Reporting of Unanticipated Problems (UP) including Serious Adverse Events and Protocol Deviations by Investigators to the SickKids Research Ethics Board

Revised April 21, 2014

BACKGROUND

This document is based on definitions and requirements stated in the Canadian Association of Research Ethics Boards (CAREB) Guidance on Reporting of Unanticipated Problems including Adverse Events (AEs) to Research Ethics Boards in Canada and the Tri-Council Policy Statement 2(TCPS 2).

Both documents were released in response to concerns related to over-reporting of internal and external AEs to REBs. The high volumes of single isolated AEs make it difficult to make meaningful judgments based on these reports. The purpose of this document is to revise the reporting system and to focus on relevant events, called Unanticipated Problems (UP) in accordance with CAREB guidance and the TCPS2. This document replaces the previous REB Adverse Event Reporting Guidelines.

The recommendations stated in this document also meet the requirements of the International Conference of Harmonization (ICH) Good Clinical Practice (GCP), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) and Health Canada guidances.

The reporting requirements in this document are directed towards Principal Investigators and research team members conducting clinical research at SickKids and outline the reporting requirements of the SickKids REB. This document clarifies which UP must be reported to the REB in expedited (timely) fashion, and which should be reported yearly as Summary Safety Updates, or Periodic Safety Update Reports. [Note: An Investigator who also fulfills the role of sponsor may have additional duties related to reporting AEs, ie. to Health Canada and/or other sponsors, agencies or institutions; these responsibilities are not covered by this document.

DEFINITIONS

**Adverse Event (AE)**

Any untoward medical occurrence experienced by 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 unfavorable 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 another centre/institution outside the SickKids REB’s direct oversight. (see REB Terms of Reference)

**Internal (Local) adverse event**

Internal 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 SickKids REB. In the context of a single-centre clinical trial, all adverse events would be considered internal 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).
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 event¹.

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 damage¹.⁶.

Serious Adverse Event (SAE) or Reaction
Defined as any untoward medical occurrence that includes one or more of:
- 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 health of the research participant or may require medical intervention to prevent one of the outcomes listed above.

Unanticipated Problem (UP)¹
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, 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, ethical or social harm) than was previously known or recognized¹.

Development Safety Update Report (DSUR)
Data and findings from interventional clinical trials* (hereafter referred to as “clinical trials”) of drugs and biologicals that are under investigation, whether or not they have a marketing approval⁷

Periodic Safety Update Report (PSUR)
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.⁸

REB of Record
The REB granted authority by SickKids for the ethical review and oversight of research conducted by SickKids researchers. Throughout this document “REB” refers to SickKids REB or an appropriately mandated REB of Record, a term widely adopted in the Canadian research ethics environment. It can refer to a local REB or to an external REB (including a central REB) providing ethics review and oversight for multiple institutions
Protocol deviation
Any planned or unforeseen diversion from the REB approved protocol and/or approved study procedures. These typically occur as a single event or involve a single participant and are not intended as a modification to the protocol as a whole.

REPORTING REQUIREMENTS

Unanticipated events that must be reported to the SickKids REB

1. Adverse Events

a) Internal (Local)
Adverse events that have been assessed by the investigators as meeting the criteria of a UP (ie unexpected, related and involve greater risk) as defined above. In circumstances where investigators have sponsor obligations it is the responsibility of the investigator to understand and comply with sponsor requirements which may preclude the UP criteria as defined above and may require reporting to other sites or regulatory agencies.

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

b) External (non-local)
Serious adverse events that meet all three criteria of a UP (ie unexpected, related and involve greater risk) as assessed and determined by the sponsor. Individual isolated external adverse events should only 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 problem

Additional information about External Reporting
The reporting of UPs from external institutions to the SickKids REB should continue only until the study is terminated at SickKids.

