

GUIDANCE NOTES FOR REPORTING LOCAL AND NON-LOCAL SERIOUS AND UNEXPECTED ADVERSE EVENTS AND TO THE REB

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INTRODUCTION

The following notes are intended to explain the information that must be submitted to the UBC C&W REB to Report Serious and Unexpected Adverse Events

ARTICLE #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 subjects 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 subjects 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 subjects in the study, including adverse events (AE's) that are considered unanticipated problems (21 CFR 56.108(a)(3)(4)(b) [FDA CRF 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, appropriate Health Canada agencies, the FDA and the US Department of Health and Human Services where applicable. [OHRP & HHS Guidance](#)

1.1. Definitions

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 reasonable 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
- 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: 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: 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.

New Information and Unanticipated problems are defined in and should be submitted under the Request for Acknowledgment Guidelines.

ARTICLE NUMBER #2: REB REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS LOCAL and NON-LOCAL

2.1. Local Serious Adverse Events: Local serious adverse events are all adverse drug reactions or adverse events which are **both** serious and unexpected, or all unanticipated medical device SAE's that occur at the UBC site for the study, **and** that are related or possibly related to the study drug or treatment. Local serious adverse events 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**, 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

2.2. Non-Local Serious Adverse Events: Non-local serious adverse events are all adverse drug reactions or adverse events which are **both** serious and unexpected and/or all unanticipated medical device SAE's that occur at other (non-UBC) sites **and** that are related or possibly related to the study drug or treatment **and** (as articulated by the US Department of Health and Human Services and the U.S. Food and Drug Administration in the January 2009 "Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting" ([FDA Guidance](#)) that would have implications for the conduct of the study (e.g. requiring a significant and usually safety-related change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent or investigator's brochure. An individual adverse event occurrence very rarely constitutes such an event. UBC's REBs have adopted the CAREB Guidance dated August, 2009. In accordance with the CAREB Guidance, non-local (external) serious adverse events should be reported to the REB **in the form of periodic summary reports**, accompanied by information that is meaningful and of use to the REB. The contents of the summary report(s) should ordinarily 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. Such reports should be submitted using the **REQUEST FOR ACKNOWLEDGEMENT FORM**.

UBC's REBs will ONLY accept individual case reports of non-local (external) SAE's in the exceptional circumstances noted in the FDA Guidance. Accordingly, such reports should only be submitted to the UBC REB if the individual non-local SAE is unexpected (not known to be associated with the underlying condition for which the experimental agent or device is being used and not previously associated with the experimental agent or device as described in the consent document(s)) and strongly associated with drug or device exposure,. Similarly, one or a small number of serious adverse events that are associated with drug or device exposure, but that are otherwise uncommon in the study population (e.g. tendon rupture, progressive multifocal leukoencephalopathy) should be considered a reportable event. **Individual reports meeting these criteria are acceptable, but only if they contain a sponsor analysis of the significance of the event or perhaps such an analysis from an independent DSMB and if applicable a corrective**

action plan. Such reports should be submitted using the Request for Acknowledgement Form.

NOTE: SAEs to be reported to the BC Cancer Agency REB must be submitted using the BCCA REB SAE Database (refer to [BCCA SAE](#)). The RISE system may ONLY be used if either of the following applies;

1. If the Study is not yet "activated", then the RISE system may be used to submit these as a Request for Acknowledgment, (**once the study is activated, you must use the BCCA REB SAE database**).

2. If the BCCA REB has granted permission to use RISE because you cannot be granted access to the BCCA SAE database. (To request access to the BCCA REB SAE database, contact the BCCA REB Administration: reb@bccancer.bc.ca)

2.3. International Safety Reports: Submit International Safety Reports (i.e. CIOMS reports, Medwatch letters, Dear Investigator letters), using the **REQUEST FOR ACKNOWLEDGEMENT FORM** and procedure.

2.4 Updated Investigator Brochures: Updated Investigator Brochures and any addendums should be submitted as an amendment so that the current version will be readily accessible in the document section of RISE application along with the current approved protocol and consent.

2.5. 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 using the **REQUEST FOR ACKNOWLEDGEMENT FORM** and procedure.

2.6. Data Safety Monitoring Board Reports: Data Safety Monitoring Board reports should be submitted as soon as possible following receipt by the Principal Investigator, using the **REQUEST FOR ACKNOWLEDGEMENT FORM** and procedure.

ARTICLE #3 REB ACKNOWLEDGEMENT OF SAE REPORTS

3.1. There is no Canadian regulatory requirement for REB acknowledgement to investigator's of the submission of serious and unexpected SAE's. However, an acknowledgment certificate will be issued within the RISE on-line system. The BCCA REB SAE database will automatically generate an acknowledgment upon entry into the BCCA REB SAE database.