

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 1 of 12	Effective Date: September 1, 2025

1. POLICY STATEMENT:

The research team is responsible for recognizing changes in subject health that may qualify as adverse events and classifying those results as defined in the relevant regulations. Adverse events, along with all protocol deviations, exceptions and violations must be recorded and reported to the sponsor, the applicable Institutional Review Board (IRB) and, when required, to the appropriate regulatory authorities. There are additional safety reporting requirements for studies where the sponsor holds an IND/IDE.

2. BACKGROUND:

The research team is responsible for protecting the safety, rights and well-being of subjects. The recording and reporting of adverse events which occur during the course of the research ensure the continuing safety of subjects.

Federal regulations specifically require the IRB of record to review proposed changes in a research activity, and to ensure that such changes in approved research are not initiated without prospective IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject [45 CFR Part 46.103(b)(4)(iii) and 21 CFR Part 56.108(a)(4)].

Research activity includes all aspects of the conduct of the research (e.g., recruitment methods, informed consent process, drug administration, data collection, procedures used to protect privacy and confidentiality, etc.) and all of the information outlined in the IRB application and/or protocol reviewed and approved by the IRB.

Non-compliance with IRB reviews, determinations, policies and procedures, DFCI IRB Policies and Procedures for the Protection of Human Subjects in Research, ODQ requirements, DF/HCC Policies or sponsor requirements during the conduct of a research study constitutes a deviation, violation or exception.

3. RESPONSIBLE PERSONNEL:

- 3.1. Principal Investigator (PI)
- 3.2. Subinvestigator
- 3.3. Research Nurse
- 3.4. Study Coordinator

4. DEFINITIONS:

Version: 14
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Version 14 Updates:

•**Section 5.2. IND Safety Reports**

- Reformatting of IND Safety Reporting (INDSR) policy section to clearly delineate the responsibilities of the sponsor vs. investigator related to INDSRs, also emphasizing that when a DF/HCC investigator holds the IND and serves as Sponsor-Investigator, they hold both sponsor and investigator responsibilities.
- Sub-sections now clearly outline review and reporting responsibilities as tied to each specific role as they apply to DF/HCC investigators.

•**Section 5.2.2. Sponsor Responsibilities Related to INDSRs**

- Apply to DF/HCC investigators that hold the IND and are serving as the Sponsor-Investigator.
- 5.2.2.3.1. Clarifies the reporting timeline for Sponsor-Investigators to notify the FDA within 15 calendar days of determining the UAP constitutes a significant risk.
- 5.2.6.1.2. New language clarifying that the Sponsor-Investigator does not need to duplicate reporting to the FDA for INDSRs received from external entities (e.g., drug manufacturers) that have already been submitted to the FDA.

•**Section 5.2.3. Investigator Responsibilities Related to INDSRs**

- Apply to DF/HCC investigators serving as the PI on an externally sponsored trial, or as the Sponsor-Investigator of an investigator-sponsored trial.
- 5.2.3.3.1. Updated to allow for the delegation to qualified study team members, as defined in the updated DF/HCC Key: Delegation of Tasks, the review of INDSRs sent from external sponsors to identify those that are clearly indicated by the sponsor as UAPs.
 - Note that for DF/HCC investigator-sponsored trials, the Sponsor-Investigator may not delegate Sponsor responsibilities related to the review and assessment of INDSRs, as outlined in section 5.2.2.

•**Definition: Unanticipated Problems Involving Risk to Subjects or Others (UPRSO)**

- Updated to include common shorthand "Unanticipated Problem (UAP)" as is used throughout the policy.

•**Section 5.3. IDE Safety Reporting (UADEs)**

- New section added to clarify DF/HCC Investigator and Sponsor-Investigator safety reporting responsibilities for device studies under an IDE.

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 2 of 12	Effective Date: September 1, 2025

- 4.1. **Adverse Event (AE) (FDA definition):** An untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.
- 4.2. **Attribution:** The determination of whether there is a causal relationship between an adverse event and the investigational product or intervention.
- 4.3. **Life-threatening Adverse Event:** An adverse event that places the subject, in the view of either the investigator or sponsor, at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.
- 4.4. **Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction (FDA definition):** An adverse event occurring at any dose that, in the view of either the investigator or sponsor, results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- 4.5. **Suspected Adverse Reaction (FDA definition):** An adverse drug event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event.
- 4.6. **Unexpected Adverse Event or Unexpected Suspected Adverse Reaction (FDA definition):** An adverse event that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current protocol. “Unexpected” as used in this definition, also refers to an adverse event or suspected adverse reaction that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the drug.

