Policy and Procedure Manual
Administrative Manual
Administrative Institutional
Department: Research Operations

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Reviewing and Reporting Unanticipated Problems and Adverse Events Involving Risk to Research Participants or Others

I. PURPOSE / BACKGROUND

The purpose of this policy is to define the requirements for reporting unanticipated problems and adverse events, the time frame for reporting, and the method to be utilized for reporting while maintaining compliance with all applicable guidelines and regulations.

City of Hope (COH) has recognized the need to have a policy that covers unanticipated problems and adverse event reporting to all applicable parties, including but not limited to the Institutional Review Board (IRB), Data and Safety Monitoring Committee (DSMC), Food and Drug Administration (FDA), National Institutes of Health (NIH) and other sponsoring entities, e.g., pharmaceutical companies.

II. DEFINITIONS

A. Unanticipated Problem [45 CFR 46.103(a) and 45 CFR 46.103(b)(5)]

Any incident, experience or outcome that meets **all** of the following criteria:[1]

1. Unexpected (in terms of nature, severity, or frequency) given the following:
   a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document, or Investigators Brochure (IB); and
   b) the characteristics of the subject population being studied; and is
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or 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 previously known or recognized.

B. Unanticipated Problems that ARE Adverse Events [45 CFR 46]

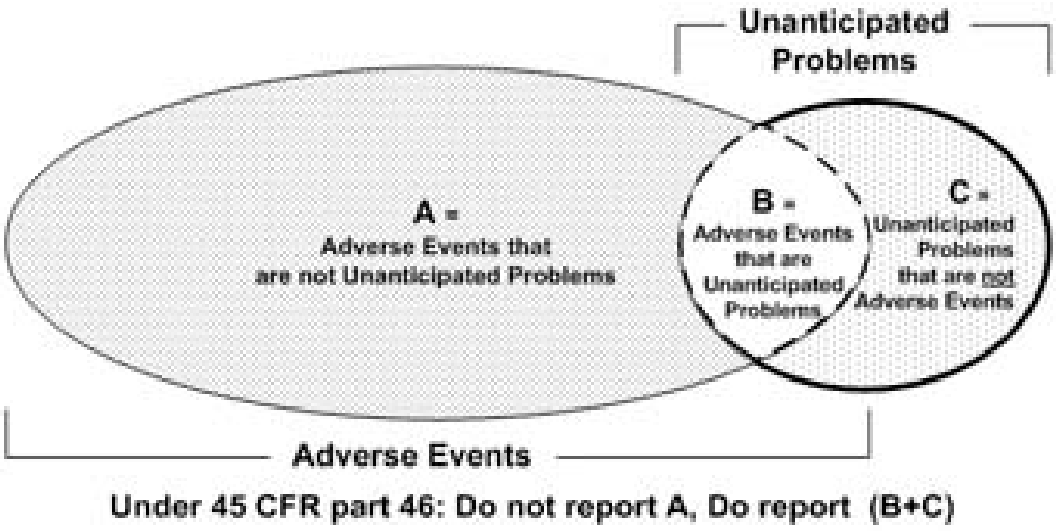
Adverse events are any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research (modified form the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

C. Unanticipated Problems that are Not Adverse Events [45 CFR 46]

Unanticipated problems that do not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. For example, report occurrences of breaches of confidentiality, accidental destruction of study records, unaccounted for study drug, or black box warnings issued by the FDA. This also includes unplanned protocol deviations/violations that have already occurred, that may adversely affect the rights, safety or welfare of the research participants, AND for which you did not seek IRB approval. Please review the 'Clinical Research Protocol Deviation Policy' for deviation reporting requirements.

Please refer to Attachment A "Reporting Unanticipated Problems and Adverse Events to IRB and DSMC" for further clarification.

The following Venn diagram[1] summarizes the general relationship between adverse events and unanticipated problems:



Under 45 CFR part 46: Do not report A, Do report (B+C)

Area A The vast majority of adverse events occurring in human subjects are not unanticipated problems and do NOT require expediting reporting to the IRB. The DSMC has different reporting requirements, see Table 1 for DSMC requirements.

Area B A small proportion of adverse events are unanticipated problems and DO require expedited reporting to the IRB and DSMC.

