



**Human Subject Protection Program
Investigator Guidance
December 17, 2019**

NEW INFORMATION THAT REQUIRES PROMPT REPORTING TO THE CHLA IRB

Overview

Federal human research regulations require institutions to have written procedures to manage new information that requires prompt reporting to the IRB. When such new information is submitted for review, the IRB must determine whether the information represents:

1. An unanticipated problem involving risks to subjects or others;
2. Non-compliance with the federal regulations or with the requirements or determinations of the IRB; and
3. Non-compliance that is serious or continuing.

The CHLA IRB reviews research protocols to ensure there are adequate provisions for monitoring the data collected to ensure the safety of subjects. For studies involving more than minimal risk to subjects, a local CHLA monitoring plan is required. For research involving no more than minimal risks to subjects, the monitoring performed by the CHLA investigator is sufficient.

IRBs are not positioned to review individual events (data) except when events are unanticipated problems involving risk to subjects or others. IRBs need information to evaluate if the protocol risk to benefit ratio has changed, and whether criteria for approval continue to be met.

The CHLA IRB relies upon the qualifications and expertise of the study investigators to determine when internal or external adverse events, protocol deviations, incidents, or violations represent new information that requires prompt reporting of the information to the CHLA IRB. Investigators should also consider whether new information warrants changes to the protocol to minimize risks to subjects, and/or a change to the informed consent document to better inform subjects of the potential risks and the procedures needed to minimize such risks.

This guidance document provides definitions of the various types of research events, and examples of reportable new information to submit promptly to CHLA IRB.

Definitions of Research Events

Adverse Event: Any untoward or unfavorable medical occurrence in a human subject (physical or psychological harm) temporally associated with the subject's participation in the research (whether or not related to participation in the research).

Deviation: Any intended or unintended variance or exception from the IRB approved protocol. This term, though sometimes used interchangeably with the term “violation,” is most often used when the variance is intended for the safety of one or more research participants, or an unintended change that is not considered as serious as a violation, and may involve no more than minimal risk to participants or others.

External Adverse Event or Outcome: An event or outcome that is experienced by subjects enrolled at study site(s) (e.g. multicenter clinical trial) under the jurisdiction of other IRBs.

Incident: An undesirable and unintended, although not necessarily unexpected, event or outcome involving any aspect of the research study.

Internal Adverse Event or Outcome: An event or outcome that is experienced by subjects enrolled at study site(s) under the jurisdiction of the Reviewing IRB (e.g., CHLA).

Noncompliance: Failure to follow the regulations, or the requirements or determinations of the Institutional Review Board (e.g., provisions of the approved research study).

Related (probably or possibly related): In the opinion of the CHLA investigator there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Serious Adverse Event: Any adverse event that may result in the following: death; is life threatening (places subject at immediate risk of death from the event as it occurred); a required or prolonged hospitalization, persistent or significant disability/incapacity; congenital anomaly/birth defect; or may require medical or surgical intervention to prevent one of the other outcomes previously listed in this definition. The occurrence of a serious adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Unanticipated Problem: Any information that is: 1) unexpected; 2) related or possibly related to participation in the research; and 3) places subjects or others at a greater risk of harm than was previously known or recognized.

Unexpected: The nature, specificity, severity or frequency of the event or outcome is not accurately reflected in the protocol-related documents, such as the IRB approved research protocol, informed consent document, and investigator brochure; and/or the characteristics of the subject population being studied.

Unexpected Adverse Event: Any adverse event where the nature, specificity or frequency of the event is not consistent with either: 1) the known or foreseeable risk associated with the procedures involved in the research that are described in the protocol-related documents (IRB approved protocol, informed consent document, investigator brochure), and relevant sources of information (product labeling/package inserts); or 2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

Violation: Any intended or unintended variance, exception or deviation from the IRB approved protocol. This term though sometimes used interchangeably with “deviation” is often considered a more serious variance from an approved protocol than a deviation, and is not normally used

when the variance is made intentionally to eliminate an immediate hazard to one or more research participants.

