PROCEDURE FOR REPORTING LOCAL AND NON-LOCAL SERIOUS AND UNEXPECTED ADVERSE EVENTS TO THE RESEARCH ETHICS REVIEW COMMITTEE (RERC)

Effective Date: July 20, 2012

Approved by: 

Kirk Barber, MD FRCPC

1 Background:

1.1 The Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (Article 11.8 and 11.9) and the ICH Harmonised Tripartite Guideline: Guideline on Good Clinical Practice (E6(R1)) (Item 3.3.8 (c)) mandate that REBs receive and review new information from clinical trials under their jurisdiction that may affect the welfare or consent of participants.

1.2 The European Commission, the US Food and Drug Administration and the Canadian Association of Research Ethics Boards (CAREB) have all developed Guidelines that outline practical procedures, e.g. summary reporting of non-local (external) serious adverse events (SAEs), with some accompanying form of analysis of the events, related to the review of new information.

1.3 This procedure sets forth the requirements of the RERC with respect to receiving new information on local and non-local serious adverse events.

2 Definitions:

2.1 **As soon as reasonably possible:** The term “as soon as reasonably possible” means that the timing of reporting will vary in accordance with the severity/seriousness of the information being reported, including the nature of the research associated with the problem. All SAEs must be reported within fifteen (15) calendar days and all life-threatening or fatal SAEs must be reported within seven (7) calendar days of the incident, occurrence, outcome event, or the Investigator’s receipt of the notice of the event.

2.2 **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.

2.3 Non-local 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 investigator(s) at other centres/institutions outside the REB’s jurisdiction.

2.4 **Local 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.

2.5 **Adverse Drug Reaction (ADR):** All noxious and unintended responses to an investigational product [which includes natural health products and biologics] related to any dose should be considered adverse drug reactions. A reaction, as opposed to an adverse event, is characterized by the fact that a causal relationship between the investigational product and an adverse event is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

2.6 **Serious Adverse Event/Experience (SAE) or Reaction:** Any untoward medical occurrence 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 health of the research participant or may require medical intervention to prevent one of the outcomes listed above.

2.7 **Medical Device Serious Adverse Event (MDSAE):** An adverse event associated with a medical device complaint meets the criteria of a medical device SAE when the event involves 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.

2.8 **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). Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

2.9 **New Information:** Any new information that might adversely affect the safety or well-being of the study participants, the conduct of the trial, or the participant’s willingness to continue in a study. New information includes, but is not limited to any relevant recent literature, interim findings, preliminary results of the study or of any other study (e.g. using the same drug).

2.10 **REB of Record or Board of Record:** The REB of record that has been granted ultimate authority by an institution for the ethics review and oversight of research conducted at that institution.

2.11 **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, and a position statement as to whether any changes are required.

2.12 **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 IRB-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.

3 Associated Documents

3.1 RERC Local SAE Report Form

3.2 RERC Non-Local SAE Report Form

3.3 RERC Safety Update Report Form

3.4 Annual / Final Report Form

4 Procedure

4.1 Local (Internal) Adverse Events

4.1.1 The principal investigator is required to report to the RERC those **LOCAL** adverse events that are deemed to be **SAEs**.

4.1.2 Upon becoming aware of a local adverse event, the investigator should assess whether the adverse event represents an SAE.

4.1.3 If the investigator determines that the adverse event represents an SAE, the investigator must report it to the RERC.

4.1.4 If the investigator determines that an adverse event is not an SAE, but the sponsor subsequently determines that it is, the sponsor should report this determination to the principal investigator, and such reports must then be submitted to the RERC.

4.1.5 A description of any proposed protocol changes or other corrective actions to be taken by the principal investigator or sponsor in response to the event must be described in the report to the RERC.

4.1.6 The following local adverse events ordinarily should **NOT** be reported to the RERC:

- 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

4.1.7 Report Timing and Process:

4.1.7.1 Local (internal) serious adverse events should be reported to the RERC as soon as reasonably possible, but in any case no later than fifteen (15) calendar days subsequent to the occurrence of the local event or the sponsor's determination that the event constitutes an SAE. If the event is considered to be **life-threatening or fatal**, the report must be made no later than seven (7) calendar days subsequent to its occurrence.

4.1.7.2 Such events should be reported using the RERC Local SAE Report Form, and should include:

- The status of the study and summary of participants enrolled
- A detailed description of the local SAE
- An opinion expressed by the local investigator that the event is both serious and unexpected and a justification of that opinion
- An opinion expressed by the local investigator that the event is related or potentially related to the study drug/procedure/device and an explanation of that opinion.
- An opinion expressed by the local investigator respecting the implications of the SAE on the continuation of the study and any further actions that may be required such as changes to the study procedure, informed consent or protocol.
- A statement of the study team response to the event and the patient outcome of the SAE.

4.2 Non-Local (External) Adverse Events

4.2.1 Non-local (external) serious adverse events should be reported to the RERC in the form of periodic safety update reports, accompanied by information that is meaningful and of use to the RERC.

4.2.2 The contents of the summary report(s) should ordinarily at a minimum, include a sponsor analysis of the significance of the adverse events or perhaps such an analysis from an independent Data Safety Monitoring Board (DSMB), with (where appropriate) a discussion of previous similar events.

4.2.3 Investigators may rely on the sponsor's assessment and provide to the RERC a periodic safety update report prepared by the sponsor. In general, the sponsor should amend the Investigator's Brochure as needed so as to keep the description of safety information updated.

4.2.4 Single isolated external adverse events rarely meet the requirements for reporting to REBs.

4.2.5 The RERC will **ONLY** accept individual case reports of non-local (external) SAEs when they meet the definition of an unanticipated problem (CAREB AE Guidance Document).

