STANDARD OPERATING PROCEDURES
Bannatyne Campus Research Ethics Boards

UNIVERSITY OF MANITOBA	**SOP TITLE:** **Local Adverse Event Reporting and REB Review**	Page 1 of 7 EFFECTIVE DATE: *January 31, 2013* SUPERSEDES: *August 1, 2011DRAFT Implementation* FILE NUMBER: REB 10

APPROVAL SIGNATURES

Dr. L. Nicolle, M.D., FCRCP
Chair, Biomedical Research Ethics Board

Date: 25 Nov 2013

Dr. J. Arnett, Ph.D.
Chair, Health Research Ethics Board

Date: 21 November 2013

PURPOSE:

To describe the procedures for investigator reporting of local unanticipated problems and adverse events to the Bannatyne Campus Research Ethics Board (REB) and the REB's review of these reports.

GENERAL DESCRIPTION:

Adverse event collection/reporting are required for all research studies (intervention and non-intervention) and should include any unfavorable change in well being (including physical, psychological, economic or social harm) of an individual or individuals participating in a research study.

The investigator must ensure the protocol outlines how adverse events will be defined, documented, monitored at the site and subsequently reported to the sponsor(s), Health Canada, applicable regulatory authorities (e.g. FDA, US Department of Health and Human Services) and the REB.

Only unanticipated adverse events (unexpected, related or possibly related and involving greater risk) require reporting to the REB. There may be other incidents, experiences, or outcomes not considered adverse events but that in the opinion of the investigator or sponsor, place research participants or others at a greater risk of harm (including physical, psychological, economic or social) than was previously anticipated or have implications for the conduct of the study or the integrity of research data that also require reporting to the REB.

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Reports of local adverse events(i.e. those that represent unanticipated problems) are reviewed by the REB to determine if new concerns are raised about 1) the risk/benefit ratio; 2) the approved informed consent document; and 3) need for re-consent.

DEFINITIONS:

The term "investigational product" refers to new or new usages of drugs, biologics, medical devices or natural health products.

An **adverse event (AE)** is defined as any occurrence in the health or well being of a research participant who is administered an investigational product (drug, natural health product, or device) or any other procedure(s) involved in the research or participants in a research activity that may or may not be caused by the administration of an investigational product or any procedure(s) involved in research.

Local (Internal) adverse event: local adverse events are those adverse events experienced by research participants enrolled by the investigator(s) at one or more centers under the jurisdiction of the University of Manitoba REB. In context of a single-centre clinical trial, all adverse events would be considered local adverse events.

A **serious adverse event (SAE)** is an adverse event that:

- Results in death; or
- Is life threatening; or
- Requires in-patient hospitalization or prolongation of existing hospitalization; or
- Results in persistent or significant disability or incapacity; or
- Causes congenital malformation/ birth defect; or
- Any other adverse event that, based upon appropriate medical judgment, is an important medical event that may jeopardize the health (physical, psychological, economic, or social) of the research participant or may require medical intervention to prevent one of the outcomes listed above.

Medical Device Serious Adverse Event: An adverse event associated with a medical device complaint meets the criteria of a medical device SAE when the event involved a medical device **and** results in death or serious deterioration in the state of health. "*Serious Deterioration in the state of health*" means: a life threatening disease, disorder or abnormal physical state; the permanent impairment of a body function or permanent damage to a body structure; or a

condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage.

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.

PROCEDURES:

Reporting Requirements for Initial and Follow-up of Local Adverse Events and other Unanticipated Problems

1. Investigators must report only those adverse events that are considered unanticipated problems. Any local unanticipated problems that are fatal or life threatening must be reported to the respective REB within **7 days** of becoming aware of the event using the *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form (Initial Form).* Any **other unanticipated problem** should be reported to the respective REB within **15 days** of becoming aware of the event using the *Bannatyne Campus Local Adverse Event Form/Unanticipated Problems Form (Initial Form).*

2. Investigators must submit follow up notification of **all reportable local adverse events or other unanticipated problems** on the *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form (Follow-up)* if the participant's condition worsened and/or relationship of the adverse event to the study treatment has changed or at the time of resolution.

3. A summary list of local adverse events or other incidents, experiences, outcomes that are deemed unanticipated problems and their REB report dates must also be included at the time of Annual Review and Study Closure.

4. Regardless of whether the local/internal adverse event is determined to be an unanticipated problem, the investigator must ensure the adverse event is reported to the study sponsor, as sponsors are responsible for submitting safety information to applicable regulatory authorities (e.g., Health Canada, FDA) in accordance with regulatory requirements.

5. When the study is funded by the US Department of Health and Human Services (e.g. NIH, CDC, etc) the sponsor or lead PI is also responsible to report the unanticipated local adverse event and other local unanticipated problems to the applicable agency head (or designee) and the Office of Human Research Protections within 1 month of becoming aware of the event on behalf of the University of Manitoba or applicable institution. For Investigator Initiated trials this responsibility lies with the lead and possibly local PI.

Pregnancy Reporting

1. Pregnancy is not considered as an adverse event however is to be reported only if there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive treatment; there was a serious complication in the pregnancy (including spontaneous miscarriage) or an elective termination was performed for medical reasons. Elective abortions do not need to be reported as an adverse event.

Death Reporting

1. Report local deaths on the *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form (Initial Form)* that meet the following criteria:
    - Occurred in an interventional study (i.e. involving a drug, biologic, device procedures and /or behavioral interventions); and
    - Was unexpected, and
    - Was related or possibility related to research participation

Reporting Exceptions

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1. The ICH Topic E2A Guidance (Section III A (2)) includes a provision for submitting a serious and expected adverse event report if there is an increase in the rate of occurrence, which is judged to be clinically important.

2. The above types of events must also be recorded on the *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form (Initial Form).*

Screening and Review of Adverse Events

1.0 The investigator completes the *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form* and submits it in duplicate to the REB in the timeframe outlined above.

2.0 REB staff date stamp and initial one copy of the *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form (Initial Form)* and returns it to the investigator to acknowledge receipt of the report. This does not imply however that the submission and accompanying documents have been assessed or checked for content, completeness or accuracy. It should be noted, there is no regulatory requirement for acknowledgement of the SAEs by REBs.

3.0 The second copy of the *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form* is forwarded to the REB coordinator to review the submission and request any clarifications, missing documents or information.

4.0 All *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form*s are then reviewed by the REB Chair or designate REB member to determine if any action or follow-up is required. The REB coordinator will contact the Investigator with concerns, recommendations or request clarifications suggested by the Chair or Board.

5.0 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 REB at the next available REB meeting(s). REB members also receive appendices to the previous month's minutes indicating sites (by ethics reference number) that have submitted local unanticipated problems reviewed by the Chair and REB Coordinator.

Investigator Documentation

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1.0 It is the investigator's responsibility to record all unanticipated problems and adverse events including serious and non serious, expected and unexpected events in participant files.

2.0 It is the investigator's responsibility to retain copies of returned REB Date Stamped *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form* in the Investigator Study File.

REB Documentation

1. All *Bannatyne Campus Local Adverse Event /Unanticipated Problems Form* will be retained in the REB study file.

References

1. *The International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines;*
2. *ICH Harmonised 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. *US Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Title 21 Part 56.*
6. *US 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 Events, January 2007.*
8. *US HHS et al, Guidance for Clinical Investigators, Sponsors, and IRBs 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 response to CAREB Guidance Document. June 29, 2010.