

## Section 25:

# Serious Adverse Event (SAE) Reporting

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The DF/HCC overall PI must report any significant adverse events (AE) for drugs, biologics, or devices to the appropriate parties (i.e., IRB, sponsor, FDA, NIH). When applicable, the DF/HCC overall PI should notify the national study chair (for multi-center/cooperative group trials). The treating investigator is responsible only for notifying the DF/HCC overall PI of the incident. In cases where an AE occurs involving a participant being treated or followed by a physician outside DF/HCC and there is a time requirement involved, all reporting should take place within the time specified based on a start date equal to the date of notification to the treating investigator or DF/HCC overall PI (whichever is first).

### 25.1 Definitions

**Adverse Event (AE):** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [NIH Guidelines, January 2001]

**Attribution:** The determination of whether an AE is related to a medical treatment or procedure.

**Disability:** A substantial disruption of a person's ability to conduct normal life functions.

**Life-threatening Adverse Event:** Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death). [21 CFR 312.32 (a)]

**Serious Adverse Event (SAE):** Any adverse drug experience, related to the research intervention, occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, any persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [21 CFR 312.32(a)]

**Unexpected Adverse Event:** Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected" as used in this definition refers to an adverse drug experience 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 pharmaceutical product. [21 CFR 312.32(a)]

### 25.2 Adverse Event Grading System

GRADING SYSTEM	DESCRIPTION
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life-threatening
Grade 5	Fatal

### 25.3 Attribution

ATTRIBUTION CATEGORIES	DESCRIPTION
Definite	The adverse event <i>is clearly related</i> to the investigational agent(s).
Probable	The adverse event <i>is likely related</i> to the investigational agent(s).
Possible	The adverse event <i>may be related</i> to the investigational agent(s).
Unlikely	The adverse event <i>is doubtfully related</i> to the investigational agent(s).
Unrelated	The adverse event <i>is clearly NOT related</i> to the investigational agent(s).

### 25.4 DFCI IRB Reporting Requirements

The DFCI IRB requires the following be reported as a SAE:

- **Grade 2 (moderate) and Grade 3 (severe) Events** – Only events that are Unexpected and Possibly, Probably or Definitely Related/Associated with the Intervention.
- **ALL Grade 4 (life threatening or disabling) Events** – Unless expected AND specifically listed in protocol as not requiring reporting.
- **ALL Grade 5 (fatal) Events** – When participant is enrolled and actively participating in the trial OR when event occurs within 30 days of the last study intervention.

Notes:

- If subject is in Long Term Follow Up, death is reported at continuing review.
- See protocol for additional reporting requirements (to sponsor, FDA, etc.).

#### Receipt and review of IND/IDE safety reports

As of March 1, 2009, the Dana-Farber Cancer Institute (DFCI) Institutional Review Board (IRB) will not accept IND/IDE Safety Reports reporting events that take place outside of the DF/HCC by outside sponsors unless the event is:

1. Serious or Life-Threatening; **and**
2. Unexpected; **and**
3. Related to the Research Intervention; **and**
4. **Has an implication for the conduct of the study you are conducting using this study**

**intervention** (Example: the new risk changes the original risk benefit ratio of the study approved by the IRB. This would also apply to informing participants previously treated with the agent of newly identified potentially serious long-term risks.)

Responsibility of DF/HCC overall Principal Investigator (PI):

It is the responsibility of the overall PI to review all IND/IDE safety reports provided by an outside sponsor (or themselves if they are the sponsor) **within 60 days of receipt** and determine that indeed the four criteria above DO NOT APPLY.

Any sponsor correspondence requiring immediate action as a result of an adverse event and requiring modifications to a protocol, informed consent document or investigator's brochure (e.g. NCI Action letters) must be submitted as an amendment to OHSR **within 10 days of receipt**.

IND/IDE meets the criteria above

If the IND/IDE safety report **meets** all of the criteria noted above, the overall PI must submit the IND/IDE safety report to the IRB, through OHSR Submit, via the amendment form **within 90 days from original date of receipt** including any applicable changes to the protocol and/or consent form.

IND/IDEs that are not submitted

The continuing review form includes a requirement that the overall PI attests to the review of all IND/IDE safety reports that have been issued during the year but not submitted to the IRB because they did not meet the reporting criteria above.

## 25.5 Serious Adverse Event (SAE) Reporting Form

The SAE Reporting Form must be used to report SAEs experienced by DF/HCC participants enrolled in a DF/HCC study including any serious adverse events on DF/HCC led Multi-Center trials where the event occurs at a non-DF/HCC site. The SAE reporting form is available on the [OHSR website](#). Full written SAE report must be submitted to OHSR as soon as possible, but no later than **10 working days** from notification of event.

If the overall PI determines that the adverse event warrants a change to the protocol and/or consent form document(s) the completed SAE form must be submitted via OHSR Submit along with an amendment form. The SAE report must be included with the amendment submission as supporting documentation for the IRB to review.

