# DFCI Institutional Review Board:
## Adverse Event Reporting Policy

The DFCI IRB defines *Adverse Events* as events that meet the following criteria:

- **CTCAE Grade 2 and Grade 3 Events** – that are *Unexpected* and there is a *Reasonable Possibility* that the *Adverse Event* is related to the study Intervention.

- **CTCAE Grade 4 Events –** Report all events that are *Unexpected*. Events that are *Expected* and *listed within the protocol and/or current consent form* do not need to be reported to the DFCI IRB. Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable. See protocol for additional reporting requirements (to sponsor, FDA, etc.).

- **ALL CTCAE Grade 5 Events.**

**Notes:**
- Adverse Events must be reported for all subjects enrolled and actively participating in a study, or when the event occurs within 30 days of the last research study intervention (e.g. drug administration).
- The version of the Common Terminology Criteria for Adverse Events (**CTCAE**) listed in the protocol should be used to grade events.
- Serious Adverse Event reporting may be different based on the sponsors protocol. Please refer to the protocol for additional required reporting to the Sponsor, FDA, etc.

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 a call to the OHRS main number at **(617) 632-3029**.

**DFCI IRB Adverse Event Reporting Procedures:**

- **ALL Grade 5 events** must be communicated via email to the DFCI OHRS Event Reporting email box at the time of initial notification of the event, if the event is < 30 days from the last study intervention. A full written report must then be submitted to OHRS as required below.

- If the subject is in Long Term Follow Up, and > 30 days from the last study intervention, the adverse event is reported at continuing review.

- For all events, a full written adverse event report must be submitted to OHRS **within 10 working days** from notification of the event.

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

- When reporting adverse events to the DFCI IRB, the DFCI IRB AE Reporting Form must be used to report AEs experienced by DF/HCC participants enrolled in a DF/HCC study including any AEs 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 AM should be submitted in iRIS. The Event Reporting form should list the iRIS AM reference number whenever possible.

When reporting an 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 AE 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 AE 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.

- **Human Gene-Transfer Studies:** The PI must report all applicable adverse events to the NIH/OBA per the OBA Guidelines outlined in Appendix M-I-C-4: http://www.osp.od.nih.gov/sites/default/files/resources/NIH_Guidelines.pdf . Additional information about Human Gene-Transfer Reporting requirements can be found in section 25.8 Gene Transfer Reporting Requirements of the DF/HCC Guide to Human Research Activities (Revised August 2014).

**References:**

**For FDA Regulated Research - FDA Guidance and Definitions** (December 2012):

**Adverse Event (21 CFR 312.32(a))**
*Adverse Event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

**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/downloads/RegulatoryInformation/Guidances/UCM126572.pdf

FDA Guidance: Safety Reporting Requirements for INDs and BA/BE Studies (December 2012):
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.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.

**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