewing a report of an unanticipated problem, REB should assess the appropriateness of any proposed corrective or preventative measures by the sponsor and/or Principal Investigator, consider any additional appropriate measures that may or may not have been identified or proposed by the sponsor and/or Principal Investigator, and consider whether the affected research still satisfies the requirements for REB approval. In particular, 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. 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 participate in the research). REB should also consider whether suspension or termination of the research or research site is warranted;
- 5.2.6 If the REB determines that the event does not raise concerns about risks to research participants, the REB may decide that no further action needs to be taken.

5.3 Documentation

- 5.3.1 The REB will **not** acknowledge receipt and review of the non-local adverse event report, as the receipt of this to the REB can be verified through the REMO system as a line in the history log;
- 5.3.2 If any follow up or clarification is required, the REB will email the study team through REMO;

5.3.3 It is the Principal Investigator's responsibility to retain copies of all non-local adverse event reports in the Investigator Study File.

6.0 References

1. The International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines;
2. ICH Harmonized Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). 27 October 1994
3. ICH E2F draft consensus guideline "Development Safety Update Report" 5 June 2008;
4. Health Canada Food and Drug Regulations, Division 5
5. U.S. Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Title 21 Part 56;
6. U.S. Department of Health and Human Services (HHS), CFR Title 45 Part 46;
7. Office for Human Research Protections (OHRP) and HHS – *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Event Reporting*, January 2009
8. U.S. HHS et al, *Guidance for Clinical Investigators, Sponsors, and IRB's Adverse Event Reporting*, January 2009
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
10. Canadian Association of Research Ethics Boards. *Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada*. July 2010
11. 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
12. Health Canada's response to CAREB Guidance Document. June 29, 2010

7.0 Revision History

SOP Code	Effective Date	Summary of Changes
REB-SOP AE 1.0	14 April 2011	Original Version
REB-SOP AE 2.0	26 September 2017	Revision to name of system from HERO to REMO.