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 3 of 12	Effective Date: September 1, 2025

4.7. **Unexpected Adverse Event (NCI definition):** Any adverse event which is not listed in the National Cancer Institute (NCI) Agent Specific Expected Adverse Event List.

4.8. **Unanticipated Adverse Device Event (UADE):** Any serious adverse effect on health or safety or 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 in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

4.9. **Unanticipated Problems Involving Risks to Subjects or Others (UPRSO)*,** also referred to shorthand as an Unanticipated Problem (UAP): Per OHRP, unanticipated problems, in general, include 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 IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- there is a reasonable possibility that the event is related to participation in the research; and
- 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.

Unanticipated problems UAPs that meet the above criteria generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

4.10. **Deviation:** Any prospective departure from the defined procedures set forth in the IRB-approved protocol.

4.11. **Exception:** Any protocol deviation that relates to the eligibility criteria, e.g., enrollment of a subject who does not meet all inclusion/exclusion criteria.

4.12. **Violation:** Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 4 of 12	Effective Date: September 1, 2025

4.13. **Research Activity:** All aspects of the conduct of the research study outlined in the protocol submission and reviewed and approved by the IRB, e.g., recruitment methods, consent process, treatment plan, data collection, procedures used to protect privacy and confidentiality, etc.

5. POLICY:

5.1. Adverse Events:

- 5.1.1. The PI and all applicable research team members will review the investigator's brochure and any safety reports released by the Sponsor at the start of the research and for the duration of the research to become familiar with the safety profile of the investigational drug/device or intervention.
- 5.1.2. The PI and all applicable research team members will review the protocol, informed consent document and the IRB's standard operating procedures to be familiar with the sponsor's and the IRB's requirements for reporting site-specific serious adverse events.
- 5.1.3. During the course of the research, the PI and all applicable research team members will identify any information that may indicate that an adverse event may have occurred. This information may come from several different sources and persistent discussions with the subject may be required to learn of these events. Possible sources of adverse event information include:
 - 5.1.3.1. Information obtained during a scheduled clinic or research visit
 - 5.1.3.2. Emergency room or other hospital records – including hospital visits which may have occurred in other cities or states
 - 5.1.3.3. Laboratory reports indicating significant harmful changes
 - 5.1.3.4. Changes in medication that the subject may be taking
 - 5.1.3.5. Visits to new physicians the subject did not previously consult
 - 5.1.3.6. Any other medically significant information or records that indicate that a negative change from baseline may have occurred.

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 5 of 12	Effective Date: September 1, 2025

5.1.4. Abnormal test results requiring changes to a subject's care (e.g., dose modification and/or other intervention such as supportive medication administration, supplementation, physical therapy, diet change, fluid administration, transfusions, additional testing) are considered clinically significant and must be reported as adverse events.

5.1.4.1.If no action is taken based on an abnormal result, the result is not reported as an adverse event unless specifically required in the protocol document.

5.1.4.2.When laboratory assessments are performed locally, the local results are reviewed and are the basis for patient care decisions. Central lab results will be reviewed and used for patient care decisions only if the same assessment was not completed locally.

5.1.5. Once an adverse event has been identified, the elements of adverse assessment (grade of severity, attribution, and duration of event) and any treatment/medication received specifically related to the event are recorded in the subject's medical record or research chart (as applicable). If the protocol requires review of reported adverse events to determine whether it is safe for a subject to proceed with a visit, treatment, or procedure, appropriately qualified research staff must evaluate any changes to reported adverse events prior to proceeding. However, it is not necessary to have all details of each adverse event documented and finalized prior to proceeding. Notwithstanding the above, comprehensive documentation of the adverse event must be completed in a timely manner or as required per the protocol.

5.1.5.1.For any serious adverse event that is at least possibly related, expectedness must be documented.

5.1.6. If an event impacts the protocol document or informed consent form and requires changes to either document, then the PI at the core site must be notified to facilitate the submission of the appropriate amendment.

5.1.7. Attribution (i.e., the causal relationship to the investigational drug/device or intervention) must be determined by the PI or a medically qualified research team member.

