DFCI Institutional Review Board:
Serious Adverse Event Reporting Policy

The following policy describes when local Serious Adverse Events must be reported to the IRB.

Definitions:

Adverse Event - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 314.80)

Serious Adverse Event - An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity, or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Please note: All locally occurring Adverse Events that are *Serious, Unexpected,* and there is a *Reasonable Possibility* the *Adverse Event* is related to the study intervention should be reported to the IRB. Please note, FDA guidance suggests there must be positive evidence of relatedness to meet the criteria that the event is likely related to study interventions, examples are provided in the references below.

Events that are *Expected* and *listed within the protocol, investigator brochure, and/or current consent form* do not need to be reported to the DFCI IRB. An event that presents at a higher severity or frequency than what is currently listed within the Investigator's Brochure, protocol, and/or current consent would be considered unexpected and reportable. See protocol for additional reporting requirements (to sponsor, FDA, etc.).

The DFCI IRB follows the Common Terminology Criteria for Adverse Events (**CTCAE**) and defines *Adverse Events* as events that meet the criteria below. Grades refer to the severity of the adverse event. Serious Adverse Event reporting may be specifically described in the protocol and reporting may follow the sponsor's protocol. Please refer to the protocol for additional required reporting to the Sponsor, FDA, etc.

- **Grade 2 Events -** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
- **Grade 3 Events** – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- **CTCAE Grade 4 Events –** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 Events –** Death related to AE

The DFCI IRB will determine whether reported Adverse Events meet the regulatory definition of an *Unanticipated Problems Involving Risks to Subjects or Others* requiring reporting to:

1) The agency(s) regulating the research (e.g., FDA, DOD, OHRP); and
2) The agency(s) funding the research (e.g., NIH, DOD); and
3) The IRB of record for the research if the DFCI IRB is not the IRB of record.

Questions: Please direct questions about this policy, or submitted AEs, to the DFCI OHRS Event Reporting email box. You should receive a response within one business day.

Any urgent inquiries should be followed up with an email to the OHRS main contact **OHRS@dfci.harvard.edu.**

DFCI IRB Serious Adverse Event Reporting Procedures:

- All life threatening and fatal Serious Adverse Events (grade 4 and 5) considered serious, unexpected, and related, must be submitted via a written adverse event report to OHRS **within 5 working days** from notification of the event.

- For all other Serious Adverse Events considered serious, unexpected, and related, a full written adverse event report must be submitted to OHRS **within 10 working days** from notification of the event.

- Any unrelated adverse event does not require reporting to OHRS except grade 5 events which must be reported at the time of continuing review.

Please Note: Serious Adverse Events must be reported to OHRS from first study intervention (e.g., first dose) until 30 days after the last study intervention.

- All Serious Adverse Event Reports must be submitted in iRIS using the Event – Adverse Event, Violation, Reportable New Information Form. No interoffice submissions, faxes, or e-mail notifications will be accepted.

  When reporting adverse events to the DFCI IRB, the Event Reporting form must be used to report SAEs experienced by DF/HCC participants enrolled in a DF/HCC study including any SAEs on DF/HCC led Multi-Center trials where the event occurs at a non-DF/HCC site. If a PI determines that the adverse event warrants a change to the protocol and/or consent form document(s), an amendment should be submitted in iRIS. The Event Reporting form should list the iRIS AM reference number whenever possible.

Unanticipated Problems:
When reporting a Serious Adverse Event that meets the criteria for an Unanticipated Problem (UAP) to the DFCI IRB, research teams should indicate whether the UAP has previously been reported to the FDA or other federal agency by the study sponsor or Principal Investigator. For

events that have already been reported to regulatory agencies, the research teams will be prompted to provide the manner and date of report, and any supporting documents. The IRB or OHRS will require documentation or evidence of appropriate federal agency reporting by sponsor/investigator or OHRS will directly report the event to the agency which oversees the research.

Other Reporting Requirements:

- **PI-Initiated/Sponsor holds IND**: The sponsor-investigator, as the holder of the IND/IDE, is responsible for reporting SAEs directly to the FDA via the FDA Form #3500a (Mandatory MedWatch Form). In addition to the Mandatory MedWatch Form, the DF/HCC PI may also be required to complete a form supplied by the investigational drug sponsor. DF/HCC investigators must comply with all reporting requirements, even if they differ from the DFCI IRB reporting requirements.

- **Industry Sponsored (Investigational)**: In addition to the DFCI IRB Event Reporting form, the DF/HCC PI may also be required to complete a form supplied by the sponsor. The DFCI IRB reporting requirements may differ from the sponsor's. DF/HCC investigators must comply with both.

- **Industry Sponsored (Commercial)**: In addition to the DFCI IRB Event Reporting form, the DF/HCC PI may also be required to complete a form supplied by the sponsor. The DFCI IRB reporting requirements may differ from the sponsor's. DF/HCC investigators must comply with both. The FDA's Form, #3500 (Voluntary MedWatch Form) may be used to voluntarily report serious adverse events, potential and actual medical product errors, and product quality problems associated with the use of FDA-regulated drugs, biologics, devices and dietary supplements.

References:

Unexpected (21 CFR 312.32(a))
Unexpected means the adverse event 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 (e.g., protocol).

Unexpected also means that while an adverse event is mentioned in the investigator brochure as occurring with a class of drugs, or as anticipated from the pharmacological properties of the drug, it is not specifically mentioned as occurring with the particular drug under investigation.

Adverse events listed in the investigator brochure as occurring with members of the same class of drugs, or as anticipated from the pharmacological properties of the drug, would be considered *unexpected* until they have been observed with the drug under investigation.

Reasonable Possibility of a Suspected Adverse Reaction (21 CFR 312.32(a))
Within the reporting requirement under 21 CFR 312.32(c)(1)(i), FDA makes clear the meaning of *reasonable possibility* by providing the following examples of types of evidence that would suggest a causal relationship between the drug and the adverse event.

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

Suspected adverse reaction means any *adverse event* for which there is a *reasonable possibility* that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

FDA Guidance: Adverse Event Reporting to IRBs – Improving Human Subject Protection (January 2009): https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adverse-event-reporting-irbs-improving-human-subject-protection

FDA Guidance: Safety Reporting Requirements for INDs and BA/BE Studies (December 2012): https://www.fda.gov/files/drugs/published/Safety-Reporting-Requirements-for-INDs-%28Investigational-New-Drug-Applications%29-and-BA-BE-%28Bioavailability-Bioequivalence%29-Studies.pdf

For HHS Regulated Research - OHRP Guidance and Definitions (January 2007):

Unanticipated Problems:
The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

1. *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;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a *reasonable possibility* that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. 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.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research.

For FDA Regulated Research – FDA Guidance and Definitions:

Unanticipated Problem:

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, only if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure).

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.

1. 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).

2. 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).

3. 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.

4. 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.

5. 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.
6. 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.

The HHS regulations at 45 CFR part 46 do not define or use the term *adverse event*. The term *adverse event* in general is used very broadly and includes any event meeting the following definition:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

OHRP Guidance: Unanticipated Problems Involving Risks and Adverse Events Guidance (January 2007): https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html