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In accordance with Federal regulations (45 CFR 46.103 (b)(5); 21 CFR 56.108 (b)(1 & 2)), investigators are responsible for ongoing requirements in the conduct of the approved research that include providing to the IRB prompt reports of (1) any unanticipated problems involving risk to subjects or others (UPIRSO), (2) serious or continuing non-compliance with the regulations or the requirements of the IRB, and (3) any suspension or termination of IRB approval.

As part of continuing oversight of research conducted at Children's Wisconsin, the Institutional Review Board (Children's IRB) expects to receive a variety of information about a study while it is active. This information allows the IRB to have current, up to date information about the research to assess whether the regulatory criteria for approval continues to be met. In the case of certain events, this information allows the IRB to assess whether specific action is needed to protect the rights, welfare and safety of subjects.

Events and information will be reported **promptly** (within 5 working days of learning of the event or information) or at the time of **Continuing Review (**unless a sponsor requires reporting sooner than at time of Continuing Review.**)** The IRB will accept and acknowledge information that does not require prompt reporting and is submitted prior to Continuing Review, if the investigator or sponsor feels it is important information of which the IRB should be aware. See section on How to Submit Reportable New Information to the Children's IRB.

The IRB has an obligation to monitor for **Unanticipated Problems** and **Serious or Continuing Non-Compliance** in order to assure the protection of subject rights and safety. This type of information must be reported to the Children's IRB **promptly** (within 5 working days of learning the information). Some events may meet the criteria for both an unanticipated problem and serious or continuing non-compliance.

Reminders:

- Anything that happens to subjects or others during participation on a study, or any new information received about a study should be assessed for whether or not it requires reporting to the IRB and in what timeframe.

- When something meets the criteria for being promptly reported, it does not matter whether or not this is external or local, or whether there are currently subjects enrolled at Children's. If the study is open to enrollment anything that meets the criteria should be reported promptly.

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Unanticipated Problems

Events such as adverse events, serious adverse event, incidents, protocol deviations, violations, or updated study information can all be, or become, unanticipated problems involving risk to subjects or others (UPIRSOs) depending on their nature and severity. Each should be assessed, when the investigator becomes aware, to determine if it is a UPIRSO. When they reach the level of an UPIRSO they should be reported promptly. See section on How to Submit Reportable New Information to the Children's IRB.

If the event meets the definition of a UPIRSO, you must also consider Children's clinical reporting requirements. Link: https://connect.chw.org/en/employee-resources/safety-event-reports/patient-or-non-patient-safety-event. *Midas+ Remote Date Entry is used to enter patient and non-patient safety events. Event reporting is integral to our patient safety program by giving us valuable information about system failures and other process deficiencies. The events reported allow us to analyze and make critical changes to ensure our children's and staff safety.* The report number must be provided on the Reportable Event/New Information form submitted to the IRB if the problem meets Children's clinical reporting requirements.

Adverse Events Determined to be Unanticipated Problems That Did Not Occur Locally
(SUSAR Reports, IND Safety Letters)

Questions often arise as to whether or not adverse events that are determined to be unanticipated problems, but did not occur locally, such as SUSAR reports or IND Safety reports from a sponsor, should be reported to the IRB.

The IRB is not able to make a meaningful assessment of these reports without having enough information to provide the context. Therefore, these reports should be submitted to the Children's IRB when they will provide meaningful information that would allow the IRB to assess its effect on the safety and welfare of subjects.

The Children's IRB will accept non-site adverse event reports submitted by investigators and from sponsors on behalf of investigators, if, in accord with 21 CFR 312.32:

- 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
- if the SUSAR or IND Safety Letter in question does NOT include this information/required analysis, then it is not yet ready for IRB submission as it will not provide meaningful

information to the IRB. In these cases, the investigator should work with the sponsor to obtain this information, and then report to the IRB once the above is available.

Children's IRB recognizes that for multicenter studies, the sponsor is in a better position to process and analyze adverse event information for the entire study, and to assess whether an occurrence is both "unanticipated" and a "problem" for the study. Accordingly, you may rely on the sponsor's assessment.

Adverse Events in FDA Regulated Drug Studies

The U.S. Food and Drug Administration (FDA) recommends that there be careful consideration of whether an AE is an unanticipated problem that must be reported to IRBs. In summary, FDA believes that only the following AEs should be considered as unanticipated problems that must be reported to the IRB.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a **specificity or severity** that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. We recommend that a discussion of the divergence from the expected specificity or severity accompany the report.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). We recommend that a discussion of the divergence from the expected rate accompany the report.
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or

would prompt other action by the IRB to ensure the protection of human subjects. We recommend that an explanation of the conclusion accompany the report. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf.