5.1.7.1.If an initial determination of attribution is recorded by a research nurse, there must be clear documentation that the PI, another protocol

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 6 of 12	Effective Date: September 1, 2025

physician, NP or PA has reviewed the adverse event information and agrees with the initial determination.

- 5.1.8. Serious adverse events or serious suspected adverse reactions will be discussed with the PI prior to submission to the sponsor or IRB. In the event that timely reporting does not permit this discussion, the PI must be informed of serious adverse events at the time of submission to the sponsor and IRB.
- 5.1.9. Adverse events occurring during the course of the research are reported to the sponsor following the sponsor's requirements.
- 5.1.10. All adverse events are followed until resolution or for the duration specified in the protocol by the PI or a medically qualified member of the research team. All relevant follow-up information, i.e. treatment and findings, are recorded in the subject's medical record.
- 5.1.11. All adverse events occurring during the course of the research are reported to the IRB following the IRB's requirements.
- 5.1.12. Additional reporting requirements may apply for investigator-held Investigational New Drug (IND) application or Investigational Device Exemptions (IDE) research, secondary malignancies or gene therapy research. Adverse events for these types of research are reported to the Food and Drug Administration (FDA) and/or other appropriate regulatory authorities following the reporting requirements set by the respective regulatory authority.

5.2. IND Safety ~~Report Distribution for DF/HCC sponsored research: Reports~~

5.2.1. For all IND-held studies, responsibilities related to the review, assessment, dissemination and reporting of IND Safety Reports (INDSR) are distinctly tied to the role of either the Sponsor or the Investigator. IND-held studies may be externally sponsored, or investigator-sponsored trials where,

5.2.1.1.A DF/HCC investigator holding the IND is the Sponsor of all research conducted under that IND and maintains **Sponsor responsibilities** related to INDSRs.

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 7 of 12	Effective Date: September 1, 2025

5.2.1.2.A DF/HCC investigator acting as the Principal Investigator (PI) on an IND-held study maintains **Investigator responsibilities** related to INDSRs.

5.2.1.3. When a DF/HCC investigator holds the IND, ~~the sponsor-investigator is and is the Sponsor, and serves as the PI at the DF/HCC Core Site,~~ they are the Sponsor-Investigator and maintain **both Sponsor and Investigator responsibilities** related to IND Safety Reports, as defined in sections 5.2.2 and 5.2.3.

5.2.2. Sponsor Responsibilities Related to IND Safety Reports

5.2.2.1. DF/HCC Investigators serving as the Sponsor (including Sponsor-Investigator), are responsible for ~~IND safety reporting. This includes reviewing external all safety events and information related to the IND, assessing and analyzing the events to determine the impact on the study and whether they meet the reporting criteria, and clearly notifying the applicable parties of events that do meet the criteria via an IND Safety Report.~~

- 5.2.2.2.1. Applicable safety events and information may occur locally at the Sponsor-Investigator's site, may occur at other participating sites, or may be safety reports ~~received from from external entities not participating directly in the research under the IND, including drug manufacturers to determine the impact (if any) on the study and any reporting requirements.~~

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5.2.2.2. The following events meet the criteria for an IND Safety Report:

- 5.2.4.2.1. Any Unanticipated Problem Involving Risk to Subject or Others (UPRSO), also known as an Unanticipated Problem (UAP) that constitutes a significant risk.

~~5.2.4.2.1.~~ 5.2.4.2.2. The Findings from epidemiological, pooled analysis of multiple studies, other clinical studies or findings from animal or in-vitro testing that suggest a significant risk in humans exposed to the drug.

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 8 of 12	Effective Date: September 1, 2025

~~5.2.4.2.2.~~5.2.4.2.3. Any serious suspected adverse reactions with a clinically important increase in the rate of occurrence of serious suspected adverse reactions over that which is listed in the protocol or investigator's brochure.

5.2.2.3. When the Sponsor determines that an event constitutes an IND Safety Report, they must comply with the following Sponsor requirements:

5.2.2.3.1. Notify the FDA via a submitted IND Safety Report (on either FDA Form 3500A or in a narrative format) within 15 calendar days of determining the UAP constitutes a significant risk.

