

**Children's Hospital and Health System, Inc.
Administrative Policy and Procedure
Children's Research Institute**

SUBJECT: Requirements for Reporting to the Institutional Review Board (IRB)

APPLIES TO: Investigators and staff involved in human subjects research under the review of Children's Hospital of Wisconsin (CHW) IRB

PURPOSE:

Federal regulations (45 CFR 46.103(b)(5) & 21 CFR 56.108(b) require written procedures for ensuring prompt reporting of unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect subjects from avoidable harm.

When conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, an investigator's responsibilities include preparing and submitting the following complete, accurate, and timely reports (§§ 812.150 & 312.64):

- o Any unanticipated problems occurring during an investigation
- o Select serious adverse device/drug events occurring during an investigation
- o Any deviation from the investigational plan made to protect the life or physical well-being of a subject in an emergency

Events which meet the prompt reporting criteria must be reported to the IRB within 5 calendar days.

Events which do not meet the prompt reporting criteria may be reported to the IRB with the Continuing Progress Report (CPR).

DEFINITIONS:

Adverse event (AE): Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or condition temporally associated with the use of any study procedure or treatment, regardless of whether it is considered related to the study procedure or treatment.

Serious adverse event (SAE): An adverse event that (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity, (5) results

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in a congenital anomaly/birth defect, or (6) is an important medical event that jeopardizes the subject or requires medical intervention to prevent one of outcomes listed above.

External: Not at a site under the purview of the CHW IRB. Also called “off-site”

External serious adverse event: A serious adverse event that occurs at any outside location and does not involve a research subject under a CHW IRB approved study.

Important medical events: Events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse events when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes (death, life-threatening, hospitalization) listed previously in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Internal: At a site under the purview of the CHW IRB. Also called “on-site”

Prompt reporting: Within 5 calendar days of when an investigator learns of the event.

Protocol deviations (violation): Any alteration or modification to the IRB approved protocol. This includes all IRB approved study materials including the detailed protocol, protocol summary, consent form, recruitment materials, questionnaires, and any other information relating to the research study.

Planned protocol deviation: Any temporary protocol deviation acknowledged by the IRB prior to its initiation. Any permanent change to the protocol constitutes an amendment that must be submitted to the IRB for approval prior to initiation.

Significant protocol deviation (violation): Significant protocol deviations are those that increase the risk to participants or others, decrease potential benefits of the study, undermine the scientific integrity of the study, or occur more than once.

Non-Compliance with IRB Policies and Procedures: Violates federal regulations or institutional policies regarding informed consent or research conduct and impact subjects' rights, welfare and/or safety or affect the scientific integrity of the study.

Possibly related: An adverse event which is possibly related is one that may have been caused by the study drug, device or intervention, however there is insufficient information to determine the likelihood of this possibility.

Probably Related: An adverse event which is likely caused by the study drug, device or intervention and there is sufficient information to determine the likelihood of this probability.

Related: An adverse event which is related to the use of the study drug, device, or intervention is one for which there is a reasonable possibility (e.g., strong temporal relationship) that the adverse event may have been caused by the study drug, device or intervention.

Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO): Any incident, experience, or outcome that meets all of the following criteria:

- (1) Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, Instructions for Use/Device Manual and/or Investigator's Brochure; and (b) the characteristics of the subject population being studied;
- (2) 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 procedures involved in the research) or test article; and
- (3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Types of UPIRSOs can include:

- **Unanticipated adverse event:** An adverse event that is not consistent in nature, frequency, or severity with the current IRB protocol, investigator's brochure, device manual/instructions for use, or consent form.
- **Unanticipated adverse device effect:** An unanticipated adverse device effect means any serious adverse event caused by or associated with a device, if that event was not previously identified in nature, severity, or degree of incidence in the study protocol, consent form, investigational plan or investigational device exemption (IDE) application; or any unanticipated serious problem associated with a device and related to the rights, safety or welfare of research subjects.

