

SickKids REB Adverse Events and Unanticipated Problem (UP) Reporting Guidance

INTRODUCTION

The SickKids Research Ethics Board (REB) has adopted the Canadian Association of Research Ethics Boards (CAREB)' [“Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada”](#). The guidance herein is also developed based on the Office for Human Research Protections (OHRP) and Federal Drug Association (FDA) guidance documents. The purpose of this guidance document is to assist the SickKids research community in understanding the requirements for submitting reports of Adverse Events and Unanticipated Problems (UPs) and reporting timelines to the SickKids REB.

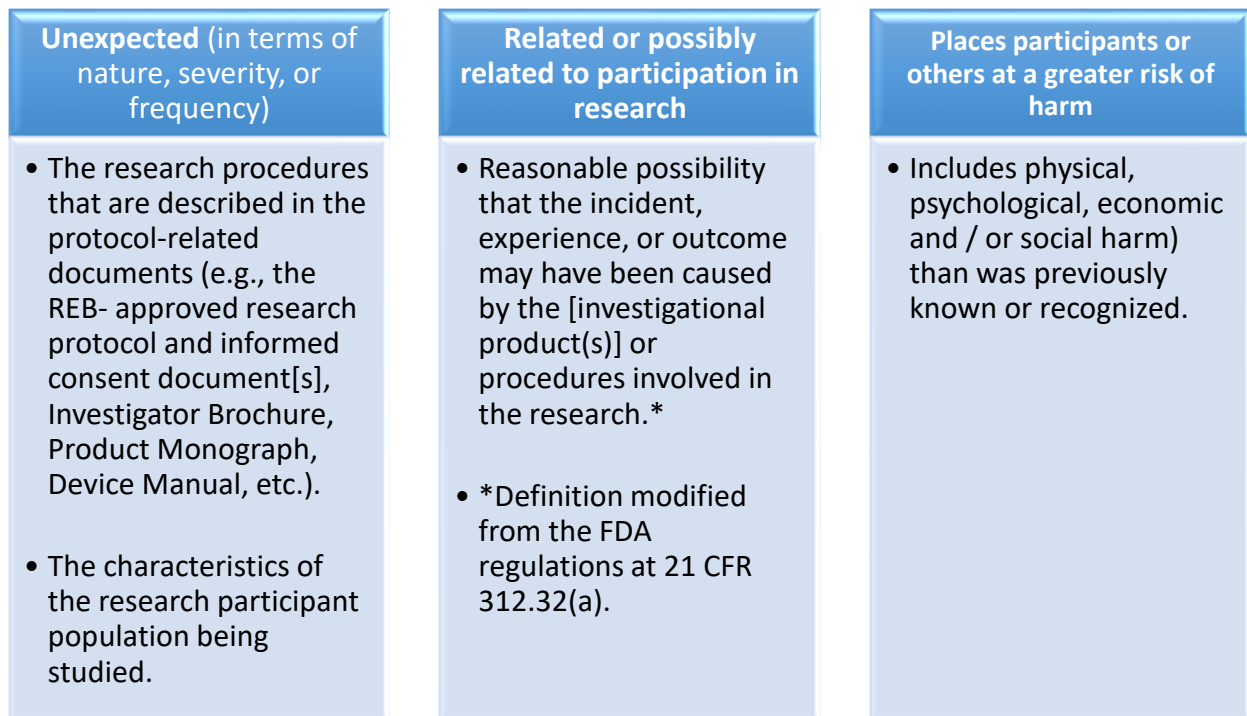
DEFINITIONS

The following section provides common definitions, which are based on the International Conference on Harmonization E-6 Guidelines for Good Clinical Practice (ICH GCP).