5.2.6.1.1. Unexpected fatal or life-threatening suspected adverse reactions (i.e., there is a reasonable possibility that the drug caused the adverse event) represent especially important safety information and must be reported no later than ~~seven~~ (7) calendar days after the sponsor's initial receipt of the information.

5.2.6.1.2. ~~A~~If the UAP is determined from an IND safety report received from an external entity (e.g., drug manufacturer) that has already been submitted to the FDA, the Sponsor-Investigator does not need to separately submit another IND safety report to the FDA.

5.2.2.3.2. Notify all participating investigators (including all investigators to whom the sponsor is providing drug under the IND) in the form of a clearly identified IND Safety Report within 15 calendar days of determining the UAP constitutes a significant risk.

~~5.2.2.3.1.~~5.2.2.3.3. Submit a follow up report ~~may be submitted as to~~ the initial INDSR if/when new relevant information becomes available.

5.2.3. Investigator Responsibilities Related to IND Safety Reports:

5.2.3.1. Investigator responsibilities apply regardless of whether the IND-held study is DF/HCC investigator-sponsored or externally sponsored. For DF/HCC Sponsor-Investigators, these responsibilities are in addition to those Sponsor responsibilities outlined in section 5.2.2.

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 9 of 12	Effective Date: September 1, 2025

~~5.2.1.1. DF/HCC It is the responsibility of the sponsor investigator to ensure that all investigators participating in a multi-center trial are promptly informed of significant new adverse effects or risks with respect to the drug used in a study protocol.~~

~~5.2.2. The FDA considers events properly reported under the criteria in 21 CFR Part 312.32 as providing valuable safety information that could have implications for study conduct, and, as such, expects that these events be reported to the IRB as unanticipated problems involving risks to subjects or others.~~

5.3. IND Safety Reports received from external sponsors:

5.2.3.2. Investigators serving as the PI of an IND-held study are responsible for ensuring that all IND Safety Reports sent directly by the sponsor that meet the definition of UAP are reported to the IRB of record, as required by IRB policy.

~~5.2.3.1.1. 5.2.3.2.1.~~ DF/HCC expects external sponsors to analyze and determine which events meet the FDA requirements for IND/~~IDE~~ safety reporting, and to clearly and directly notify ~~DF/HCC~~ investigators of potential serious risks. (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR 812.150). Sponsors must analyze the significance of new safety events and provide sufficient information to support a substantive review by investigators (and the IRB, when applicable).
the DF/HCC PI that these events meet the definition of a UAP.

5.2.3.2.1.1. DF/HCC requires external sponsors utilizing web portals, ~~DF/HCC requires to send~~ a direct notification to the research team when a new IND safety report is posted to the portal.

5.2.3.3. Each DF/HCC PI listed on the Form FDA 1572 is responsible for ensuring that all IND Safety Reports received from an external sponsor are reviewed.

~~5.2.3.1.2. 5.2.3.3.1.~~ The ~~be sent to the~~ DF/HCC PI may delegate review of IND Safety Reports to appropriate trained research staff ~~to alert them~~ that a new IND/~~IDE~~ safety report has been posted to the portal members, as per the DF/HCC Key: Delegation of Tasks for Clinical Research.

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 10 of 12	Effective Date: September 1, 2025

~~5.3.1.1. DF/HCC expects IND/IDE safety reports to include 1) a brief narrative description of the event; 2) the sponsor's analysis of the significance of the event and/or basis for determining that the event poses a potential serious risk and is reportable under the above regulations; and 3) a description of any changes to the protocol or other actions that have been taken or are requested as a result.~~

~~In the event that a DF/HCC investigator receives unevaluable reports (e.g., the report does not appropriately analyze or communicate the significance of new information, the event does not meet IND safety reporting criteria, or the report contains insufficient information for PI/IRB review), DF/HCC PIs are not required to acknowledge, sign, print, retain or take action.~~

~~5.2.3.3.2. The DF/HCC PI must review all IND Safety Reports that are clearly identified by the sponsor as a UAP to determine reporting requirements per the IRB of record.~~

~~5.3.1.2. Each DF/HCC PI is responsible ensuring that the appropriate review of IND safety reports occurs. The DF/HCC PI may delegate this task to appropriately trained and qualified subinvestigators listed on the Form FDA-1572. Review of IND safety reports by a qualified investigator must be documented based on either institutional practice or via a sponsor's online web portal. Documentation is not required to be in a sponsor's safety reporting system or database if the review is documented locally in the research files.~~