Area C Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events and DO require expedited reporting to the IRB and DSMC.[1]

D. Adverse Events

1. Adverse Reaction

   Any adverse event caused by the drug or device. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug or device caused the event.[2]

2. Suspected Adverse Reaction

   Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug or device caused the adverse event. For the purposes of

Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug or device and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by the drug or device.[2]

3. Unexpected Adverse Event [Modified from the definition of unexpected adverse drug experience in FDA regulations 21 CFR 312.32(a)]

   An adverse event or suspected adverse reaction is considered "unexpected" if:

   - it is not listed in the IB and/or package insert,
   - is not listed at the specificity or severity that has been observed,
   - if an IB/Package Insert is not required or available, it is not consistent with the risk information described in the protocol and/or the informed consent,
   - is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.[2]

4. Expected Adverse Event

   Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.[3]

5. Serious Adverse Event [Modified from the definition of unexpected adverse drug experience in FDA regulations 21 CFR 312.32]

   Any adverse event, adverse reaction, or suspected adverse reaction that results in any of the following outcomes:

   a) death;
   b) is life threatening (places the subject at immediate risk of death from the event as it occurred);
   c) requires inpatient hospitalization or prolongation of existing hospitalization;
   d) a persistent or significant disability/incapacity;
   e) a congenital anomaly/birth defect;
   f) secondary malignancy, or
   g) any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

   NOTE: If either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting.[1]

6. Non-Serious Adverse Event

   Any event that does not meet the definition of a serious adverse event.

7. Internal Adverse Event

   An adverse event that occurs in a research participant enrolled in a study conducted at COH, or at a COH participating site.

8. External Adverse Event

   IND Safety Reports that are forwarded to the COH Principal Investigator (PI) from the study Sponsor (e.g., Pharmaceutical Companies, drug or device manufacturer or suppliers, NCI, Cooperative Groups, etc.) regarding Serious Adverse Events that have occurred at other sites conducting the same study or using the same Investigational Agent.

E. Regulatory Agencies and/or Committees

1. Data and Safety Monitoring Committee (DSMC)

   The DSMC is responsible for assessing safety and efficacy considerations for certain human research studies conducted at City of Hope, including COH investigator-initiated human research studies and those consortium studies which require reporting to the local/COH DSMC. Additionally, the DSMC monitors the overall compliant conduct of these studies and makes recommendations about stopping or continuing trials. To contribute to enhancing the integrity of trials, the DSMC may also formulate recommendations relating to improving adherence to protocol-specific regimens and procedures for data management and quality control.

2. Institutional Review Board (IRB)

   The Board has the responsibility to review, approve the initiation of, and changes to research and conduct periodic review of research involving human research participants. The primary purpose of such review is to assure the protection of the rights and welfare of human subjects.

3. Office of IND Development and Regulatory Affairs (OIDRA)

   The office at COH responsible for the submission of all adverse events to the federal agencies (e.g. FDA, OBA, etc) on any related investigator –initiated study.

4. Western Institutional Review Board (WIRB)

   An external IRB that COH contracts with to manage regulatory affairs for Pharmaceutical research studies conducted at City of Hope (except first in man and gene therapy trials).

5. Central Institutional Review Board (CIRB)

   An external IRB, sponsored by the National Cancer Institute (NCI) in consultation with the Department of Health and Human Services Office for Human Research Protections (OHRP), which enables investigators to enroll patients into NCI-sponsored clinical trials.

6. Institutional Biosafety Committee (IBC)

   The Committee has the responsibility to review all research involving the use of recombinant nucleic acids, including transgenic animal, plants and all human subjects' protocols involving gene transfer or gene therapy as defined in the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines).[6]

7. Food and Drug Administration (FDA)

   An agency of the United States (US) Department of Health and Human Services (HHS), responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and

over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics.

8. Office of Biotechnology Activities (OBA)

   An agency of the US National Institutes of Health responsible for promoting science, safety, and ethics in biotechnology through advancement of knowledge, enhancement of public understanding, and development of sound public policies. OBA oversees several advisory boards among which is the Recombinant DNA Advisory Committee, a public review group for human gene transfer research.

9. National Institutes of Health (NIH)

   An agency of the US Dept of HHS, the primary agency of the US government responsible for biomedical and health-related research. It consists of 27 separate institutes and offices, and includes the National Cancer Institute (NCI) and OBA.

10. Office of Human Research Protections (OHRP)

    An agency of the US Dept of HHS, the Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP helps ensure this by providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research.