Note: Adverse events that meet the criteria of a UPIRSO should be promptly reported regardless of whether they occur on-site or off-site. Off -site adverse events that do not meet the criteria for prompt reporting do not need to be reported to the Children's IRB unless the sponsor requires this, in which case these can be reported at the time of Continuing Review.

Non-Compliance

Non-compliance includes violations and protocol deviations. When the actual or alleged/suspected non-compliance is serious or continuing, it must reported promptly (within 5 working days of learning of the non-compliance.) Otherwise, these can be compiled on a summary log and reported at the time of Continuing Review. See section on How to Submit Reportable New Information to the Children's IRB.

New or Updated Study Information

As a study progresses, new and updated information about that study may become known, either through a sponsor or through interim analysis. This is information that does not necessarily constitute a problem, non-compliance, adverse event etc. However, this information must still be reported to the IRB. The IRB is charged with providing continued oversight of the study and the safety to human subjects. This new information may affect the IRBs assessment of the regulatory criteria for approval and/or may warrant some type of action.

This information should be reported to the IRB as investigators learn about it. However, there are some situations in which this new information warrants immediate reporting. When the information meets the criteria of a UPRISO, this new information should be reported promptly (within 5 working days of learning the information.)

See section on How to Submit Reportable New Information to the Children's IRB.

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Other Problems or Information

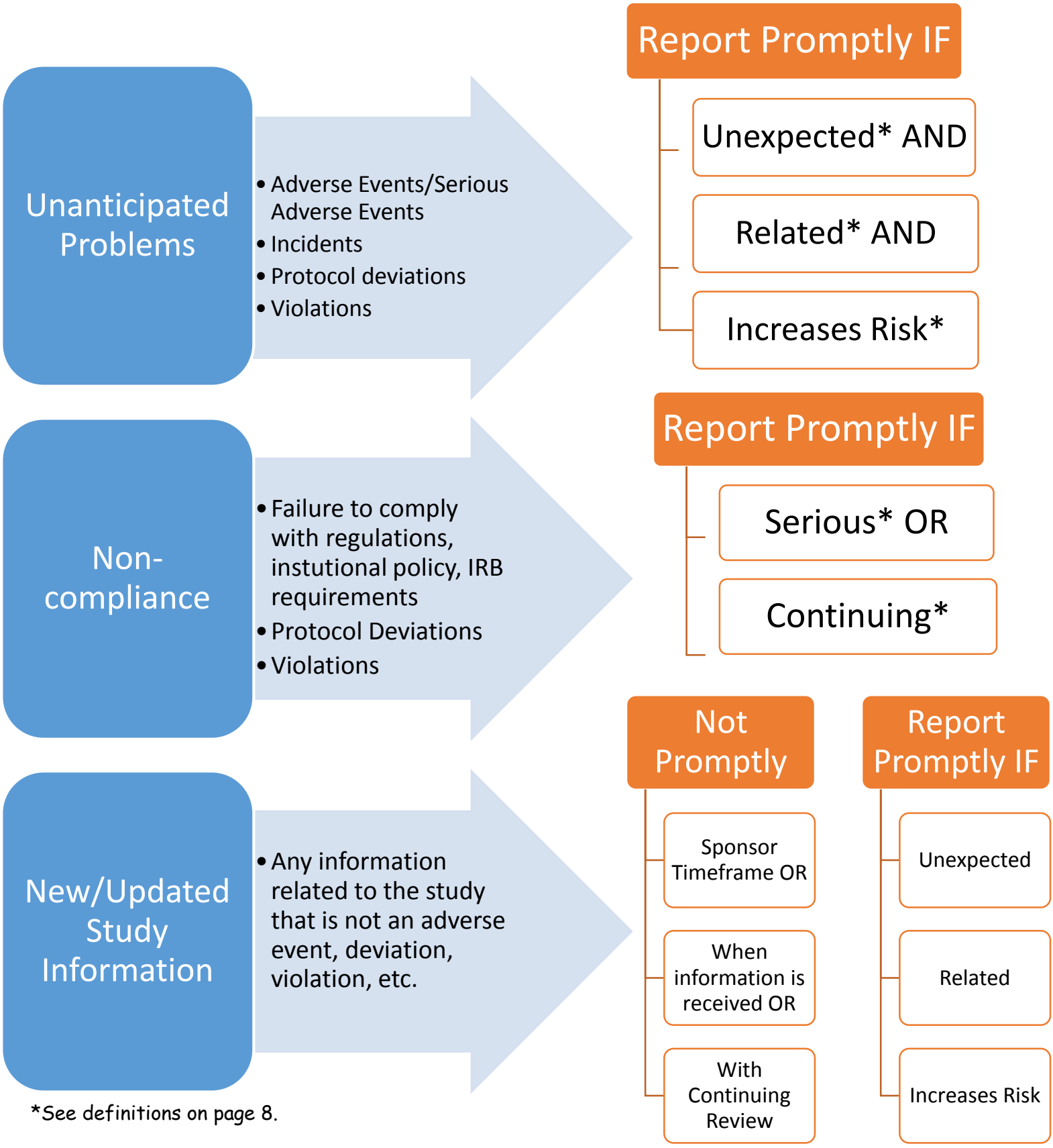
New or revised Investigator's Brochures:

- Please reference *Guidance – Submission of New or Revised Investigator's Brochures to the Institutional Review Board* for detailed instructions on timing and content of submission.

