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## POLICY

The Research Ethics Board (REB) of Mount Sinai Hospital (MSH) exists to ensure that all research involving human subjects conducted under the auspices of Mount Sinai Hospital meets the highest ethical and acceptable scientific and safety standards in accordance with the Tri-Council Policy Statement: Guidelines on Research Involving Human Subjects and the International Conference on Harmonization Good Clinical Practice: Consolidated Guideline.

The MSH REB distinguishes Serious Adverse Events (SAEs) as being either internal (events happening to MSH study subjects) or external (events happening to study subjects at other participating institutions).

Definitions of Serious Adverse Events are supplied in Appendix 1. See also ICH: GCP E6 and ICH E2A for further reference

It is the responsibility of the MSH Principal Investigator (PI) to promptly review and report all internal SAEs and any concerns, changes or new information to the REB. The Principal Investigator is also responsible to review and report any external Adverse Events that are determined to be ***both serious and unexpected***; this includes Serious Unexpected Adverse Drug Reactions (SUADR).

Please refer to Appendix 1 for the definition of Serious Unexpected Adverse Drug Reactions.

The REB will not accept an SAE Reporting Form (Appendices 2 & 3) without an original signature and initials from the PI. This signature attests that the PI has reviewed the SAE and its safety implications and has assessed the relationship to the study intervention of the SAE (if internal). It also attests to the accuracy of the form.

**PROCEDURES**

1. REPORTING INTERNAL SAEs

All internal SAEs should be reported to the REB providing all available information, as soon as the study staff is aware, by using the MSH Internal Serious Adverse Event Reporting Form (Version date July 29, 2004) (Appendix 2). A comprehensive, follow up report must be submitted to the REB within 7 calendar days of the date that study staff is aware of the SAE. Any sponsor specific SAE Report Forms should accompany the completion of the MSH Internal Serious Adverse Event Reporting Form (Version date July 29, 2004) (Appendix 2). Referencing to "the attached sponsor report" is not acceptable.

In addition, the Internal SAE Form directs the PI to provide recommendations on:

- any actions that necessitate a revision to the protocol and/or consent form, Investigator's Brochure (IB) or any other study related document. If so, the revisions should be described on the Form and then submitted under separate cover for REB review and approval, and
- whether the event is expected or unexpected.

2. REPORTING EXTERNAL SAEs

All external SAE reports should be reviewed as expeditiously as possible. Submit those Adverse Events that are determined to be ***both serious and unexpected***; including SUADRs, to the REB within 15 days of that review by using the MSH REB Serious And Unexpected Adverse Event Summary Reporting Form (Version date July 29, 2004) (Appendix 3). Relevant supporting documentation issued by the sponsor (CIOMS or MedWatch forms) must be retained by the PI and a copy forwarded to the REB. The REB may request any relevant documentation at a later date. Any external Adverse

Events received prior to the initial REB approval, that are *both serious and unexpected* must accompany the Toronto Academic Health Sciences (TAHSC) Ethics Application Form or as they arrive prior to the initial REB approval.

In addition, the PI is asked to provide recommendations on the following points:

- any actions that necessitate a revision to the protocol and/or consent form, and/or any other study related document. If so, submit under separate cover for REB review and approval

and

- the relationship of the Adverse Event to the study being conducted at MSH.

**OTHER SAFETY REPORTS**

All relevant summarized safety reports must be submitted to the REB as they are issued or at the time of annual renewal and/or termination of the study. These include:

- Data Safety Monitoring Board (DSMB)
- Safety Committee (SC)
- Current IB or Product Monograph

**REB ACKNOWLEDGMENT OF RECEIPT**

The REB has no regulatory obligation to acknowledge receipt of SAEs. It is the responsibility of the sender to retain proof of submission.

**REFERENCES**

- ICH Harmonized Tripartite Guideline E6: Guideline for Good Clinical Practice, 1997.
- ICH Harmonized Tripartite Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 1994.
- Tri Council Policy Statement 2, 2010

**APPENDIX 1**

**DEFINITIONS**

1. **Adverse Event (AE)** is any unfavorable or unintended medical occurrence or change in current health status in a subject participating in a research study. An AE may also be referred to as Adverse Reaction, Adverse Experience, or Side Effect. An Adverse Drug Reaction (ADR) specifically refers to an AE for which a causal relationship between the product/device is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

2. **Causality** is the relationship between an adverse event and the test agent in terms defined in the Protocol (i.e. unrelated, unlikely related, possibly related, probably related, related).

3. **External SAE** is any serious adverse event that occurs with a Non-MSH study subject

4. **Internal SAE** is any serious adverse event that occurs with a MSH study subject

5. **Principal Investigator:** Under Health Canada guidelines, this is the Qualified Investigator who is responsible for the conduct of the study at MSH. Under ICH: GCP Guidelines, the investigator is such individual who is qualified by education, training and experience to assume responsibility for the proper conduct of the trial.

6. **Risk/Benefit Ratio:** When the Principal Investigator determines that an increased number and/or severity of risks (toxicities) outweighs the anticipated benefits, this alters the ratio.

7. **Serious Adverse Event (SAE)** or reaction is any untoward medical occurrence that,
    - Results in death,
    - Is life threatening (an event in which the study subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe),

- Requires patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect. An occurrence is also considered an SAE if it represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the Investigator(s).

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations. For instance, important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should be reported. These should also be considered serious.

Section 2 of ICH E2A, 1994

8. **Serious Unexpected Adverse Drug Reaction:** All noxious and unintended responses to a medicinal product related to any dose, the frequency, nature, severity of which is not consistent with the applicable product information (e.g Investigator's Brochure for an unapproved investigational medicinal product, or Health Canada approved Product Monograph for marketed products), and that also fulfills the criteria of Seriousness, as per the definition of SAE.

   Section 2 of ICH E2A, 1994.

9. **Sponsor** is an individual, corporate body, institution, or organization that conducts a clinical trial.

10. **Unexpected Adverse Event** is any adverse event which is not identified in nature, severity, or frequency in the current Investigator's Brochure (IB) or on the label of the drug (i.e. Health Canada approved Product Monograph).

**APPENDIX 2**

MSH REB INTERNAL SERIOUS ADVERSE EVENT REPORTING FORM

**APPENDIX 3**

MSH REB EXTERNAL SERIOUS AND UNEXPECTED ADVERSE EVENT SUMMARY FORM

**APPENDIX 4**

SAE REPORT CONTENT

**(See Appendices 2 and 3 for SAE Reporting Forms)**

An SAE report should include:

- Submission Date: dd-mmm-yy
- Protocol Title
- MSH REB Reference Number
- Name of Principal Investigator at MSH
- Name of the person completing the Reporting Form
- Sponsor
- SAE serial number (external) or Subject study code number (internal)
- Name of Drug(s), Device or Intervention
- Name/medical term of the SAE
- Description of SAE
  - Type of report (initial/follow-up)
  - Required dates:

    -onset of SAE

    -resolution of SAE

    - SAE report submission date to the MSH REB
  - Outcome (recovered with/without sequelae, hospitalization, medical intervention, death)
  - Response to Event (unblinding information, drug withdrawal, re-start, if applicable)
  - Relationship to drug/device, or study intervention (Internal SAEs only)
  - Relationship to study at this site.
  - Study action recommended by PI. State whether changes to the Protocol, Consent Form, or IB are required, and submit relevant documents to MSH REB under separate cover.
- Printed Name and Signature of the MSH Principal Investigator/Co Investigator for the study.
- Date signed by PI.