III. POLICY

A. PROCESS FOR REPORTING

1. Unanticipated Problems

   All reports of unanticipated problems must be submitted by the PI within the timeframes that follow unless otherwise noted in the protocol. Reporting requirements for the Institution may differ from the Sponsor of the trial.

   For trials where an external IRB is the IRB of record (e.g. WIRB, CIRB, etc.), the IRB will contact the City of Hope IRB Operations Director regarding UP determinations, serious or continuing non-compliance and/or study suspension/termination. The COH IRB Operations Director will forward any such information to the appropriate officials, including but not limited to the Institutional Official, IRB Executive Committee, the DSMC and the IBC (as applicable, e.g. for gene transfer or gene therapy studies). The DSMC will review the report and determine whether the study will be allowed to continue, amended, suspended, or terminated.

   a) Unanticipated Problems that ARE NOT Adverse Events

      Within **5 calendar days** of notification of an unanticipated problem from an internal or external source, the PI or his/her designee will input the problem into the electronic reporting system as noted in the study protocol. Any follow-up information shall be submitted as soon as the relevant information is available.

   b) Unanticipated Problems that ARE Adverse Events

      Within **5 calendar days** of notification of an unanticipated problem from an

internal or participating site in a multi-site study, the Principal Investigator (PI) or his/her designee will input the problem into the electronic reporting system as noted in the study protocol, unless the adverse event is death after 30 days of last active treatment/therapy and unlikely related. All other unanticipated problems should be reported within **5 calendar days**, unless Grade 1 or 2 AE and unlikely related or unrelated (reference Tables I/II/III for Adverse Event Reporting Timelines for the IRB and DSMC)**.** Any follow-up information shall be submitted as soon as the relevant information is available.

Any report of external unanticipated problems that are adverse events **must** meet the following:[1]

1) Involves an event that is both serious and unexpected
2) Identifies all previous safety reports concerning similar adverse experiences
3) Analyzes the significance of the current adverse experience in light of the previous reports
4) Outlines a corrective action plan (such as a consent form or protocol change).

NOTE: If the adverse event is clearly NOT related to the study drug, device or procedures or wash-out process, it would not represent a risk to other subjects in the research or a problem for the study and therefore, does not have to be reported to the IRB of record. The DSMC has different reporting requirements, please see below for requirements.[1]

2. Adverse Events

a) Internal Adverse Events

1) Serious Adverse Events

All serious adverse events that occur on studies conducted at COH or a participating site conducting a protocol under the guidance of COH must be submitted by the PI to the DSMC as designated in the study protocol in accordance with the tables below. Any follow-up information shall be submitted as soon as the relevant information is available.

SAEs that are not UPs do not need to be reported within the stated timelines to the IRB.

Note, in accordance with 21 CFR 312.32 Serious Adverse Events with an outcome of death or life-threatening and meet the requirements for expedited safety reporting are due to the FDA within 7 days from receipt of notification of the event. To allow the Office of IND Development and Regulatory Affairs (OIDRA) to meet those timelines on Serious Adverse Events that occur on COH-held INDs, the timeline for submission is **5 calendar days**. SAE's with all other outcomes and meeting the requirements for expedited safety reporting are due to the FDA within 15 days from receipt of notification of the event.

SAEs requiring reporting to NIH OBA for gene transfer trials in accordance with NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, Appendix M-1-C-4, will be reported simultaneously with the FDA report to ensure prompt reporting.

2) Non-Serious Adverse Events

For IRB reporting, all adverse events must be reported at the time of continuing review to the IRB for first-in-human, Phase I, and first in pediatric studies as indicated in the table below. For all other studies, only adverse events that are grades 3-5 events must be reported to the IRB at the time of continuing review as indicated in the table below.

For DSMC reporting, all events should be reported as part of the PMT progress report submissions.

For the IBC only studies that involve gene transfer or gene therapy, the IBC will review the PMT progress reports.

The Clinical Trials Office is responsible for the continued monitoring and tracking of all adverse events in order to ensure non reportable events are reviewed and monitored and do not rise to a reporting level.

For COH-held INDs, the FDA and OBA require annual reporting of possibly, probably, definitely related AEs including serious and non-serious. To meet the FDA reporting requirements, all AE data must be entered into the electronic reporting system at least 45 days prior to the IND annual report due date. Note- this may not match the IRB annual continuing review date.