PROCEDURE:

Events which meet Prompt Reporting Criteria

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- 1) With respect to each research study an Investigator is conducting, he or she must ensure that the following problems, events and/or information involving risk to research participants or others are reported to the IRB not later than 5 calendar days after becoming aware of the problem, event or information.
 - a) UPIRSO's or any incident, experience, or outcome that meets all of the following criteria:
 - i. unexpected with reference to procedure/risks defined in initial IRB application
 - ii. possibly, probably, or definitely related to participation in the research study, and
 - iii. suggests the research places subjects or others at greater risk of harm than was previously known or recognized.

Examples include but are not limited to the following:

- Breach of privacy or confidentiality including lost or stolen study records that contain private identifiable subject information.
 - Any other problem that the investigator considers to be unanticipated and indicates that subjects or others are at increased risk of harm.
 - Incarceration of a subject in a protocol not approved to enroll prisoners.
 - Complaint of a subject when the complaint indicates unexpected risks or cannot be resolved by the research team.
- b) Any Internal Adverse Events, Adverse Device Effects, or Serious Adverse Events that meet all of these criteria (these qualify as Unanticipated Problems):
 - i. Unexpected
 - ii. possibly, probably, or definitely related to the research
 - iii. Suggests the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized.
 - iv. A series of adverse events that meet the criteria above
 - c) Internal Serious Adverse Events that meet the following criteria:
 - i. Is possibly, probably or definitely related to study participation
 - ii. Is a Life-threatening Serious Adverse Event: Any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the event that has occurred. This does not include any event that, had it occurred in a more severe form, might have caused death.
 - iii. Results in Death of a study subject.

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- d) Follow-up reports to initially reported Adverse Events which meet the above criteria.
- e) Safety Notice/Report from Sponsor or Central Site if report describes new information regarding risks or unanticipated problems involving risks.

Examples include but are not limited to the following:

- Sponsor imposed suspension for risk.
 - Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
 - Any safety reporting requirements specified by the IRB as a condition of approval.
 - A paper is published from another study that shows that the risks or potential benefits of the research might be different from those initially presented to the IRB.
 - Suspension or Termination of the Study by the Sponsor
- f) Report from a Data Safety Monitoring Board (DSMB) or equivalent if the report describes new information regarding risks or unanticipated problems involving risks.

Examples include but are not limited to the following:

- An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits might be different from those initially presented to the IRB.
- g) Significant Protocol Deviation: Examples include but are not limited to the following:
- Any departure from the protocol (deviation or violation) that harmed subjects or others; that indicates subjects or others might be at increased risk of harm; or that compromises the integrity of the research data.
 - Any change made to the research protocol without prior IRB approval in order to eliminate apparent immediate harm to a subject or others.
- h) Planned Protocol Deviation which increases the risk to participants or others, decreases potential benefits of the study, or undermines the scientific integrity of the study.

Examples include but are not limited to the following:

- Enrolling a subject who does not meet eligibility criteria

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- Not performing a specific screening procedure for a patient as indicated in the protocol
- i) Non-Compliance with IRB Policies and/or Procedures includes but is not limited to:
- Any allegation of non-compliance with protocol requirements (including protocol deviations or violations) or IRB policies.
 - QI routine review reports which recommend immediate reporting of events
- 2) If an Investigator determines the event, problem, or information meets the prompt reporting criteria; they should complete and submit a Reportable Event Form for the study. If the event applies to several studies, a Reportable Event Form should be submitted for each study which is affected.
- If an investigator does not have enough information to determine if the event meets all of the above criteria, it is recommended to report the event to the IRB and if possible update the reportable event with additional information later.
- 3) If an event occurs when an investigator is unreachable or unavailable to submit the Reportable Event Form, the study team should complete the following steps to ensure IRB notification:
- i. Ensure that the investigator is notified as soon as possible
 - ii. Contact the IRB Coordinator to report the event
 - iii. Complete the Reportable Event Form and submit the form to the IRB office via IRBnet.