~~5.2.3.4. The DF/HCC Core Site is responsible for IRB submission of any IND/IDE safety reports that are determined to meet IRB reporting requirements by the PI of any DF/HCC participating site.~~

5.3. IDE Safety Reporting (UADEs)

~~5.3.3. For device studies under an IDE, the DF/HCC Investigator maintains specific review, reporting, and dissemination responsibilities for any event that meets the definition of an Unanticipated Adverse Device Event (UADE) that poses significant risk. When the DF/HCC Investigator also holds the IDE and is therefore the Sponsor-Investigator, they maintain additional Sponsor responsibilities related to UADEs.~~

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 11 of 12	Effective Date: September 1, 2025

5.3.4. Investigator responsibilities related to UADEs:

5.3.4.1. Identify and report any potential UADEs specific to the device to the Sponsor and the IRB of record no later than 10 working days after the investigator first learns of the event.

5.3.5. Sponsor responsibilities related to UADEs:

5.3.5.1. For investigator-sponsored IDE trials, the DF/HCC Sponsor-Investigator maintains the investigator responsibilities outlined above in addition to the following Sponsor responsibilities:

5.3.5.1.1. Evaluate all UADEs submitted by participating investigators and report the results of the evaluation to the FDA (on either FDA Form 3500A or in a narrative format), all reviewing IRBs, and all participating investigators within 10 working days of receiving notice of the UADE.

5.3.5.4. Protocol Deviations, Exceptions and Violations:

5.3.3.5.4.3. Except in emergency situations, a protocol exception or deviation request must be reported to the PI and requires prior IRB and sponsor approval. In an emergency, a protocol deviation may be implemented to eliminate or reduce an apparent immediate hazard to a subject. Prior IRB approval is not required, but the deviation must be promptly reported to the IRB for review and to the sponsor, according to the protocol or contract requirements.

5.3.4.5.4.4. Source documents within the medical records or research charts must explain all deviations, exceptions and violations.

5.3.5.5.4.5. When a research team member learns that a deviation or exception is necessary, or a violation has occurred, he/she will contact the PI who will assess the event and determine the required reporting.

5.3.6.5.4.6. It is the responsibility of the PI to ensure proper reporting. The PI, or designee, must promptly report protocol violations and/or non-compliance that occurs during the course of the research to the sponsor and IRB, according to the protocol and/or contract requirements and the IRB of record's reporting policy.

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025

**DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH**

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	Page: 12 of 12	Effective Date: September 1, 2025

~~5.3.6.1~~5.4.6.1. The PI, or designee, must maintain a comprehensive log of all deviations and violations that occur during the course of the research inclusive of events occurring at their site.

~~5.3.6.2~~5.4.6.2. Conflicts with a subject's work schedule or planned vacation are generally considered non-compliance, or an unanticipated problem, and must be reported to the PI and the IRB of record per the IRB's reporting requirements. The PI must determine if a subject's scheduling delays require reporting to the IRB of record. All scheduling delays, regardless of IRB reporting requirements, must be explained in the subject's medical record or research chart.

6. APPLICABLE REGULATIONS & GUIDELINES:

21 CFR 50 – Protection of Human Research Subjects
21 CFR 54 – Financial Disclosure by Clinical Investigators
21 CFR 56 – Institutional Review Boards
21 CFR 312 - Investigational New Drugs – Drugs for Human Use
21 CFR 812 – Investigational New Device Exemptions
45 CFR 46 – Human Subject Protections
FDA Industry Guidelines and Information Sheets
FDA Compliance Policy Guidance Programs: 7348.809, 7348.810, and 7348.811

7. RELATED REFERENCES:

International Conference on Harmonisation – E6
DF/HCC Key: Delegation of Clinical Tasks

8. RELATED RESOURCES:

DICI IRB Serious Adverse Event Reporting Form
DICI IRB Policy: Adverse Event and INDSR Reporting
DICI IRB Policy: Deviation, Violation, Exception and Other Event Reporting
DICI IRB Major Deviation/Violation/Exception Reporting Form
DICI Minor Deviation/Violation Log
NCI Common Toxicity Criteria for Adverse Events (CTCAE)

Version: 14
Effective Date: September 1, 2025
Last Reviewed Date: July 10, 2025