2. Other Unanticipated Problems (non-SAEs)

Other Unanticipated Problems (non-SAEs) that may influence benefit-risk assessment and prompt change of study procedures, study documents and/or require notifying research participants because of changed risk/benefit ratio events should only be reported to the REB if they are unanticipated problem.
These may include:
- Increase of rate of occurrence of expected Serious, related AEs
- A significant hazard to participants, eg. Lack of efficacy of the investigational product used in life-threatening disease
- A major safety finding from newly completed animal studies, suggesting significant risk to participants, e.g. carcinogenicity
- Breaches of privacy and confidentiality in the conduct of the research
- Medically Significant Protocol Deviations
- Acts of nature that impact study data or data integrity
- All study related participant Complaints
3. **Protocol Deviations**

Good documentation practices dictate that all protocol deviations be documented, including the rationale/justification for the deviation and PI sign-off. These should be kept in a deviations log in the study documentation that is maintained by the PI.

Investigators must determine whether the protocol deviation alters the level of risk or harm to research participants (or has other ethical implications for participants) and if this meets the criteria of Unanticipated Problems. Reportable protocol deviations that meet the criteria of a UP and must be reported to the SickKids REB in expedited fashion are those that:

- Impact the patient’s rights, safety or welfare,
- Impact study efficacy
- Impact data integrity

Protocol deviations that are planned in order to protect research participants from imminent physical or psychological harm based on new information obtained during the course of the study must be reported to the REB along with the corresponding safety information and the PI’s plan to update the study as required. A protocol amendment should then be submitted to the REB.

Protocol deviations that meet the criteria of UP require expedited reporting to the REB. All other deviations can be summarized in annual status reports.

NB. Report submissions not meeting these reporting requirements for UPs will be returned to the submitter.

**EXPEDITED (TIMELY) REPORTING TIMELINES OF UPs**

All reportable UP should be reported to the REB using the Adverse Event and Unanticipated Problems Reporting Form.

Investigators should submit documentation from the sponsor including:

- Confirmation that the event has been assessed as both serious and unexpected,
- All previous relevant safety reports outlining similar events,
- The significance of the new adverse event as related to the previous reports
- An outline of any proposed actions and changes to the study documents including study protocol, consent forms that the Sponsor intends to make.

1. **Adverse Events**

   **a) Internal UP Reporting**
   All reportable internal UP must be reported to the REB within 15 calendar days from the day of the event.
   - Exception of death and life-threatening reportable local SAEs, which need REB notification within 48 hours and a full report to be submitted to the REB within 7 calendar days from the time of the event.

   **b) External UP Reporting**
   Reportable external SAEs should be submitted to the REB within 15 calendar days from the time the investigator became aware of them.
[Note: in order to meet FDA guidance related to medical devices in USA\textsuperscript{5}, the unanticipated adverse device effect must be reported by the investigator to the REB within \textit{10 working days}.]

2. \textbf{Other UP reporting}

All other events that influence the risk/benefit ratio for participants should be treated as UP and reported to the REB within \textbf{15 calendar days} from the day the investigator became aware of them using the \textit{Adverse Event and Unanticipated Problems Reporting form} (link).

- \textbf{Privacy breaches}  
  Privacy breaches related to research should be reported to the REB \textbf{within 15 calendar days} from the time the investigator became aware of them. The investigator must also notify the SickKids Privacy office through the SickKids Safety Reporting system.

- \textbf{Safety Updates}  
  Periodic Safety Update Reports and updates to product safety information such as Investigator Brochures, Product Monographs, Device Manuals, etc. should be reported only when the new information impacts the risk/benefit ratio for study participants and then \textbf{within 15 calendar days of receipt}. All changes to product information must be highlighted.

- \textbf{Change in Causality Assessment}  
  Causality of an AE must be determined by the sponsor or the investigator. In rare cases, if the investigator determines an AE is non-reportable (not related) but the sponsor, later, determines that the AE was related to the medicinal product, such an AE should be submitted to the REB promptly. The first report should be submitted to the REB \textbf{within 15 calendar days} from the causality decision, except in the case of death or life threatening reportable SAE’s which must be submitted to the REB \textbf{within 7 calendar days} from the time the investigator became aware of the change in causality decision.

3. \textbf{Protocol Deviations}

Deviations that are determined by the PI as meeting the criteria of UP should be reported to the REB \textbf{within 15 calendar days} from the time the PI becomes aware of the deviation.

Protocol Deviations that result in death and/or life threatening reportable local SAEs, need REB notification \textbf{within 48 hours} and a full report to be submitted to the REB \textbf{within 7 calendar days} from the time the investigator becomes aware of the deviation.