Table I: COH IRB Adverse Event Reporting Timelines

Required Reporting Timeframe to COH IRB		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment/therapy or within 30 days of the last day of active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days[1]	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4	
Possibly, Probably, Definitely	5 calendar days[1]	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2	
Possibly, Probably, Definitely	5 calendar days[1]	Annual[2]
Unlikely, Unrelated	Annual[2]	Annual[2]

[1] These events must be reported in the time frame if they meet the definition of an unanticipated problem.
[2] For studies that are not first in human, Phase I and first in pediatric trials, only grades 3-5 must be reported at annual review.

Table II: DSMC Risk Level 3 and Risk Level 4 Protocol Reporting Timelines

Required Reporting Timeframe to the DSMC		
Attribution	**Unexpected**	**Expected**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Within 30 days of last active treatment/therapy	
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in hospitalization	
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days
After 30 days of last active treatment/therapy		
Grades 3 and 4 AND meeting the definition of serious		
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
Grades 1 and 2 AND resulting in hospitalization		
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required

Table III: DSMC Risk Level 1 and Risk Level 2 Protocol Reporting Timelines

Required Reporting Timeframe to DSMC		
Attribution	**Unexpected**	**Expected**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	5 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required

b) External Adverse Events

All serious, unexpected adverse events that meet the criteria of unanticipated problems as defined in Section II above that did not occur at COH (such as IND Safety Reports, Suspected Unexpected Serious Adverse Reactions [SUSAR]) but pertain to a drug, device or procedure currently used under a study protocol at COH, must be input into the electronic reporting system designated in the study protocol within 5 calendar days from receipt of notification.

3. External Reporting of Adverse Events

a) Reporting to the FDA

Upon notification of any adverse event that pertains to a study protocol being conducted under a COH-sponsored IND, OIDRA will:

1) prepare and submit a safety report to the FDA (OIDRA must report within 7 calendar days or 15 calendars to the FDA – refer to Section 2 (a) i) for any event that is serious; unexpected; and possibly, probably, or definitely related to the investigational agent in accordance with the timeframes as written in Code of Federal Regulations 21 CFR 312.32; and

2) submit all other events in the IND annual report.

b) Reporting for Federally Funded or Cooperative Group Studies

Reporting of Adverse Events for studies federally funded or Cooperative Group studies should refer to the reporting requirements specified in the study protocol.

c) Reporting to NIH/OBA-Reviewed Studies (gene-therapy):

For a COH-sponsored IND that requires reporting to NIH Office of Biotechnology Activities / Recombinant DNA Advisory Committee (OBA/RAC), the PI/designee will submit the event through the electronic reporting system and OIDRA will handle submissions of adverse events to NIH/OBA with a copy to the COH IBC.

d) Cancer Therapy Evaluation Program (CTEP) Sponsored Studies

Investigators must immediately report to the NCI ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention. Reporting of adverse events associated with a protocol being conducted under a CTEP IND requires electronic submission to the Adverse Event Expedited Reporting System (AdEERS) according to the timeframes outlined in **Table 1V** (AdEERS Reporting Timelines). This applies to all adverse events that occur within 30 days of the last dose of the Investigational Agent. For any study protocol approved **prior to** March 28, 2011, please reference http://ctep.cancer.gov for the appropriate reporting timelines.

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. This subset of AEs (ASAEL) contains events that are considered “expected” for expedited reporting purposes only. Refer to the protocol for your specific study agent CAEPR list.

Table IV: AdEERS Reporting Timelines for CTEP Sponsored Studies Only[4]

Phase 0		
	Expected / Unexpected	
Grades 3-5	24 hr / 5 calendar [a]	
Grade 1 and 2	10 calendar [b]	
Phase 1 and Early Phase 2		
	Expected / Unexpected	
	w/hosp	**w/o hosp**
Grade 3-5	24 hr / 5 calendar [a]	24 hr / 5 calendar [a]
Grade 2	10 calendar [b]	NR
Grade 1	NR	NR
Late Phase 2 and Phase 3 Studies		
	Expected / Unexpected	
	w/ hosp	**w/o hosp**
Grade 4 - 5	24 hr / 5 calendar [a]	24 hr / 5 calendar [a]
Grade 3	10 calendar [b]	10 calendar [b]
Grade 2	10 calendar [b]	NR
Grade 1	NR	NR
Cancer Imaging Program Involving Commercial (Non-IND/IDE) Agents Only		
	Expected / Unexpected	
	w/ hosp	**w/o hosp**
Grade 4 - 5	24 hr / 5 calendar [a]	24 hr / 5 calendar [a]
Grade 3	10 calendar [b]	10 calendar [b]
Grade 2	10 calendar [b]	NR
Grade 1	NR	NR