4.2.6 **Individual** isolated external serious adverse events should **ONLY** be reported to the RERC if they are unanticipated problems (using the Non-local SAE Report Form). The report must include all of the following information:

- Justification of the assessment that the event described is both serious and unexpected,
- Identification of all previous safety reports concerning similar adverse experiences,
- Analysis of the significance of the current adverse experience in light of the previous reports, and
- Outline of any proposed protocol changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the unanticipated problem

4.2.7 Reports **NOT** meeting these requirements will be returned to the submitter with a description of the RERC reporting requirements as outlined above.

4.2.8 Report Timing and Process:

4.2.8.1 Periodic Safety Update Reports should be reported to the RERC as soon as reasonably possible, but in any case no later than fifteen (15) calendar days, after the Principal Investigator has received the report from the Sponsor (using the Safety Update Report Form).

4.2.8.2 At the time of submission of the application for Annual Renewal, the Principal Investigator will be expected to provide a summary of the impact of all safety data that has been received from the sponsor, and any new information that they have become aware of, together with recommendations for any proposed changes to the study, if applicable.

4.2.8.3 Investigators should append any periodic safety update reports issued by the sponsor within the previous year, **ONLY** if they have not been previously submitted to the RERC. If the sponsor is unwilling to or has been unable to provide the Investigator with an assessment of safety information at least once annually, the Investigator should report this to the RERC when submitting the request for annual renewal.

4.2.8.4 Individual reportable external serious adverse events that represent unanticipated problems should be reported to the RERC using the Non-local SAE Report Form.

4.2.8.5 Individual reportable external serious adverse events should be reported to the RERC as soon as reasonably possible, but in any event, no later than within fifteen (15) calendar days after the Investigator has received the report from the sponsor.

4.3 Other unanticipated problems

4.3.1 There may be other incidents, experiences, or outcomes not considered adverse events but that meet the definition of unanticipated problems that, in the opinion of the investigator or sponsor, place research participants or others at a greater risk of physical or psychological harm than was previously anticipated, or have implications for the conduct of the study or the integrity of research data.

4.3.2 Upon becoming aware of any other incident, experience, or outcome that may represent an unanticipated problem, the investigator should assess whether it does constitute an unanticipated problem.

4.3.3 If the investigator determines that it is an unanticipated problem, the investigator must report the problem to the RERC.

4.3.4 In general, **ONLY** those incidents, experiences, or outcomes that require a change to the study procedures, study documents and/or require notifying the research participants of a change in the risk/benefit ratio should be reported to the RERC. This may include:

- 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,
- Protocol deviations that impact data integrity or the safety of research participants.
- Acts of nature that impact the study conduct or data integrity (e.g. – floods, hurricanes, earthquakes, pandemics, etc.)

4.3.5 Report Timing and Process

4.3.5.1 Other unanticipated problems should be reported to the RERC as soon as reasonably possible but in any event within fifteen (15) calendar days of occurrence of the event or the receipt of the report of the unanticipated problem by the Investigator from the Sponsor.

4.3.5.2 **Local** other unanticipated problems should be reported using the Local SAE Report Form.

4.3.5.3 **Non-local** other unanticipated problems should be reported using the Non-local SAE Report Form.

4.4 RERC Internal Handling Procedure

4.4.1 Local SAEs

4.4.1.1 All local SAEs must be received using the RERC Local SAE Report Form, a template of which will be posted on the RERC website.

4.4.1.2 This form should be sent by email.

4.4.1.3 Once received, the RERC Manager will forward to the RERC Chair or designate for review.

4.4.1.4 The RERC Chair or designate will:

- If appropriate, confirm that no further action is required, or
- Request more information, as appropriate, from the investigator before indicating the disposition of the form, or
- Bring the case to the committee for discussion and disposition.

4.4.1.5 Once the RERC Chair or designate has indicated the disposition of the form, the RERC Manager or designate will enter the information in the RERC Serious Adverse Event database.

4.4.2 Non-local SAEs

4.4.2.1 All non-local SAE reports will be received using the RERC Non-local SAE Report Form, a template of which will be posted on the RERC website. Non-local SAE reports should be sent by email.

4.4.2.2 Review of non-local SAEs will be as described in step 4.4.1.3 to 4.4.1.4.

4.4.2.3 Once the RERC Chair or designate has indicated the disposition of the form, the RERC Manager or designate will enter the information in the RERC Serious Adverse Event database.

4.4.3 Safety Update Report (SURs)

4.4.3.1 All SURs must be received using the RERC SUR Report Form or the Annual / Final Report, templates of which will be posted on the RERC website.

4.4.3.2 This form and SUR should be sent by email.

4.4.3.3 Once received, the RERC Manager will forward to the RERC Chair or designate for review.

4.4.3.4 The RERC Chair or designate will:

- If appropriate, confirm that no further action is required, or
- Request more information, as appropriate, from the investigator before indicating the disposition of the form, or
- Bring the case to the committee for discussion and disposition.

4.4.3.5 Once the RERC Chair or designate has indicated the disposition of the form, the RERC Manager or designate will enter the information in the RERC Serious Adverse Event database.

4.4.4 Other unanticipated problems

4.4.4.1 Other unanticipated problems will be reported to the RERC as described in steps 4.4.1 or 4.4.2 depending upon whether they are local or non-local

4.4.4.2 Once the RERC Chair or designate has indicated the disposition of the form, the RERC Manager or designate will enter the information in the RERC Serious Adverse Event database.

4.4.5 General Procedure

4.4.5.1 Forms received by email transmission will be verified (checked for correct title and RERC file number) and stored electronically.

4.4.5.2 Completed electronic forms and the spreadsheets will be maintained for 25 years from the end of the year in which they were generated.