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

TITLE: Safety and Event Reporting		
POLICY #: RCO-204	**Page:** 1 of 11	**Effective Date:** ~~9/1/21~~2/28/22

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.

Commented [SC1]: **Key changes:**
- Eliminate different process for Phase I and I/II studies. Consistent policy applies to all studies under an IND/IDE.
- Allows delegation of INDSR review to an appropriately qualified subinvestigator.
- Allows documentation of review to occur per institutional practice outside of sponsor systems.

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:

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.

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):** 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 that meet the above criterial 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

~~4.9.~~4.10. **Deviation:** Any prospective departure from the defined procedures set forth in the IRB-approved protocol.

~~4.10.~~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.

~~4.11.~~4.12. **Violation:** Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

~~4.12.~~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.

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.

5.1.5. 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). Review and documentation of the adverse event must be completed in a timely manner no later than the next study period (e.g. next cycle for studies that include cycles).

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. If an adverse event is not related to the investigational drug/device or research intervention, then documentation of expectedness is not required.

5.1.8. 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.

5.1.8.1. If an initial determination of attribution is recorded by a research nurse, there must be clear documentation that the PI, another protocol physician, NP or PA has reviewed the adverse event information and agrees with the initial determination.

5.1.9. 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.

5.1.10. Adverse events occurring during the course of the research are reported to the sponsor following the sponsor's requirements.

5.1.11. 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.

5.1.12. All adverse events occurring during the course of the research are reported to the IRB following the IRB's requirements.

5.1.13. 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:**

5.2.1. For all investigator-sponsored trials where a DF/HCC investigator holds the IND, the sponsor-investigator is responsible for IND safety reporting. This includes reviewing external safety reports received from manufacturers to determine the impact (if any) on the study and any reporting requirements.

~~5.2.1.~~5.2.2. The sponsor-investigator is required to notify the FDA and all participating investigators in an IND safety report of potentially serious risks within 15 calendar days after the sponsor-investigator receives the safety information. Participating investigators include all investigators to whom the sponsor is providing drug under any of its INDs.

~~5.2.2.~~5.2.3. The sponsor-investigator must submit an IND safety report (on either FDA Form 3500A or in a narrative format) when any of the following criteria are met:

~~5.2.2.1.~~5.2.3.1. Suspected adverse ~~reaction~~reactions that ~~is both~~are serious ~~and~~, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event.

~~5.2.2.2.~~5.2.3.2. 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.

~~5.2.2.3.~~5.2.3.3. ~~An increased~~Any clinically important increase in the occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure.

~~5.2.2.4.~~5.2.3.4. 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.

~~5.2.2.5.~~5.2.3.5. A follow up report may be submitted as relevant information becomes available.

~~5.2.2.6.~~5.2.3.6. 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.

5.2.4. 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:**

~~5.3.1.~~ DF/HCC expects external study sponsors to determine which events meet the FDA requirements for IND/IDE safety reporting and to directly notify DF/HCC ~~Investigators~~ investigators of ~~unanticipated problems and important safety information that has implications for the conduct of the research~~ potential serious risks. (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR 812.150). ~~DF/HCC Investigators are not required to check Industry, CRO, or third-party web portals for possible new information in the absence of a notification (e.g., email).~~

~~5.3.1.1.For All DF/HCC investigator-sponsored trials and externally sponsored with a pilot or phase I component, it is the responsibility of each DF/HCC PI to review all IND/IDE safety reports while the study is in the pilot phase or in phase I.~~

~~5.3.1.2.For all externally sponsored trials in phase II, II/III, III and/or IV, no action will be taken with external safety reports that do not have a clear indication of an unanticipated problem classification. Such reports will not be acknowledged, signed, printed, or retained for the study file.~~

~~5.3.2.~~5.3.1. ~~It is the sponsor's responsibility to provide an explanation of why an event was determined to be an unanticipated problem and clearly indicate the implications for the conduct of the study.~~ Sponsors must analyze the significance of new safety events and provide sufficient information to support a substantive review by investigators ~~and the IRB for any event that results in changes to study conduct or the informed consent document.~~(and the IRB, when applicable).

~~5.3.2.1.Each PI will assess whether IND/IDE safety reports need to be reported to the IRB based on the IRB's policies.~~

5.3.1.1.For studies utilizing web portals, DF/HCC requires a direct notification to be sent to the research staff to alert them that a new IND/IDE safety report has been posted to the portal.

5.3.1.2.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.

5.3.1.3.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.

5.3.2. DF/HCC PIs must ensure that all unanticipated problems involving risks to subjects or others are reported to the IRB of record, as required by IRB policy.

5.3.2.1.The FDA considers events properly reported under the criteria in 21 CFR 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.

5.3.2.2.DF/HCC PIs may rely on the sponsor's assessment of new information and report new information to the IRB based on the sponsor report. The sponsor often has greater experience, expertise, and access to information regarding the investigational agent. DF/HCC PIs may also choose to make a separate determination that the new information is an unanticipated problem and report it to the IRB.

5.3.2.3.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.

~~5.3.2.2.~~5.3.2.4. The DF/HCC Core Site is responsible for submitting IND/IDE safety reports that are determined to require IRB reporting. If ~~it's determined~~a DF/HCC subsite PI determines that an IND/IDE

Safety Report needs to be reported to the IRB ~~per IRB policy~~, the subsite PI ~~will~~should consult with the core site PI and sponsor prior to IRB submission. ~~The core site is responsible for submitting IND/IDE safety reports that are determined to need IRB reporting.~~

- ~~If the sponsor did not take action or provide an amendment as a result of the IND/IDE Safety report, the core site will indicate what action will be taken at DF/HCC (if any) in the submission to the IRB.~~

5.4. **Protocol Deviations, Exceptions and Violations:**

5.4.1. 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.

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

5.4.3. 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.

5.4.4. 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.

5.4.4.1. 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.

5.4.4.2. 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' 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
OHRS Information Sheet: DFCI IRB Adverse Event Reporting Policy
OHRS Information Sheet: Policy on Receipt and Review of IND/IDE Safety Reports

8. RELATED RESOURCES:

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