Type of Event	Definition
Adverse Event (AE)	<ul style="list-style-type: none"> Any untoward occurrence or unfavourable and unintended sign, symptom or disease that impacts the health or well-being of a research participant who is administered an investigational product or any other research procedure(s), and which does not necessarily have a causal relationship with this [product].
Serious Adverse Event/Experience (SAE) or Reaction	<ul style="list-style-type: none"> 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.
Local (Internal) Adverse Event	<ul style="list-style-type: none"> AEs experienced by research participants enrolled by the investigator(s) at one or more centers under the jurisdiction of the REB of Record.* In the context of a single-center clinical trial, all AEs would be considered local AEs. <div style="border: 2px solid red; padding: 5px; margin-top: 10px;"> <p>*REB of Record or Board of Record: the REB that has been granted ultimate authority for the ethics review & oversight of a research study.</p> </div>

Type of Event	Definition
External (Non-Local) Adverse Event	<ul style="list-style-type: none"> • AEs experienced by research participants enrolled by investigator(s) at other centers / institutions outside the REB of Record’s jurisdiction.
Adverse Drug Reaction (ADR)	<ul style="list-style-type: none"> • All noxious & unintended responses to an investigational product [which includes natural health products and biologics] related to any dose should be considered adverse drug reactions. <ul style="list-style-type: none"> ➤ Responses to an investigational product means that a causal relationship between the investigational product & an AE is at least a reasonable possibility

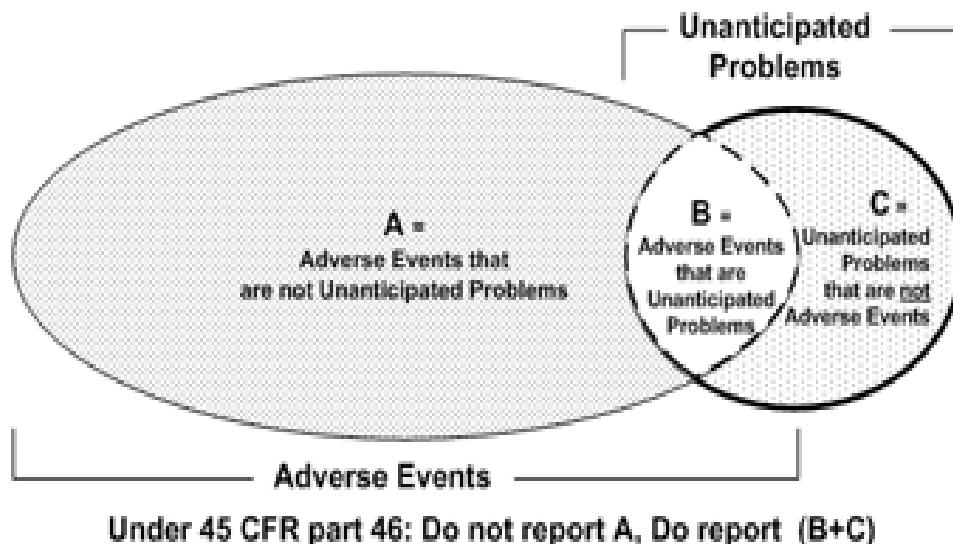
Unanticipated Problems (UPs). any incident, event, experience, or outcome that meets all of the following criteria (CAREB; 2010):



UNDERSTANDING THE RELATIONSHIP BETWEEN ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

The SickKids REB notes that an incident, experience, or outcome that meets the **three criteria above related to UPs** generally will warrant consideration of substantive changes in the research protocol, informed consent process / document or other corrective actions in order to protect the safety, welfare, or rights of participants or others. The diagram illustrates three key points:

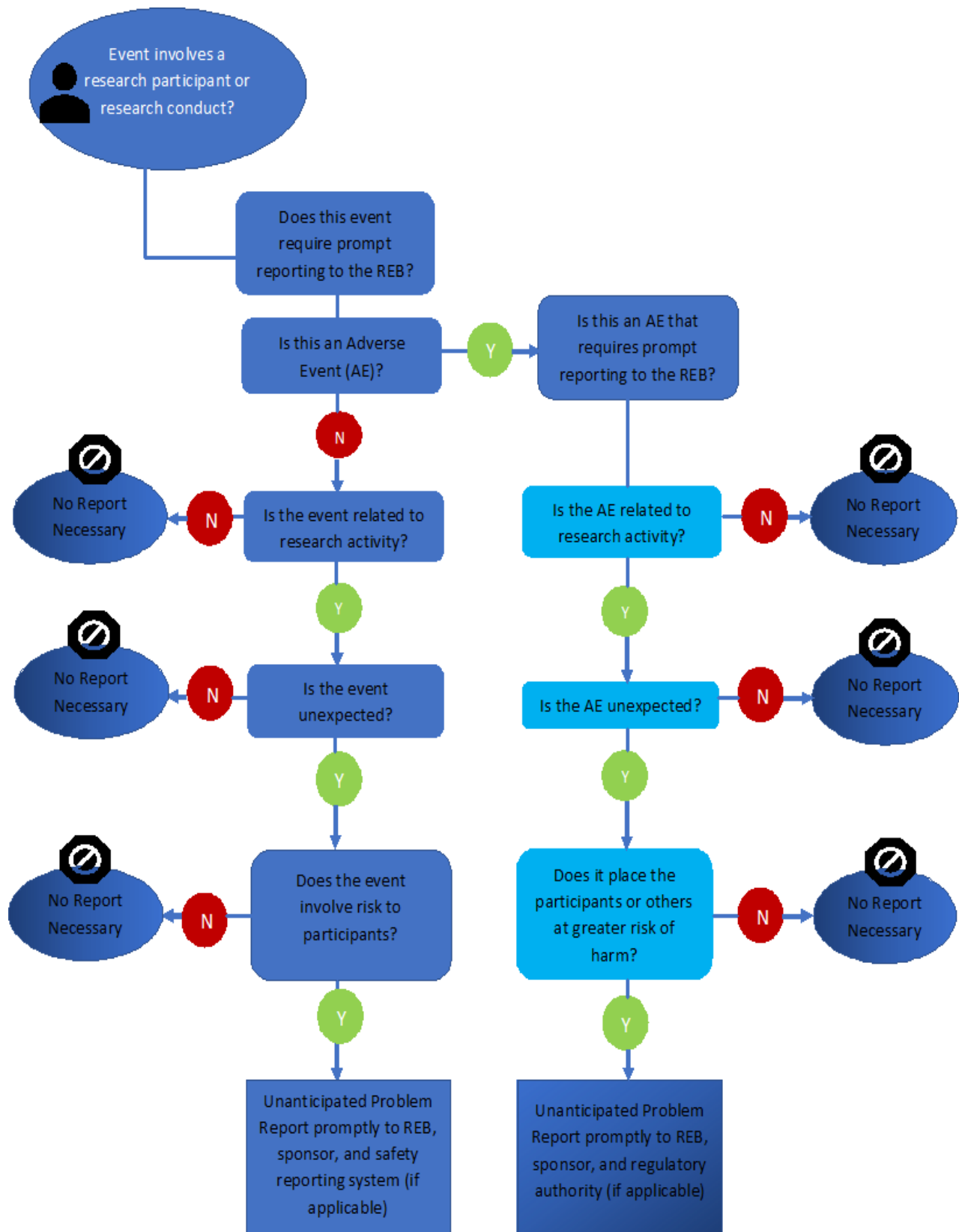
1. The vast majority of Adverse Events occurring in human subjects are not Unanticipated Problems (**Area A**).
2. A small proportion of Adverse Events are Unanticipated Problems (**Area B**)
3. Unanticipated Problems include other incidents, experiences, and outcomes that are not adverse events (**Area C**).



Under 45 CFR Part 46: Do not Report A; Report B and C.

The flowchart below provides an algorithm for determining whether an AE represents an Unanticipated Problem that needs to be reported under 45 CFR Part 46.

