Unless otherwise specified, the International Conference on Harmonization E-6 Guidelines for Good Clinical Practice (ICH GCP) definitions are used. However, the term “investigational product” is used in place of “medicinal product” and refers to new or new usages of drugs, biologics, medical devices or natural health products; and “research participant” is used in place of “clinical investigation subject.”

You may find the following concepts and definitions useful when completing this form:

**Unanticipated problems:**

Adverse effects or unexpected events resulting from the research must be reported to the REB Secretariat immediately by submitting the ‘Unanticipated Problem Form’. For some protocols, the Research Ethics Board (REB) may require that a monitoring committee be established.

The REB considers unanticipated problems, in general, to include 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; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The REB recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. The REB notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- Changes to the research protocol initiated by the investigator prior to obtaining REB approval to eliminate apparent immediate hazards to participants;
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring participants;
- Suspension of enrolment of new participants;
- Suspension of research procedures in currently enrolled participants;
- Modification of informed consent documents to include a description of newly recognized risks; and
- Provision of additional information about newly recognized risks to previously enrolled participants.
Office of Research Ethics
Unanticipated Problem Guidance Form

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.

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: local adverse events are 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.

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. The phrase “responses to an investigational product” means 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).

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.

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 involves a medical device and results in death or serious deterioration in 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.

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). 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.
## Office of Research Ethics

### Unanticipated Problem Guidance Form

**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.

### Periodic 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.

### Clinical Trial section of the Unanticipated Problem Report

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 that may adversely affect 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.

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.