## 25.6 Adverse Event Expedited Reporting System (AdEERS)

The NCI AdEERS form may be used in place of the DFCI IRB SAE Reporting Form for NCI or cooperative group trials only. Reporting via AdEERS is available only through the Internet and can be found at [https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers\\_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). AdEERS will automatically file the report with the respective cooperative group. If the AdEERS form is used, the OHSR (ohrs@dfci.harvard.edu) **must** be included on the email to the NCI.

The following information **MUST** be included in the e-mail and within the description section of the AdEERS form:

1. DF/HCC Protocol Number
2. DF/HCC Overall Principal Investigator's Full Name
3. Whether the event warrants a change to the protocol/consent documents and/or procedures

If the overall PI determines that the adverse event warrants a change to the protocol and/or consent form document(s) the completed AdEERS report must be submitted via OHRS Submit along with an amendment form. The AdEERS report must be included with the amendment submission as supporting documentation for the IRB to review.

## 25.7 SAE Follow-up Reports

When submitting a follow-up report to a previously reported SAE or AdEERS, **attach a copy of the original report and any prior IRB determinations to the follow up report.** This gives the reviewer information required to conduct a thorough review and eliminates questions that might otherwise be raised.

### Reminders when submitting SAE reports to OHRS

1. Copies of *all* reports must be submitted to OHRS. SAE and AdEERS reports may be:
  - a. Reviewed by an IRB member via expedited review procedures; or
  - b. Reviewed by the full IRB.
2. For trials that require a report to be filed with other agencies (trial sponsor, FDA, NIH/OBA, institutional biosafety committees, etc.), submission to OHRS does *not* relieve you from filing a report directly with these agencies.
3. For confidentiality reasons, patient identifiers (i.e., name, social security number, address) *must* be removed.
4. All submission must be made electronically via OHRS Submit. OHRS does *not* accept faxed or emailed reports, unless otherwise authorized (e.g. AdEERS reports).
5. Handwritten reports will *not* be accepted. All reports must be typed.
6. Please do *not* send laboratory reports and/or discharge summaries or other information from medical records. These will be requested if required by the IRB reviewer.
7. The “historical information” requested should be available from the study files based on the previously filed SAE reports.

## 25.8 Gene Transfer Reporting Requirements

The PI is responsible for reporting all applicable adverse events to the NIH/OBA. Per the OBA Guidelines outlined in Appendix M-I-C-4 ([http://oba.od.nih.gov/oba/rac/guidelines\\_02/NIH\\_Guidelines\\_Apr\\_02.htm](http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm)), the following must be reported:

1. Any SAE that is both unexpected and associated with the use of the gene transfer product; and
2. Any new finding from animal testing that presents a significant risk for human research.

Reports must be sent:

1. Within 15 days if unexpected and associated;
2. Within 7 days if fatal or life-threatening, unexpected, and associated;
3. No later than 15 days of receipt by the investigator/sponsor for follow-ups for previously reported events;
4. Within 15 days of the determination that an event that occurs after the end of a trial is associated with the use of the gene transfer product; and
5. As soon as possible but no later than 15 days after the sponsor's initial receipt of information of any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity must be reported as soon as possible.

Submit the appropriate IRB form, after removing *all* patient identifiers, to the following:

- Institutional Biosafety Officer
- Sponsor, if applicable (The sponsor may have its own reporting form.)
- FDA (if serious and unexpected, or death)
- NIH/OBA

**Note:** Under the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, a PI may delegate the reporting responsibilities set forth in [Appendix M-I-C](#) to another party (i.e., the sponsor), with written notification of the delegation to the OBA. The protocol document should outline the reporting policy.

## 25.9 PI-Initiated/IND Holder Reporting Requirements

If a DF/HCC investigator holds an IND/IDE on the agent/device, he or she *must* report directly to the FDA. He or she also has a responsibility to communicate that information *to any other investigators conducting the trial* under the IND/IDE.

Submit the *Mandatory* FDA Form #3500a (Mandatory MedWatch Form), available on the FDA website at <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>, to the following:

- FDA
- Other investigators conducting trials under the IND/IDE

## 25.10 PI-initiated/Sponsor Holds IND Reporting Requirements

The sponsor, as the holder of the IND/IDE, is responsible for reporting serious adverse events directly to the FDA. In addition to the FDA Form #3500a (Mandatory Medwatch Form), the DF/HCC overall 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.

## **25.11 Industry-sponsored (Investigational) Reporting Requirements**

Refer to the above section entitled PI-initiated/Sponsor Holds IND Reporting Requirements.

## **25.12 Industry-sponsored (Commercial) Reporting Requirements**

The *Voluntary* FDA form #3500 (MedWatch) may be used to voluntarily report an SAE, potential and actual medical product errors, and product quality problems associated with the use of FDA-regulated drugs, biologics, devices, and dietary supplements. The form is available on the FDA website at <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>. The sponsor of the trial, however, may have its own form.