Events which do not meet Prompt Reporting Criteria

Reportable at time of Continuing Review

- 1) Any Reportable Event which did not meet the Prompt Reporting Criteria as outlined in this policy and procedure should be reported to the IRB with a study's continuing review forms. The continuing review forms prompt investigators to provide information regarding all reportable events in summary format. This is to provide the IRB a full picture of what has occurred since the initial approval or most recent CPR.
- 2) All Reportable Events not previously submitted to the IRB must be submitted with the CPR. This information should be submitted in a summary worksheet (such as excel) and be clearly labeled (e.g., "Internal Adverse Events", "External Adverse Events", etc.). Guidance for these summary reports is outlined below:
 - a) Internal Adverse Events for Studies where CHW is the Only Site or Central Coordinating Site: Unless there is a DSMB in place to review these events, the researcher's summary should include all internal adverse events, regardless of severity (serious and non-serious), expectedness (anticipated and unanticipated), and relatedness (may or may not be related to the study). The summary should demonstrate that the nature, frequency, and severity of these events are monitored on a continuous basis. There should be ongoing consideration as to whether particular events are expected and related to the study. A simple list of events is not an acceptable summary. *If a DSMB is established for this study, their required safety report may be submitted in place of this summary.*
 - b) Internal Serious Adverse Events for Multi-Center Study: For studies in which the sponsor or central site is responsible for monitoring adverse events, a summary of all serious adverse events reported from this site to the sponsor or central site must be submitted.
 - c) External Serious Adverse Events: If this is a multi-center study, the IRB expects a summary of serious adverse events from the sponsor or central coordinating center. The summary should include a statement or indication related whether these events do or do not reflect a change to the overall risk benefit ratio of the study. A summary is desired, but not required from the central site or sponsor.
 - d) Protocol Deviations: A summary of all protocol deviations not previously submitted under prompt reporting requirements.

IRB Review of Promptly Reportable events

(For IRB use only)

All on-site events that qualify for prompt reporting, as defined above (see definitions) require review by the fully convened IRB. All members will receive the Reportable Event report and any supporting documentation, as applicable.

- a) The IRB Coordinators and Chair(s) will perform an initial review of the reported event to determine if the event meets the requirements for prompt reporting, if additional information is needed, or if any action is required immediately for the safety of research subjects or others.
- b) The IRB committee will collect and assess all information related to the reported event to determine if it is an UPIRSO. This process may include discussing the matter with the investigator and providing the investigator an opportunity to provide further information. The IRB chairs or committees may, at their discretion, request consultation with experts in the particular area of research, and engage the services of a specially-convened committee.
- c) At any time during these reviews, the IRB or IRB Chairs may take emergency corrective action (including an order to temporarily stop research activities) if, in the IRB Chair's assessment, it appears that research subjects or others may be at risk of harm due to the reported event. If a study is suspended under this emergency procedure, the IRB Chair and/or committee will make every effort to conclude its inquiry in as expeditious a manner as possible, including calling for an emergency meeting of the full IRB to review its preliminary conclusions.
- d) Events reported to the IRB that appear to require outside reporting per Federal regulations along with any emergency corrective action taken by the IRB will be immediately reported to CHW institutional officials in accordance with the requirements outlined in the "IRB Reporting" policy. IRB shall not issue any such reports on its own, nor instruct any investigator to send any reports or notifications without prior consultation with and approval of the CHW institutional officials.

IRB Actions on Promptly Reportable events

(For IRB use only)

1. Any event that, upon review, does not require action by the IRB.
 - Event will be recorded in the IRB study file
 - A letter of acknowledgement will be sent to the investigator, and a copy of the letter filed in the IRB study file.
 - No other action will be taken.

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Q:Corporate/Legal/Policies/Requirements For Reporting To The IRB