[a] "24-Hour; 5 calendar Days": AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
[b] "10 calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.
NR = Not reported

e) Pharmaceutical Sponsored Studies

Adverse events for those studies where the IND is held by a pharmaceutical company shall comply with the reporting requirements as outlined by the study Sponsor in either the study protocol or contractual agreement, if applicable.

f) COH Studies Exempt from IND/IDE Application

For those studies deemed to be exempt from either an IND or IDE application, either based on exemption following submission of an IND or IDE to the FDA or upon the approval of the IRB, the PI/designee shall

1) provide funding sponsor with adverse event data as stated per terms of the contract, if contractually obligated **and**

2) report any unanticipated problems involving risks to human subjects or others, as defined in 21 CFR 312.2(b)(iv) to the IRB of record within **5 calendar days** from receipt of the notification using the electronic reporting system specified in the study protocol.

IV. PROCEDURE

Role	Procedure Description
PI / Designee	1. Unanticipated Problems that ARE NOT Adverse Events: a. Input problem into the electronic reporting system as noted in the study protocol, within **five (5) calendar days** of notification of an unanticipated problem from either an internal or external source. Submit relevant follow-up information as available. 2. Unanticipated Problems that ARE Adverse Events: a. Input problem into the electronic reporting system as noted in the study protocol, within **five (5) calendar days** of notification of an unanticipated problem from either an internal or external source. Submit relevant follow-up information as available. (See policy section III-A-1-b for required information in report.) 3. Internal Adverse Events: a. Serious Adverse Events: Submit in accordance with Tables I-III. (See policy section III-A-1). Submit relevant follow-up information as available. b. Non-Serious Adverse Events: Report as designated in section III-A-2). 4. External Adverse Events (IND Safety Reports, SUSAR): a. Enter into the electronic reporting system designated in the study protocol in a timeframe not to exceed **five (5) calendar days** from receipt of notification, all serious, unexpected adverse events that meet the criteria of unanticipated problems that did not occur at COH. (See policy section III-A-2-b.) b. No DSMC reporting is required. 5. External Reporting of Adverse Events: a. Federally-Funded Sponsored Studies: Reporting of Adverse Events for studies federally funded or Cooperative Group studies should refer to the reporting requirements specified in the study protocol. b. Cancer Therapy Evaluation Program (CTEP) Sponsored Studies: Report IMMEDIATELY to the NCI ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention. (See policy section III-A-3-d.) c. Pharmaceutical Sponsored Studies: Comply with reporting requirements for adverse events as outlined by the study Sponsor in either the study protocol or contractual agreement, if applicable. (See policy section III-A-3-e.) d. Studies Exempt from IND/IDE Application: Provide funding sponsor with adverse event data as stated per terms of the contract, or elect to voluntarily report any adverse events to the manufacturer of the investigational agent using the *MedWatch Form 3500*. (See policy section II-A-3-f).

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References:

1. Office for Human Research Protections (OHRP) "Guidance on Reviewing and Reporting Unanticipated Problems

Involving Risks to Subjects or Others and Adverse Events", January 15, 2007.
2. Code of Federal Regulations, Part 21 §312.32(a), effective March 29, 2011.
3. "Clinical Research Definitions and Procedures", as presented by Steven Hirschfeld, MD, PhD, US Department of Health and Human Services, National Institutes of Health (date not provided).
4. "NCI Guidelines for Investigators: Adverse Event Reporting Requirements", Effective February 25, 2011.
5. S.I. Bearman, F.R. Appelbaum, C.D. Buckner et al., Regimen-related toxicity in patients undergoing bone marrow transplantation. J Clin Oncol 6 (1988), pp. 1562–1568.

