GUIDANCE NOTES FOR REPORTING UNANTICIPATED PROBLEMS TO THE FHREB

INTRODUCTION

The purpose of this Guidance Note is to instruct investigators on the Fraser Health Research Ethics Board (FHREB) requirements for reporting unanticipated problems to the ethics board. The Guidance Notes (GN), which is comprised of the Fraser Health Research Ethics Board's (FHREB) standard operating policies and procedures, are intended to ensure that the researcher has the necessary information to correctly report unanticipated problems including local and non-local serious adverse events (SAEs) to the FHREB. These Guidance Notes have been adapted with the permission of the University of British Columbia. The Guidance Notes are not meant to be a substitute. Please refer to the original documents highlighted in the document for complete information.
For multijurisdictional studies where the FHREB is the Board of Record (BoR), where applicable, the event should be reported via UBC RISe.
For Fraser Health only studies, the unanticipated event where applicable should be reported via the ROMEO Research Platform. A Request for Acknowledgment event form must be submitted.

The FHREB operates under the authority of the current Fraser Health Research Policy and The Ethical Conduct of Research and Other Studies Involving Human Participants.

FHREB policies/procedures correspond to the ICH Good Clinical Practice (ICH GCP) Guidelines. Specifically, the FHREB requirements for submitting adverse event reports follow Health Canada's mandatory reporting requirements for serious and unexpected adverse drug reactions and for incidents involving medical devices.

GUIDANCE NOTE #1: REGULATORY REQUIREMENTS

In Canada, under the Food and Drug Act Regulations Division 5, Clinical Trials, a clinical trial sponsor is legally required to report serious unexpected adverse drug reactions to the Minister (Health Canada) either within 15 days (not fatal or life-threatening) or within 7 days (fatal or life threatening) of becoming aware of the information.

The ICH Good Clinical Practice Guidelines stipulate that Research Ethics Boards must establish, document in writing and follow procedures for:

- Determining the frequency of continuing review as appropriate (including adverse drug reactions and adverse events) and
- Requiring that the Investigator should promptly report to the REB
- Changes increasing the risk to participants and/or affecting significantly the conduct of the trial;
- All adverse drug reactions that are both serious and unexpected
- New information may affect adversely, the safety of the participants or the conduct of the trial.

In the United States, US Federal Regulations require REBs to have among other things, information concerning unanticipated problems involving risk to human participants in the study, including adverse events (AE's) that are considered unanticipated problems (21 CFR 56.108)

Investigators are reminded that in addition to being required to report serious and unexpected adverse events / reactions to the REB, they are required to report such events to the study sponsor and, appropriate Health Canada agencies where applicable. The Office of Research Ethics will report all reportable unanticipated

problems to the Office of Human Protections or the US Food & Drug Administration, if the unanticipated problem occurs in a study that is funded by or supported by the US Federal Government or that is subject to the U.S. Food & Drug Regulations. Investigators MUST indicate in the Request for Acknowledgement form that the unanticipated problem relates to a US funded or regulated study, including providing where applicable, the US IND or IDE number.

GUIDANCE NOTE #2: DEFINITIONS

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.

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.

Non-Local (External) Adverse Event: From the perspective of the REB overseeing one of 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.

Adverse Reaction: Any response to a drug, biologic, or natural health product which is noxious and unintended, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function. A reaction, as opposed to an adverse event, is characterized by the fact that a causal relationship between the product and the occurrence is suspected (i.e. judged to be at least a reasonably possibility).

Serious Adverse Event (SAE): Any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Based upon appropriate medical judgement, is an important medical event that may jeopardize the patient 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 or package insert/summary of product characteristics for an approved product).

Medical Device Serious Adverse Event (MDSAE): An adverse event associated with a medical device complaint meets the criteria of a medical device SAE when both of the following are fulfilled:

- The event involves contact with the medical device **and**
- The event results in death or serious deterioration in state of health. This includes:
    - Life-threatening illness or injury
    - Permanent impairment of a body function
    - Permanent damage to a body structure
    - A condition that requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

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.

New Information is defined in the Request for Acknowledgement Guidelines.

GUIDANCE NOTE #3: REB REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS LOCAL and NON-LOCAL

3.1. Local Serious Adverse Events:

Only those local (internal) serious adverse events that meet the definition of an **unanticipated problem** (i.e. unexpected, related and involving greater risk – see definition above) are required to be reported to the REB. Local serious adverse events that meet the definition of an unanticipated problem should be reported to the REB promptly, but in any case no later than **seven (7)** days subsequent to the occurrence of the local event. Such events should be reported using the REQUEST FOR ACKNOWLEDGEMENT FORM on the ROMEO Research Platform, and should include:

- The status of the study and summary of participants enrolled
- A detailed description of the local event including an assessment as to whether the event reaction was mild, moderate or severe
- 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

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

3.2. Non-Local Serious Adverse Events:

The Fraser Health REB has adopted the CAREB Guidance on Reporting on Unanticipated Problems including Adverse Events to Research Ethics Board in Canada (July, 2010) for reporting non-local (external)serious adverse events.

In accordance with the CAREB Guidance, non-local serious adverse events should be reported to the REB in the form of **periodic safety update reports,** accompanied by information that is meaningful and of use to the REB. The contents of the safety report(s) should, 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. 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 for annual safety reports is acceptable. Such reports should be submitted using the request for acknowledgment form on the ROMEO Research Platform.

The FHREB will ONLY accept individual case reports of non-local (external) SAE's if they are unanticipated problems. 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

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

3.3. International Safety Reports:

Submit International Safety Reports (i.e. CIOMS reports, Medwatch letters, Dear Investigator letters), as a request for acknowledgement on the ROMEO Research Platform.

3.4 Updated Investigator Brochures:

Updated Investigator Brochures and any addendums should be submitted as an acknowledgement request on the ROMEO Research Platform, unless it is accompanied by changes to the protocol and/or consent form, in which case all documents should be submitted as an amendment via the ROMEO Research Platform.

3.5. Summary Reports:

Summary Reports, including periodic line listings submitted in accordance with the provisions of the European Union directive or the FDA Guidance on Adverse Event Reporting to IRB's, should be submitted as a request for acknowledgement on the ROMEO Research Platform.

3.6. Data Safety Monitoring Board Reports:

Data Safety Monitoring Board reports should be submitted as soon as possible following receipt by the Principal Investigator, as a request for acknowledgement using the event form on the ROMEO Research Platform.

GUIDANCE NOTE #4: REB ACKNOWLEDGEMENT OF SAE REPORTS

There is no Canadian regulatory requirement for REB acknowledgement to investigators for the submission of serious and unexpected SAEs. However, an acknowledgement certificate from the FHREB will be issued to the researcher following the review.