UNIVERSITY OF SASKATCHEWAN

Research Ethics Office

Diane Martz, Director
Research Ethics Office (REO)
Box 5000 RPO University
University of Saskatchewan
Saskatoon, SK Canada S7N 4J8
Phone (306)966-2975 Fax (306)966-2069
Email: diane.martz@usask.ca

MEMORANDUM

To: All Researchers and Research Personnel

From: Diane Martz

Date: August 2012

Re: Change to Reporting Requirements for local serious adverse events as well as non-local (external) serious adverse events

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The Research Ethics Office (REO) has developed a set of Standard Operating Procedures (SOPs) that are compliant with provincial, national and international policies and laws. These includes Canada's Food and Drug and Medical Devices Regulations, the Tri-Council Policy Statement (TCPS2): Ethical Conduct for Research Involving Humans, December 2010, the US Food and Drug Administration (USFDA) and the regulations overseen by the Office of Human Research Protections (OHRP). The SOPS came into full effect July 1, 2012 after being approved by the University Committee on Ethics in Human Research (UCEHR) and further reviewed and signed off by the Associate Vice President of Research.

As a result of the adoption of these SOPS and to align with recent guidance developed by the USFDA, the OHRP, and the Canadian Association of Research Ethics Boards (CAREB), the University of Saskatchewan's has implemented a change in regard to the reporting requirements for local serious adverse events as well as non-local (external) serious adverse events. **The policy change is effective immediately. Reporting of local serious adverse events or non-local (external) serious adverse events must follow these new reporting guidelines. Reports not meeting these guidelines will be returned to the submitter with a description of the REB reporting requirements as outlined below.**

Policy:

A. Local (Internal) Adverse Events

The principal investigator is required to report to the REB only those local adverse events that are deemed to be unanticipated problems as defined below (unexpected, related and involving greater risk).

Unanticipated Problem: Any incident, experience, or outcome (including an SAE, MDSAE, or UADR) that meets all 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, 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

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.

Once an investigator is aware of a local adverse event, he/she should assess whether the adverse event represents an unanticipated problem. If the investigator determines that the adverse event represents an unanticipated problem, it must be reported to the REB. I f the investigator determines that an adverse event is not an unanticipated problem, but the sponsor subsequently determines that it is, the sponsor should report this determination to the principal investigator, and a report must then be submitted to the REB. The principal investigator must clearly explain how she/he determined that the event meets the definition of an "unanticipated problem". The report must also describe any proposed protocol changes or other corrective actions to be taken by the principal investigator or sponsor in response to the event.

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 the research procedures, whether the event is expected or not;
- Non-serious adverse events, whether expected or not.

Report Timing and Process:

Local (internal) serious adverse events that meet the definition of an unanticipated problem should be reported to the REB as soon as reasonably possible, but in any case no later than **seven (7)** calendar days subsequent to the occurrence of the local event or the sponsor's determination that the event constitutes an unanticipated problem. Such events should be reported using the UNANTICIPATED PROBLEM(S) REPORT FORM, and should include:

- The status of the study and summary of participants enrolled
- A detailed description of the local event
- 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

B. Non-Local (External) Adverse Events

Non-local (external) serious adverse events should be reported to the REB in the form of periodic safety update report. The contents of the periodic safety update report should include, at a minimum, a summary analysis of the significance of the adverse events or, an analysis from an independent Data

Safety Monitoring Board (DSMB), with (where appropriate) a comprehensive listing of previous similar events. Investigators may rely on the sponsor's assessment and provide to the REB a periodic safety update report prepared by the sponsor.

The format used by the sponsor for annual safety reports is acceptable. In general, the sponsor should amend the Investigator's Brochure as needed so as to keep the description of safety information updated. Single isolated external adverse events rarely meet the requirements for reporting to REBs.

Individual external adverse events should only be reported when a determination has been made that the event meets all of the criteria for an unanticipated problem. University of Saskatchewan's REBs will ONLY accept individual case reports of non-local (external) SAEs in the exceptional circumstances that they meet the definition of an unanticipated problem (see above).