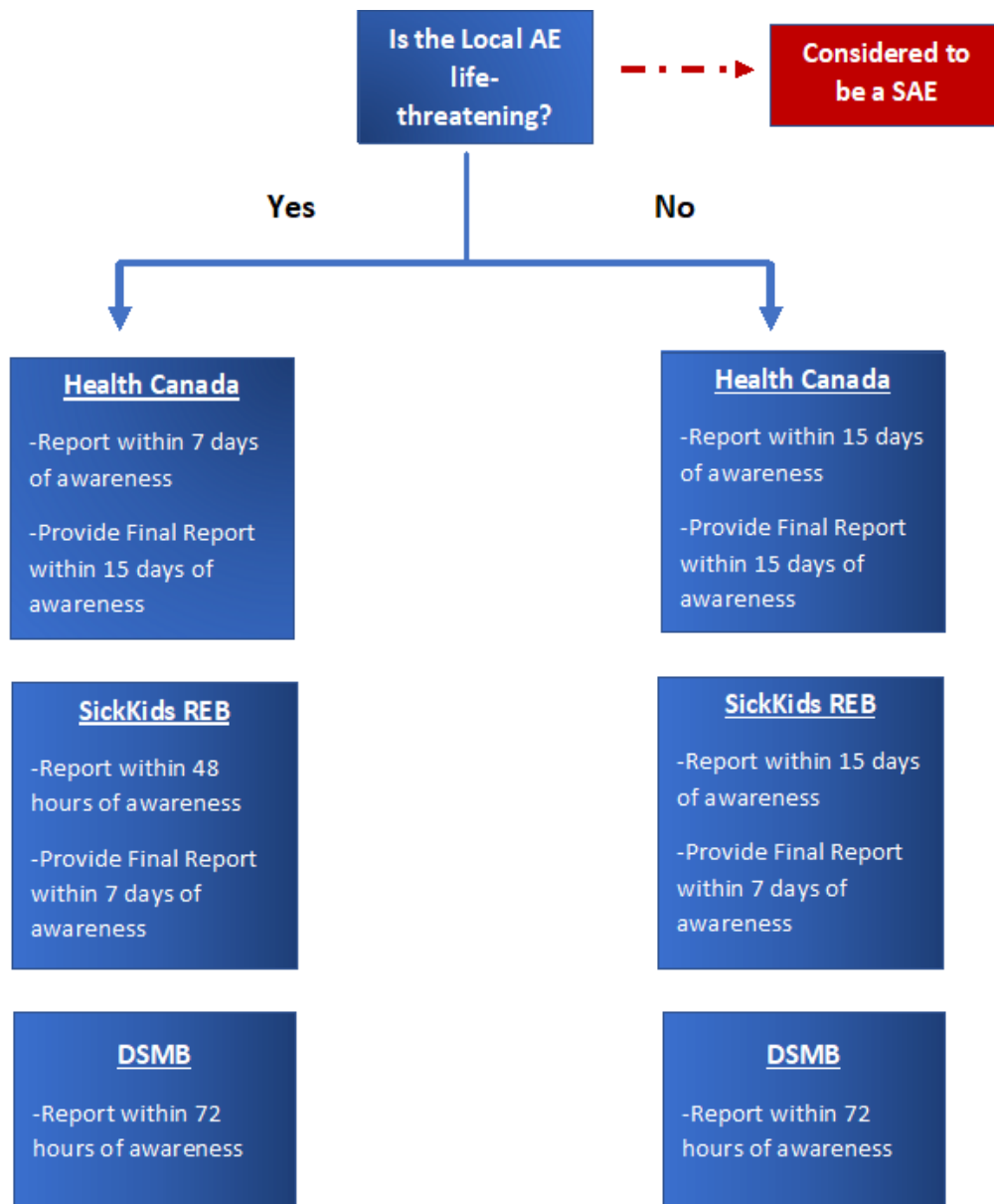
Flow Chart: Algorithm for Determining Whether an Adverse Event Represents an Unanticipated Problem



REPORTING LOCAL (INTERNAL) ADVERSE EVENTS TO THE REB

A Local (Internal) Adverse Event is required to be reported to REB only if it is assessed by the Principal Investigator (PI) / Qualified Investigator (QI) to be an **Unanticipated Problem** based on the following criteria: unexpected, related to research, and if it places the participants or others at greater risk of harm.

