

Hospital for Sick Children (SickKids) Research Ethics Board Adverse Event Reporting Requirements

Introduction

Human subject research is subject to continuing ethics review by the REB. As described in Article 1.13 of the Tri-Council Policy Statement (TCPS), the REB review of adverse events is one component of its continuing review. For all drug studies in Canada, Health Canada Food & Drug (Division 5) regulations and ICH guidelines also apply. SickKids reporting requirements are based on these regulations and guidelines.

Adverse event reporting is the responsibility of the SickKids primary investigator who must complete the SickKids Adverse Event (AE) form including information on the seriousness of the adverse event, assessing whether or not it is a direct consequence of the research intervention and proposing any further action. Adverse events are reviewed promptly by the REB, normally within 2 business days, and any required followup communicated back to the primary investigator.

Definitions

Adverse Event (AE): An adverse event is any unfavorable or unintended clinical or other occurrence during the study period that may or may not be the result of participation in the research study.

ICH-Drug trial definition of Adverse Event (AE):

Any untoward medical occurrence

- In a patient or clinical investigation subject
- Following administration of a product or use of a medical device
- The event need not necessarily have a causal relationship with the treatment or usage.
- includes adverse reactions which are a noxious and unintended *response* to a medicinal product or to a medical or surgical device.

Examples of adverse events include;

- Clinically significant signs and symptoms
- Abnormal test findings eg., laboratory, x-ray, ECG
- Mild reactions or side effects that do not require treatment intervention eg., mild skin rash, mild headache, slight nausea
- A study interview that causes an unexpected emotional reaction
- Complaints about alleged research misconduct

Each adverse event can be classified according to severity or intensity and in relation to the study treatment;

Intensity Grades

- Mild: Does not interfere with subject's usual function

- Moderate: Interferes to some extent with usual function
- Severe: Interferes significantly with usual function

Serious Adverse Event (SAE):

Any untoward medical occurrence (at any dose *–for drug trials*) that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, *or*
- Is a congenital anomaly/birth defect
- Includes serious adverse reactions to drugs

AE Reporting Requirements of Investigators

1. Define and grade the event referring to the definitions noted above.
2. Report all local unexpected adverse events (not just unexpected, *serious* events) on the REB AE form (see enclosed). The REB is interested in increases in the rate of ‘non-serious’ events because these can also be clinically important.
3. For multi-site research projects, report all unexpected *serious* drug reactions experienced at study sites external to SickKids.
4. When followup reports are necessary, they must be clearly indicated as such on the AE form. The initial report should be appended to the followup report to facilitate review.

Report Timing

5. For unexpected adverse events, investigators are obliged to inform the REB, in addition to their clinical chief, and external sponsor (where applicable) within 7 days of learning of the event.
6. For unexpected **serious adverse events**, investigators are obliged to inform the REB, in addition to their clinical chief, and external sponsor (where applicable) immediately ie., within 48 hours of learning of the event (by AE form, telephone or email) **even if the information is incomplete**. A complete followup AE report should be submitted as soon as possible but no later than 7 days after the initial reporting.

Report Recipients

SickKids REB

7. All adverse events must be reported to the REB on individual SickKids AE forms. This standardized format facilitates the REB review of high volumes of AE reports. Any supporting documentation or safety reports generated by the study sponsor or other collaborating sites should be appended to the completed AE form.

Data Safety Monitoring Committee (DSMC)

8. If the study has a data safety monitoring committee (DSMC), adverse event reporting will be set out according to procedures set by the DSMC. Correspondence between the DSMC and investigator should be copied to the REB.

Collaborating Study Sites

9. If the research involves other study sites, the SickKids primary investigator must also submit to the SickKids REB information received from other sites. This information is frequently generated by study sponsors and along with supporting documentation should be appended to the SickKids AE form.

10. Conversely, adverse events that occur at SickKids should be communicated by the primary investigator to collaborating sites, as their local requirements dictate.

External Sponsors

11. All adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

Health Canada when SickKids is the Sponsor (PI-initiated protocols)

12. Only adverse drug reactions (ADR) that are both serious and unexpected are subject to expedited reporting to Health Canada *by the sponsor*. These include reactions;

- where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information
- a complete follow up report within 8 days which includes an assessment of the importance and implication of any findings including relevant previous experience with the same or similar drugs
- where it is neither fatal nor life-threatening within 15 days after becoming aware of the information

13. Each ADR which is subject to expedited reporting should be reported individually in accordance with the data element(s) specified in the Health Canada/ICH Guidance Document E2A: *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

Additional Considerations

14. There may be additional situations that require rapid communication to Health Canada. Appropriate scientific and medical judgment should be applied to each situation. These could include;

- for an 'expected' serious adverse drug reaction, an increase in the rate of occurrence which is judged clinically important,

- a significant hazard to the patient population, such as lack of efficacy with a drug used in treating life-threatening disease, and
- a major safety finding from a newly completed animal study

SickKids REB Review & Followup

15. Completed AE forms are reviewed by the REB Chair, normally within 2 business days. At the Chair's request, the Vice Chair or other REB member may also review the AE report and provide their recommendations for any followup action. Other Hospital expertise eg, Pharmacy may also be consulted when necessary.

16. The primary investigator may be contacted for additional information or clarification.

17. Based on the investigator's recommendations, the REB Chair will determine any necessary followup eg., revise the consent forms based on new information, inform current research subjects, temporarily halt the study until further analysis and recommendations can be made etc.

18. A copy of the signed AE form with the REB Chair's required actions is sent to the investigator.

19. The Clinical Research Monitor may assist with followup activities as identified by the Chair in the signed report. If necessary, a copy of the signed report is sent to the Monitor.

20. Non-compliance with these requirements including reporting timeframes will be reviewed by the REB Chair and action taken.

Source Documents

- *TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans* 1998
- *ICH E2A Guidance for Industry: Clinical Safety Data Management: Definitions and Standards for expedited Reporting*
- *ICH E6 Good Clinical Practice: Consolidated Guideline* 1997
- *ICH E8 Guidance for Industry: General Considerations for Clinical Trials* 1997
- *ICH E11 Guidance for Industry: Clinical Investigation of Medicinal Products in the Pediatric Population* 2003
- *ICH E11 Addendum: Guidance for Industry: Clinical Investigation of Medicinal Products in the Pediatric Population*
- *Guidance for Clinical Trial Sponsors: Clinical Trial Applications* 2003
Division 5, Food & Drug Act, Health Canada