Individual isolated external adverse events should NOT to be reported to the REB UNLESS they are unanticipated problems. If such an event meets the reporting criteria, the report that is submitted 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,
- An analysis of the significance of the current adverse experience in light of the previous reports, **and**
- An 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

Reports not meeting these requirements will be returned to the submitter with a description of the REB reporting requirements as outlined above.

Report Timing and Process:
Periodic Safety Update Reports should be reported to the REB as soon as reasonably possible, but in any case no later than **fifteen (15)** calendar days, after the Principal Investigator or designate has received the report from the Sponsor.

The University of Saskatchewan's REB's expect that sponsors will be amending their reporting processes to provide for periodic safety update reports at least semi-annually. 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. Investigators should bring to the attention or append any periodic safety update reports issued by the sponsor within the previous year, if they have not been previously submitted to the REB. 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 REB when submitting the request for annual renewal. Periodic Safety Update Reports and individual reportable external adverse events that represent unanticipated problems should be reported to the REB using the Unanticipated Problem(s) Report Form.

In the limited circumstances where an Individual Non-Local (external) SAE constitutes an unanticipated problem the report of the Individual Non-Local (external) SAE should be reported to the REB as soon as

reasonably possible, but in any event, no later than within **seven (7)** calendar days after the Investigator has made the determination that the event is reportable.

C. Other Unanticipated Problems

Other incidents, experiences, or outcomes not considered adverse events may meet the definition of unanticipated problems. These events, 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.

When an investigator becomes aware of any other incident, experience, or outcome that may represent an unanticipated problem, he/she should assess whether it does constitute an unanticipated problem. If the investigator determines that it is an unanticipated problem, the investigator must report the problem to the REB.

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 REB. 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.)

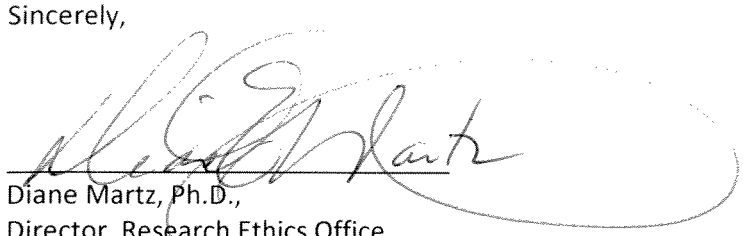
Report Timing and Process:

Other unanticipated problems should be reported to the REB as soon as reasonably possible but in any event within **seven (7)** calendar days of awareness of the occurrence of the event or the receipt of the report of the unanticipated problem by the Investigator from the Sponsor using the Unanticipated Problem(s) Report Form.

The SOPs are now posted on the REO website at:
http://www.usask.ca/research/ethics_review/policies.php

Questions pertaining to the reporting requirements should be directed to the Chair of the Biomedical Research Ethics Board, Dr. Gordon McKay or to the Chair of the Behavioral Research Ethics Board, Dr. Beth Bilson.

Sincerely,



Diane Martz, Ph.D.,
Director, Research Ethics Office
University of Saskatchewan

cc: J. Basinger, Associate Vice-President Research
J. Thornhill, Acting, Associate Vice-President Research
G. McKay, Chair, Biomedical Research Ethics Board
B. Bilson, Chair, Behavioural Research Ethics Board
S. Corley, Director of Operations, Saskatoon Centre for Patient-Oriented Research (SCPOR)

Definitions:

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. However, unless the event is a routine safety letter, DSMB report, periodic safety update report, or a summary of changes to the Investigator's brochure that are minor and/or routine in nature, all new information and unanticipated problems must be reported within **seven (7)** days of the incident, occurrence, outcome event, or the Investigator's receipt of the notice of the event or the new information.

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.

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).

External adverse event: From the perspective of the REB overseeing one or 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.

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 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.

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).

Periodic Safety Update Report (PSUR): 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.

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. Throughout this document "REB" refers to "REB of Record".

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 judgment, 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.

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.

Unanticipated Problem: Any incident, experience, or outcome (including an SAE, MDSAE, or UADR) 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.