Reporting Timeline of Local (Internal) AE



REPORTING EXTERNAL (NON-LOCAL) ADVERSE EVENTS TO THE REB

Only AE External reports that meet the definition of an **Unanticipated Problem** should be shared with the REB; the investigator should store external reports in their study binders but need not forward these to the REB.

- The AE External Report is to be submitted to the SickKids REB within **seven (7) calendar days** after the study team has received the report.
 - Sponsor's letters often state that the report should be filed with the REB if required by local policy.
- Reports that suggest that participants or others are placed at a greater risk of harm than initially anticipated **should be accompanied** by an **Action Plan** that outlines the steps that will be taken to mitigate the newly identified risk(s).

If the sponsor of a multicenter study does not propose any changes, it is suggestive that the event **does not meet** all of the criteria for a UP.

The **Action Plan** should include one or more of the following:

- A modification to the protocol
- A modification to the consent form
- A change in the study procedures
- Changes to the investigative team education or oversight procedures; and / or
- A notification of current or former study participants

REPORTING UNANTICIPATED PROBLEMS TO THE REB: WHAT TO INCLUDE?

Event Information	Response Plan (Including additional follow-up)
<ul style="list-style-type: none"> • Date the PI / study team member became aware of the event, how they became aware. 	<ul style="list-style-type: none"> • Describe actions planned / taken to address the event and to reduce the likelihood of the event happening again.
<ul style="list-style-type: none"> • Describe the problem / event, including the nature & severity of the problem, who the UP affects, and the outcome of the event. <ul style="list-style-type: none"> ➤ NOTE: When submitting a UP report in the eREB, please provide as much detail about the event as possible. 	<ul style="list-style-type: none"> • Plan to inform local research participants, regulatory sponsors / funders, institution about the UP, if applicable.
<ul style="list-style-type: none"> • Some of the questions in the eREB UP Application form may not ask questions that are relevant to your event. If this is the case, answer the questions as best as possible and use the box at the end of the form section to provide any further details. 	

ADDITIONAL REPORTING REQUIREMENTS

In addition to reporting UPs to the SickKids REB, there are also other regulatory and Institutional reporting requirements that must be met.

Some events may not meet the UP-reporting requirements; however, they must be reported appropriately to the sponsor, regulatory authority, or hospital. Below is a summary of additional reporting requirements.

Internal Hospital Reporting Requirements

- If a Serious Adverse Event / Medical event occurs in the hospital, it must also be reported to the [Safety Reporting System](#)

Privacy Incidents – Reported to Safety Reporting System

- The [Safety Reporting System](#) is an online tool that captures safety events, safety concerns, hazards and breaches.

Any SickKids staff member (employees, physicians, and volunteers) can complete a safety report.

- Safety reporting facilitates the identification, trending and communication of safety issues. Event follow up allows for the identification of opportunities for system improvement with the goals of preventing similar situations to keep patients and staff safe.
- **Submission:** Safety Reports should be submitted as soon as possible after an event has occurred or is identified.

Safety reports allow the hospital to monitor and trend safety issues, identify improvement priorities and learn from experience. The resulting analysis triggers action on system-wide safety issues.



Regulatory, Sponsor and / or Funder:

- An Investigator who also fulfills the role of the study sponsor may have additional duties related to reporting UP's
 - I.e., to the institution, Health Canada and / or other sponsors, agencies or institutions irrespective of whether or not the event constitutes a UP at SickKids
 - Regulators, Sponsors, Funders and Institutions may have different definitions & categorizations for the events covered by this REB guidance document, as well as documentation and reporting requirements.

It is the responsibility of the Investigator to familiarize themselves with and follow the requirements applicable to their study. Refer to the Safety Reporting to Health Canada Document.

Participants and Families:

- It is strongly recommended that researchers consult with independent clinicians and / or the REB when trying to assess events as Unanticipated Problems (UPs).
- Researchers should always inform research study participants and / or their family members once an UP has been determined.