Any of the following issues must be reported immediately (as soon as possible once aware) to the Children's Wisconsin HRPP/IRB office by phone or email:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after the FDA has the opportunity to review any responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections;
- Any litigation, arbitration, or settlements initiated related to human research protections; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding Children's Wisconsin's HRPP.

Examples Adverse Events (not all inclusive)	**Examples Incidents** (not all inclusive)	**Examples Protocol Deviations** (not all inclusive)	**Examples Violations** (not all inclusive)	**Examples New Study Information** (not all inclusive)
Study related deaths or life threatening events Abnormal lab values New symptom or injury Unanticipated Adverse Device Affect (UADE)	Complaint by study subject or other Breach of confidentiality or privacy Incarceration of a study subject on a study not approved to enroll prisoners Loss of adequate resources to support the study Pregnancy of a subject Unexpected incident (fire, natural disaster, system failure) that destroys records or disrupts scheduling Withdrawal, restriction, or modification of a marketed approval of a drug, device or biologic used in a research protocol Failure of subject to comply with protocol Death or unexpected unavailability of the Principal Investigator Medication or Lab errors	Enrolling subjects who do meet eligibility criteria Labs or procedures done outside the time frame described in the protocol Missing a lab, procedure or medication Failure to adhere to the protocol prescribed reporting requirements Failure to withdraw a subject who meets withdrawal criteria Improper consent procedure (wrong consent version, documented incorrectly, etc.)	Beginning study procedures without legally effective informed consent Conducting study procedures without current IRB approval Enacting modifications to research without prior IRB approval Breach of confidentiality or HIPAA violations **Enforcement actions** – unfavorable audit or monitoring report, inspection or inquiry; suspension or disqualification of an investigator; Protocol-specific FDA 483 or Warning Letter from a Federal agency Working under an expired professional license Lapse in study approval where there is continuation of study procedures or data analysis Frequent protocol deviations that individually did not meet the criteria for prompt reporting	Interim analysis, findings, safety or action letter DSMB report Publication in the literature Sponsor report New information from sponsor (e.g. permanent or unscheduled closure to enrollment Withdrawal from marketing of a test article Investigator finding that indicates an increase in frequency or magnitude of a known risk or uncovers a new risk IRB required report Monitoring or audit report



*See definitions on page 8.

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How is Reportable New Information Submitted to the Children's IRB?

Information that is reported to the Children's IRB is reported on either the Reportable Events/New Information Form **OR** on the Reportable Event Summary Log, depending on the timing of the report.

Events reported promptly and/or prior to Continuing Review:

- **Complete the Reportable Events/New Information Form**
  - This form is required regardless of whether other forms (e.g., sponsor IND safety reports or CRO/monitoring reports, Medwatch reports, etc.) are included.
  - Information such as a summary of the event, and/or reports from coordinating center or sponsor may be attached and submitted **with** the form.
  - The reportable event form should **summarize** key information from the Medwatch, sponsor letter or report or other such external reports and documentation. The form should **not** include information verbatim and cut and pasted from other, external reports.

- **Create and submit a package in IRBNet** appropriate to the information being submitted. Include the Reportable Events/New Information form and any supporting documentation (other reports such as Medwatch forms, sponsor forms, monitoring reports, sponsor's analysis of the event, etc.)
  - Protocol Deviation/Violation
  - Unanticipated Problem
  - Other Reportable Event

Events reported at the time of Continuing Review:

- Non-compliance and Unanticipated Problems that were **not previously** reported (did not require prompt reporting) should be summarized on the Reportable Event Log available in IRBNet or on the HRPP website.
- New Study information that was not previously reported can be summarized on the Continuing Report Form.
- You do not need to complete a Reportable Events/New Information Form for each of the entries on the summary log.
- The summary log and Continuing Review form should **also** include, in a summarized format, anything **previously** reported via the Reportable Events/New Information Form and a reportable events package throughout the year. Although an IRB may become familiar with various individual aspects of the research project's conduct, such familiarity does not relieve the IRB of the responsibility to conduct Continuing Review at least annually, which provides an opportunity to reassess the totality of the project and assure that, among other things, risks to subjects are being minimized and are still reasonable in relation to anticipated benefits, if any, to the subjects and the knowledge that is expected to result.

