	REB REVIEW OF RESEARCH	
POLICY: REB-407	**UNANTICIPATED PROBLEMS**	
This policy pertains to:	The activities of researchers operating under the authority of Baycrest and the Research Ethics Board (REB) operating under the authority of Baycrest	
Responsibility for executing this policy:	Chair, Baycrest REB (or designate)	
Approval authority:	Chair, Baycrest REB President & Chief Scientist, Baycrest Academy for Research and Education	
Effective Dated:	October 15, 2025	**Supersedes documents dated:** September 26, 2013
Approved:	Chair, Baycrest REB President & Chief Scientist, Baycrest Academy for Research and Education	

1. PURPOSE

The purpose of this SOP is to describe the reporting requirements of unanticipated problems to the Baycrest REB.

2. POLICY

REFERENCES

In addition to scheduled annual (interval) renewal, the REB must receive information about and review unanticipated problems that may affect the safety, rights, and well-being of research participants.

TCPS2 Article 6.15
45 CFR 46.103(5i)
21 CFR 56.108(b1)

3. DEFINITIONS

Unanticipated Problem: Any incident, experience, or outcome that meet 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 and (b) the characteristics of the population being studied;
2) Related or possibly related to participation in the research (i.e., at least a reasonable possibility exists that the incident, experience, or outcome may have been caused by the drugs, devices, or procedures involved in the research); and
3) 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.

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 subjects or others.

ICH GCP E6 (R2)
Health Canada Food and Drugs Act, Div 5, C.05.001

Adverse Event (AE): any untoward medical occurrence in a research participant given an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an

abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Non-Local (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 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).

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 the 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".*

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR): any untoward medical occurrence that at any dose:

- 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 study 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 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.

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. Unless, however, the event is a routine safety letter, DSMB report, summary report or changes to the Investigator's Brochure that are minor and/or routine in nature, **all new information and unanticipated problems must be reported as soon as possible after** the incident, occurrence, outcome event, or the Investigator's receipt of the notice of the event or the new information.

Periodic Safety Update Report: A summary report, created by the sponsor, listing all of the suspected unexpected serious adverse reactions (SUSARs) 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.

Health Canada Food and Drugs Act, Div 5/ ICH GCP E6 (R2)

HHS regulations at 45 CFR part 46

4. SPECIFIC POLICIES

4.1. Unanticipated Problems that are Adverse Events

Only a small subset of adverse events occurring in research participants will meet the criteria for an unanticipated problem. An adverse event may be considered unexpected if it occurs in a research participant where the nature, severity, or frequency is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the REB-approved research protocol, investigator brochure, and informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

IHC GCP 5.17.1

- the expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event.

4.1.1 Local (internal) adverse events

The PI must report to the Baycrest REB only those local adverse events that are deemed to be *unanticipated problems*. If the investigator determines that an adverse event is not an unanticipated problem, but the sponsor subsequently determines that it is, the sponsor must report this determination to the PI, and such reports must then be submitted to the REB. The PI must clearly explain how the event represents an unanticipated problem. A description of any proposed protocol changes or other corrective actions to be taken by the local Principal Investigator or sponsor in response to the event must also be described in the report.

4.1.2 Non-local (external) adverse events:

Single isolated external adverse events rarely meet the requirements for reporting to REBs. Individual external adverse events should be reported when a determination has been made that the event meets all of the criteria for an unanticipated problem. Individual isolated external adverse events should be reported to the REB if they are unanticipated problems and the report includes all of the following information:

- the event described is both **serious and unexpected**
- the report identifies all previous safety reports concerning similar adverse experiences
- the report analyzes the significance of the current adverse experience in light of the previous reports and
- the report outlines any proposed protocol changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the unanticipated problems.

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

4.2 Other Unanticipated Problems Not Considered Adverse Events

There may be other incidents, experiences, or outcomes not considered adverse events but that meet the definition of unanticipated problems; such events, in the opinion of the PI or sponsor, place research participants or others at a greater risk of physical or psychological harm. This may include:

- A significant hazard to the research participant population, such as lack of efficacy with an investigational product used in treating life-threatening disease,
- Breaches of privacy and confidentiality,
- Acts of nature that impact the study conduct or data integrity (e.g., floods, hurricanes, earthquakes, pandemics, etc.)

4.3 Unanticipated Problem Reporting – Adverse Events

4.3.1 Responsibility of the Sponsor and Investigator

Local unanticipated problems must be reported to the REB as soon as possible. Fatal or life-threatening local unanticipated problems must be reported to the REB immediately.

Periodic safety update reports, external study serious adverse events, and other local unanticipated problems must be reported to the REB as soon as possible.

The local Principal Investigator must continue to report unanticipated problems to the REB for the duration of the study (i.e., until the study is closed at the principal investigator's institution). If arrangements have been made for the sponsor to report the unanticipated problem directly to the REB, the LPI should not provide the REB with a duplicate copy of the report(s) received from the sponsor.

Health Canada Food and Drugs Act, Div 5/ICH GCP E6 (R2)

Local unanticipated problems occurring in research covered by a US Office for Human Research Protections (OHRP) approved assurance also must be reported by the institution to the supporting US Department of Human Health Services agency head (or designee) and OHRP.

Unanticipated Problem Reporting - Breaches of Confidentiality and Privacy

Research staff must notify the Research Ethics Office staff member for all suspected Research breaches of privacy.

The REB will communicate with PI and the Privacy Office will be notified accordingly. The REB Chair will determine the appropriate management plan.

When required, the BARE Privacy Office will notify the Provincial Privacy office about the breach. The REB Chair or designate will be consulted.

Please refer to the Baycrest Academy Privacy Policy for the Privacy breach protocol.

4.3.2 Content of Reports of Unanticipated Problems

Reports of unanticipated problems shall be submitted to the REB using the Baycrest REB Adverse Event/Unanticipated Problem Report Form and shall include:

- A detailed description of the event and, if the event is local, an assessment as to whether the event reaction was mild, moderate, or severe
- An opinion expressed by the investigator (if local) or the sponsor (if a qualifying reportable non-local adverse event) that the event is both serious and unexpected and a justification of that opinion
- An opinion expressed by the investigator (if local) or the

sponsor (if a qualifying reportable non-local adverse event) 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 investigator (if local) or the sponsor (if a qualifying reportable non-local adverse event) respecting the implications of the event 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 response or action taken and the patient outcome of the event.

4.4 REB Review of Unanticipated Problems

Unanticipated problems will be reviewed by the REB Chair or a delegated REB member. The Chair or other assigned REB member may choose to act on the information immediately (e.g., suspend enrolment); however, unexpected *serious* adverse events that are assessed to be unanticipated problems will be reported to the full REB at the next convened meeting.

When reviewing a report of an unanticipated problem, the REB will assess the appropriateness of any proposed corrective or preventative measures by the sponsor and/or PI, consider any additional appropriate measures that may or may not have been identified or proposed by the sponsor and/or PI, and consider whether the affected research still satisfies the requirements for REB approval.

In particular, the REB will consider whether risks to research participants are still minimized and reasonable in relation to the anticipated benefits, if any, to the research participants and the importance of the knowledge that may reasonably be expected to result.

Corrective actions or substantive changes required by the REB may include:
- Implementation of additional procedures for monitoring research participants;
- Suspension of enrollment of new research participants;
- Suspension of research procedures on currently enrolled research 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 research participants.