Reportable New Information

It is the policy of the CHLA IRB that study investigators report new information (reportable events) if it falls into one or more of the categories below. Reportable new information must be submitted to the CHLA IRB **within 5 business days**. Information that does not fall under any of these categories does not require reporting to the IRB.

If the reportable event does not require a change to the research, it should be submitted alone. If the event requires an amendment (e.g., change in the study status, protocol revisions, consent form changes, etc.), submit an amendment **concurrently** with the reportable event. If an amendment is not ready for submission, describe what amendments are forthcoming.

1. Information that indicates a new or increased risk, or a new safety issue.

Examples:

- New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicating an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
- Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol
- Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
- Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm
- Any changes significantly affecting the conduct of the research
- Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device)

2. Harm experienced by a subject or other individual, which in the opinion of the investigator are unexpected and probably or possibly related to the research procedures.

- A harm is “unexpected” when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
- A harm is “probably or possibly related” to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.

3. Non-compliance with the federal regulations governing human research, or with the requirements or determinations of the IRB, or an allegation of such non-compliance.

Examples:

- Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g., FDA Form 483.)

- Written reports of study monitors that identify non-compliance with the approved protocol
- Repeated failure to follow the protocol due to the action or inaction of the investigator or research staff that suggests non-compliance with the protocol
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject
- Incarceration of a subject in a study not approved by the IRB to involve prisoners
- Complaint of a subject that cannot be resolved by the research team
- Premature suspension or termination of the protocol by the sponsor, investigator, or institution

Reporting of Violations, Deviations, and Incidents

Violations, deviations, and incidents should be reported to the IRB only if it affects the safety and welfare of subjects, indicates a new or increased risk, or a new safety issue, or has caused harm to a subject or other individual(s); or noncompliance with federal regulations or the requirements or determinations of the IRB.

Examples of violations and deviations include, but are not limited to the following:

- Any unintended or intended deviation from the IRB approved protocol that involves potential risks or has the potential to recur
- Use of expired or incorrect informed consent documents
- Enrollment of subjects not eligible according to the IRB approved protocol
- Any medication error involving dosing, administration and/or preparation of the study drug(s)
- Any lapse in study approval where there is a continuation of research activities (i.e., recruitment, enrollment, procedures, data analysis)
- Any identified noncompliance with federal regulations and/or requirements or determinations of the IRB or provisions of the approved research study
- Any event that requires prompt reporting according to the protocol or the study sponsor

Examples of incidents include, but are not limited to the following:

- Any complaint of a study subject that indicates an unexpected risk or the complaint cannot be resolved by the research staff
- Any breach of confidentiality
- Incarceration of a study subject in a medical study not approved to enroll prisoners
- Loss of adequate resources to support continued research activities
- An unexpected natural disaster, such as an earthquake, that destroys records or disrupts study scheduling
- Computer data security breach (e.g., lost or stolen computer/laptop and/or removable media used as storage devices, such as a flash drive or CD) in which personally identifiable information may have been or be acquired by an unauthorized person. **Note:** this information must also be reported to the CHLA Compliance Office.

IRB Responsibilities and Review Procedures

The IRB is responsible for reviewing new information and determining if it meets the criteria of an unanticipated problem involving risk to subjects and others, and/or non-compliance. The IRB will reassess the risk to benefit ratio of the study, and whether the criteria for approval continue to be met. The IRB may require additional action from the investigator such as:

- Changes to the study protocol and consenting documents
- Procedures to inform subjects of new information that may affect their willingness to continue participation in the study
- Additional safeguards to protect the safety and welfare of subjects, including subject privacy and the confidentiality of data
- Changes to the corrective action plan to prevent the event or problem from recurring

IRB Reporting Requirements

Unanticipated problems involving risks to subjects or others; any serious or continuing noncompliance; and any suspension or termination of IRB approval are reportable to the CHLA institutional official and appropriate federal department or agency head(s).