| **TITLE:** Reporting Adverse Events | | |
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| **POLICY #:** RCO-204 | **Page:** 1 of 7 | **Effective Date:** ~~1/31/18~~ |

## 1. POLICY STATEMENT:

The research team is responsible for recognizing changes in subject health that may qualify as adverse events, classifying those results as defined in the relevant regulations and reporting those events to the sponsor, the applicable Institutional Review Board (IRB) and, when required, to the appropriate regulatory authorities.

## 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.

## 3. RESPONSIBLE PERSONNEL:

3.1. Overall Principal Investigator (PI)
3.2. Site Responsible Investigator
3.3. Subinvestigator
3.4. Research Nurse
3.5. 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

**Commented [CC1]:** Language moved into policy from RCO-100 regarding IND Safety Reports

**Commented [CC2R1]:** Additional edits to 5.4 regarding documentation requirements for abnormal lab results determined not to be clinically significant/AE reportable

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.~~1.1. ~~**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.~~

~~4.7.~~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.

~~4.8.~~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.

**5. POLICY:**

5.1. The Overall 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.

5.2. The Overall 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~~sponsor's and the IRB's requirements for reporting site-specific serious adverse events.

5.3. During the course of the research, the Overall 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:

5.3.1. Information obtained during a scheduled clinic or research visit

5.3.2. Emergency room or other hospital records – including hospital visits which may have occurred in other cities or states

5.3.3. Laboratory reports indicating significant harmful changes

5.3.4. Changes in medication that the subject may be taking

5.3.5. Visits to new physicians the subject did not previously consult

5.3.6. Any other medically significant information or records that indicate that a negative change from baseline may have occurred.

5.4. 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.

5.4.1. 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.

5.5. 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). ~~This must be done in a reasonable amount of time.~~
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).

~~5.4.~~5.6. If an adverse event is not related to the investigational drug/device or intervention then documentation of expectedness is not required.

~~5.5.~~5.7. Attribution (i.e. the causal relationship to the investigational drug/device or intervention) must be determined by the Overall PI or a medically-qualified research team member.

~~5.5.1.~~5.7.1. If an initial determination of attribution is recorded by a research nurse or study coordinator, there must be clear documentation that the Overall PI,
another protocol physician, NP or PA has reviewed the adverse event information and agrees with the initial determination~~. Co-signatures without a statement of affirmation are not acceptable.~~..

~~5.6.~~5.8. Serious adverse events or serious suspected adverse reactions will be discussed with the Overall PI prior to submission to the ~~Sponsor~~sponsor or IRB. In the event that timely reporting does not permit this discussion, the Overall PI must be informed of serious adverse events at the time of submission to the ~~Sponsor~~sponsor and IRB.

~~5.7.~~5.9. Adverse events occurring during the course of the research are reported to the ~~Sponsor~~sponsor following the sponsor's requirements.

~~5.8.~~5.10. All adverse events are followed until resolution or for the duration specified in the protocol by the Overall 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.

~~5.9.~~5.11. All adverse events occurring during the course of the research are reported to the IRB following the IRB's requirements.

~~5.10.~~5.12. 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.

5.13. IND Safety Report Distribution for DF/HCC-sponsored research:

Commented [CC3]: Language moved from RCO-100

5.13.1. The sponsor 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 receives the safety information. Participating investigators include all investigators to whom the sponsor is providing drug under any of its INDs.

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

5.13.2.1. Suspected adverse reaction that is both serious and unexpected.

5.13.2.2. Findings from clinical studies or findings from animal or in-vitro testing that suggest a significant risk in humans exposed to the drug.

5.13.2.3. An increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure.

5.13.2.4. Unexpected fatal or life-threatening suspected adverse reactions 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.

5.13.2.5. A follow up report may be submitted as relevant information becomes available.

5.13.2.6. It is the responsibility of the sponsor 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.

~~5.11.~~5.14. For IND Safety Reports received from external sponsors:

~~5.11.1.~~5.14.1. DF/HCC expects external study sponsors to directly notify DF/HCC Investigators of unanticipated problems and important safety information that has implications for the conduct of the research (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR 812.150). ~~It is the sponsor's responsibility to provide an explanation of why it has been determined to be an unanticipated problem and clearly indicate the implications for the conduct of the study.~~
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).

~~For~~

5.14.1.1. For All DF/HCC investigator-sponsored trials and externally sponsored pilot, phase I and phase I/II studies, it is the responsibility of the DF/HCC Overall PI to review all IND/IDE safety reports.

5.14.2.

~~5.11.1.1.~~5.14.2.1. For all externally sponsored phase II, II/III, III and IV trials, 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 ~~reviewed, processed,~~ acknowledged ~~by the Overall PI~~, signed, printed, or ~~electronically~~ retained for the study file.

~~5.11.2. Sponsors are expected to bring such information to~~ It is the ~~attention~~sponsor's responsibility to provide an explanation of ~~DF/HCC investigators~~why an event was determined to be an unanticipated problem and ~~not simply post to Industry, CRO, or third-party web portals.~~

~~5.11.2.1.~~5.14.2.2. clearly indicate the implications for the conduct of the study. Sponsors must provide sufficient information ~~about any individual event~~ 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.

~~5.11.2.2.~~5.14.2.3. The Overall PI will follow the IRB's policy on receipt and review of IND/IDE Safety Reports to determine how and when events from other sites must be reported to the IRB. If an external sponsor

does not provide an amendment for submission with the report, the Overall PI will indicate any immediate action they plan to take, if any, when notifying the IRB.

## 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
NCI Common Toxicity Criteria for Adverse Events (CTCAE)