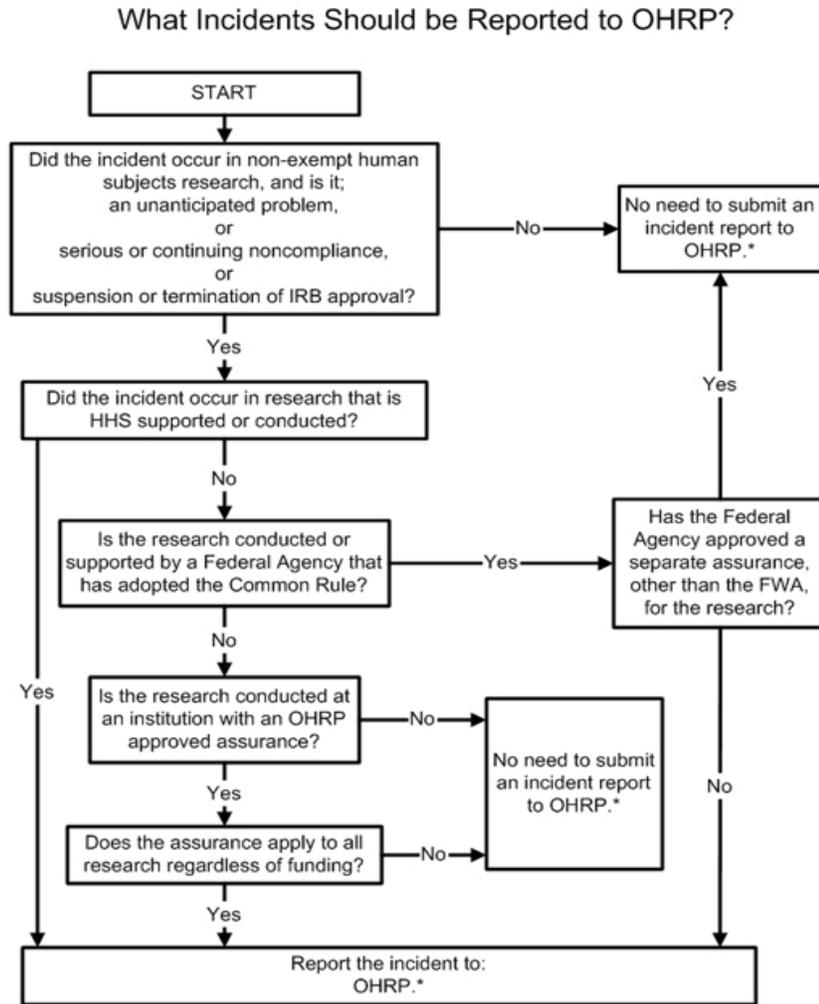
2. Any event that, upon review, requires the IRB to take any action.

Note: If any reported event is confirmed as a UPIRSO or serious or continuing noncompliance, or if the IRB determines or recommends that a notice or reporting to any government agency, person (including current or past study participants), firm or organization may be necessary or prudent, the IRB shall promptly notify CHW Institutional Officials and follow the “IRB Reporting” Policy. The IRB will work with CHW Institutional Officials to develop any such reports or notices. Neither the CHW IRB nor the Investigator will send any such reports or notices without prior review and approval of CHW institutional officials.

- The required actions will be documented in the meeting minutes and in a letter to the investigator. The range of actions includes items listed below, but the list does not preclude the IRB from taking additional actions as determined on a case-by-case basis.
 - a) Suspension or termination of the study (Note: If this action is taken, CHW’s designated Institutional Official will be notified to initiate any reporting actions that may be required under “IRB Reporting” policy).
 - b) Modification of the protocol, informed consent document, or information disclosed during the consent process.
 - c) Requiring current subjects to re-consent or providing additional information to current participants (Note: Additional information must be provided whenever the information may relate to the participant’s willingness to continue participation.
 - d) Providing additional information to past participants.
 - e) Alteration of the frequency for continuing review.
 - f) Requiring review by an outside monitoring committee (e.g., Data Safety and Monitoring Committee).

3. Once the IRB review is complete the Investigator will receive either an acknowledgement letter of the event, notification of IRB actions taken, or a request for modifications or follow up.

The following decision chart developed by OHRP will help guide IRB decision making process on when to report events to OHRP.



* Other reporting requirements may apply, whether or not a report to OHRP is required.

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REFERENCES:

21 CFR 50.25(b)(5)

21 CFR 56. 1 08(b)(1),(3) 21 CFR 56.113

21 CFR 312.66

21 CFR 812.3(8)

21 CFR 812.40

21 CFR 812.150(a)(1) 21 CFR 812.150(b)(1) 45 CFR 46.103(b)(5) 45 CFR 46.113

45 CFR 46.116(b)(5)

ATTACHMENT: Reportable Event Form

(signed copy on file)

Peggy Troy, President of CHHS