The PI is responsible for ensuring that all protocol deviations are reported to the sponsor according to the obligations outlined in their Sponsor Agreement.

\textbf{REPORTING PROBLEMS, INFORMATION OR EVENTS THAT DO NOT QUALIFY AS UP}

All problems/events that do NOT meet the definition of an UP can be reported to the REB in summary form (using a table or spreadsheet) at the time of Annual Continuing Review. Accompanying documentation (sponsor report forms, etc.) need NOT be included with this summary.

\textbf{Protocol Deviations}  
Some protocol deviations do not impact the safety, rights or wellbeing of research participants and they do not impact the study in a meaningful way. These typically involve only logistical or administrative aspects of the study. If the principal investigator determines the deviation is minor and has no impact on the study or welfare of participants, no further action is necessary and the deviation can be reported in the next REB annual progress report.
Summary Safety Updates
The periodic (yearly) analysis of safety information is crucial to the ongoing assessment of risk to trial participants. In industry-driven studies, the sponsor has an obligation to prepare a PSUR (Periodic Safety Update Report), a DSUR, and to update the Investigator’s Brochure on a yearly basis. Any of the 3 documents will fulfill the requirement for Summary Safety Updates to the REB. In cases, where such information does not exist (e.g. the study is sponsored by SickKids), the Summary Safety Update should be prepared by the Investigator.

Summary Safety Updates should be submitted yearly to the REB, as part of the annual renewal process. These can be submitted in table format and should include information that clarifies the type, relatedness and unexpectedness of each event and if any follow up action was executed. Each page of the table documents must be initialed by the PI.

SICKKIDS REB REVIEW & FOLLOW-UP OF UP
Completed UP forms are reviewed by the REB Chair or delegate, normally within 2 business days from receipt in the REB Office. At the Chair’s request, any other REB member may also review the report and provide their recommendations for any follow up action as needed. Other Hospital expertise e.g., Research Support Pharmacy may also be consulted when necessary. The primary investigator may be contacted for additional information or clarification.

The REB will determine any necessary follow up actions required e.g., revise the consent forms based on new information, inform current and/or past research participants, temporarily halt the study until further analysis etc. A process to show evidence that materials mailed or sent to participants or parents of participants regarding new information was received should also be provided.
A copy of the signed report with the REB’s required actions is sent to the investigator. All follow up actions recommended by the REB must be completed and documented by the PI. The REB should be informed of the implementation and completion of these actions by the study team by way of a follow up report within 15 days of receiving the initial signed report. When the REB is satisfied that all follow up activities have been completed the PI will receive notification by way of the returned, signed follow up report.

The persons or entity responsible for audits of these studies may be privy to and involved in the follow-up activities of any reported UP at the discretion of the REB.

Non-compliance with these requirements including non-adherence to reporting timeframes will be reviewed by the REB Chair and appropriate action taken.
References

7. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, E2F.

**SUMMARY OF REPORTING TIMELINES REFERENCE TABLE**

<table>
<thead>
<tr>
<th>Event</th>
<th>Reporting Timelines</th>
<th>Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal AE UP reporting</td>
<td>15 calendar days from the time of the event</td>
<td>Death or life threatening 48 hour notification; 7 days full report</td>
</tr>
<tr>
<td>External SAE UP reporting</td>
<td>15 calendar days from the day the PI becomes aware</td>
<td>Unanticipated adverse device effect – 10 working days</td>
</tr>
<tr>
<td>Other UP reporting (other events that influence risk/benefit ratio) including participant complaints</td>
<td>15 calendar days from the day the PI becomes aware</td>
<td></td>
</tr>
<tr>
<td>Privacy Breaches</td>
<td>15 calendar days from the day the PI becomes aware</td>
<td>Also notify SickKids Privacy Office</td>
</tr>
<tr>
<td>Periodic Safety Update Reports</td>
<td>15 calendar days from receipt</td>
<td>Only if new information impacts risk/benefit ratio</td>
</tr>
<tr>
<td>Causality Assessment change by Sponsor</td>
<td>15 calendar days from the decision</td>
<td>Death or life threatening 7 day full report</td>
</tr>
<tr>
<td>Summary Safety Updates</td>
<td>Annually with REB renewal</td>
<td></td>
</tr>
</tbody>
</table>