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- **Tip**: To save time compiling the events for the log at the time of Continuing Review, it is suggested that you add these events to the summary log as they occur or are being reported, to keep this current in between Continuing Reviews.

Who Can Submit Reportable New Information?

Investigators: Investigators are required to inform the IRB of the occurrence of reportable new information in non-exempt research studies. A member of the study team can submit this on behalf of the PI, but the PI must review the information and any proposed corrective actions, and confirm review/agreement by signing the package in IRBNet.

Study Team Members: Study team members may need to initiate a reportable new information submission that involves suspected non-compliance by an investigator. For example, a study team member becomes aware that the investigator is not following regulations or Children's policy, or conducting research in a way that was not approved by the Children's IRB (please see Children's Wisconsin Policy: Corporate Compliance).

IRB Staff: IRB staff may also initiate reportable new information submissions if they receive a complaint from a study participant, or a member of the research community.

Description of terms

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical examination or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research.

Off-Site Adverse Event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical examination or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research that is experience by subjects at study sites in multi-center clinical trials under the jurisdiction of an external IRB.

Incident (non-adverse event): An undesirable and unintended event or outcome involving any aspect of the research that is not an adverse event.

On-Site Adverse Event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical examination or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research that is experienced by a subject

enrolled on a study under the jurisdiction of the Children's IRB (occurs locally at a Children's site or at a site for which Children's IRB is the IRB of record).

Non-Compliance: A failure to follow requirements in the conduct of research. This includes allegations of suspected non-compliance. This can take the form of either:

1. **Violations** of/failure to comply with Federal regulations, state laws, institutional policies, requirements or determinations of the IRB
2. **Deviations/**departures/divergences from the IRB approval protocol

Note: It is not considered non-compliance when there is a need to deviate from the approved protocol in order to protect the welfare of research participants, but this should be promptly reported. Failure on the part of subjects to comply with the protocol is also not considered non-compliance, but may be considered an incident that requires prompt reporting if it rises to the level of a UPIRSO.

Protocol Deviations: Failure to follow the current, IRB approved protocol as written due to the action or inaction of the investigator or research staff. Failure of the subject to comply with the protocol instructions are incidents that should also be reported, but are not also considered non-compliance as this is outside the investigator's control.

Serious Adverse Event (Federal definition): Any adverse event that:

1. Results in death
2. Is life threatening (places the subject at immediate risk of death from the event as it occurred)
3. Results in inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. Results in congenital abnormality/birth defect OR
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above

Serious or Continuing Non-Compliance: Non-compliance becomes **serious or continuing** when it results in harm, increases risk of harm, adversely affects the rights or welfare of participants, may affect the subject willingness to participate in the study, or undermines the scientific integrity of the data. This includes allegations of suspected non-compliance.

1. **Continuing:** repeated occurrences of non-compliance by the same investigator/study team or by the institution. This repetition may occur in the same **or different** protocols by the same investigator/study team. This repetition, if unaddressed may affect the protection of human subjects. Non-compliance does not need to be continuing to be serious.

2. **Serious:** there is an actual or potential increased risk to the safety, rights, or welfare of subjects. The event may have only occurred once, but still be considered serious depending of the effect on risk.

Related or Possibly Related: The event, information, situation, issue arises from the conduct of the research and is determined to be related or possibly related to the research and is of concern for the research participants or others directly affected by the research. It may be caused by one or more of the following:

1. Procedures involved in the research. An inability to rule out the research drug or procedure should deem the event as possibly related to the research.
2. Failures or errors in general systems out of the research, or factors that are not controlled by the researcher but on which ethical conduct of the research depends, according to the protocol.

Risk: The information, incident, experience, outcome caused actual harm; **or** suggests that the research places human subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no actual harm occurs. An event places the subject at a greater risk of harm than previously recognized if the event is:

1. A serious adverse event
2. An adverse event occurring at a higher frequency or severity than initially identified
3. Compromises the subject's, or others, safety, privacy or confidentiality

Unanticipated Adverse Device Affect (UADE): Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence; or any unanticipated serious problem associated with a device that relates to the rights, safety or welfare of patients.

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

1. Unexpected; **AND**
2. Related or possibly related to the research; **AND**
3. Suggests that the research places subjects or others at a greater risk of harm than previously known or recognized.

Unexpected: Event is unexpected or unforeseen in type, frequency, scope, consequences or severity.

1. It is not listed in the current protocol, investigator's brochure, consent form, product labeling or package inserts, or other relevant sources of information; OR

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2. If anticipated, or referred to in part, is not fully addressed or specified in any of the above sources of information.
3. In terms of the nature, severity or frequency, it is inconsistent with the information previously reviewed by the Children's IRB (i.e. it is not expected given the procedures and risks described in the research protocol documents) and with the characteristics of the human population being studied.