Related Policies:

1. Clinical Research Protocol Deviation Policy

Appendix One – Acronyms, Terms and Definitions Applicable to this Policy:

1. **AdEERS** – Adverse Event Expedited Reporting System
2. **AE** – Adverse event
3. **ASAEL** – Agent Specific Adverse Event List
4. **CAEPR** – Comprehensive Adverse Event and Potential Risks list
5. **CIRB** – Central Institutional Review Board
6. **City of Hope (COH)** – City of Hope National Medical Center (COHNMC), Beckman Research Institute (BRI), and the City of Hope Medical Foundation (COHMF) collectively referred to as City of Hope (COH), for purposes of this policy.
7. **Community Practices** – Refers to non-hospital practices operated by City of Hope Medical Foundation (COHMF).
8. **CTEP** – Cancer Therapy Evaluation Program
9. **DSMC** – Data and Safety Monitoring Committee
10. **ERED** – Electromagnetic radiation emitting devices
11. **FDA** – Food and Drug Administration
12. **HHS** – U.S. Department of Health and Human Services
13. **IB** – Investigators Brochure
14. **IBC** – Institutional Biosafety Committee
15. **IND** – Investigational New Drug
16. **IRB** – Institutional Review Board
17. **Medical Center** – Refers to all facilities covered by City of Hope National Medical Center's hospital license.
18. **NIH** – National Institutes of Health
19. **OBA** – Office of Biotechnology Activities
20. **OHRP** – Office of Human Research Protections
21. **OIDRA** – Office of IND Development and Regulatory Affairs
22. **PI** – Principal investigator
23. **RAC** – Recombinant DNA Advisory Committee
24. **SAE** – Serious adverse event
25. **UP** – Unanticipated problem
26. **WIRB** – Western Institutional Review Board

Attachments:

- Appendix A: Adverse Event Grading Systems (2 pages)
- Attachment A: Unanticipated Problem Reporting Map

APPENDIX A: Adverse Event Grading Systems

1. Common Terminology Criteria for Adverse Events (CTCAE)

A grading system developed by the NCI to define adverse events. It is a 5-point scale generally corresponding to mild, moderate, severe, life-threatening and death. Grading is based on specific clinical criteria that usually require evaluation by the clinician. A link to the grading scale can be found at the following address:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

2. Clinical Islet Transplantation Terminology Criteria for Adverse Events (CIT TCAE)

An adverse event grading system modified on the CTCAE that is specific to patients who undergo islet transplantation. It is also a 5 point scale. A link to the grading scale can be found at the following address:
http://www.isletstudy.org/CITDocs/CIT-CAE%20V4.1_clean_16Jul2008.pdf

3. Division of AIDS (DAIDS)

A descriptive terminology, which can be utilized for adverse event reporting. A grading (severity) scale is provided for each item. It is established for use in Adult and Pediatric patients and includes parameters for both populations. Terminology is standardized for those patients with HIV/AIDS. A link to the grading scale can be found at the following address:
http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/daidsaegradingtable.pdf

4. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

The Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" recommends severity of clinical and laboratory abnormalities and a grading system can be useful in defining stopping rules. The guidelines are not enforceable; however, are suggested by the FDA. A link to the grading scale can be found at the following address:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm

5. Bearman Toxicity Grading Scale

This scale, developed by Bearman et al, was designed to carry out Phase I and II studies of new high-dose treatment regimens in transplant patients. The scale estimates the non-hematologic toxicities directly caused by a given transplant treatment regimen. Morbidity is assessed in eight organ systems; with toxicity graded on a 0 to 4 scale with grade 3 being life-threatening and grade 4 being fatal. Toxicities due to graft-versus-host disease are excluded from this grading system. [5]

Regimen-Related Toxicity According to Organ System

	Grade I	Grade II	Grade III
Cardiac Toxicity	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on chest x-ray with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder Toxicity	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal Toxicity	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary Toxicity	Dyspnea without chest x-ray changes not caused by infection or congestive heart failure; or chest x-ray showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	Chest x-ray with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO2 (> 10% from baseline) but not requiring mechanical ventilation or > 50% O2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or > 50% oxygen on mask and not caused by infection or CHF
Hepatic Toxicity	Mild hepatic dysfunction with bilirubin ≥ 2.0 mg/dL and ≤ 6.0 mg/dL or weight gain > 2.5% and < 5% from baseline, of non-cardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin > 6.0 mg/dL and < 20 mg/dL; or SGOT increase > 5-fold from preconditioning; or clinical ascites or image documented ascites > 100 mL; or weight gain > 5% from baseline of non-cardiac origin	Severe hepatic dysfunction with bilirubin > 20 mg/dL; or hepatic encephalopathy; or ascitis compromising respiratory function
CNS Toxicity	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI Toxicity	Watery stools > 500 mL but < 2,000 mL every day not related to infection	Watery stools > 2,000 mL every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

Note: Grade IV regimen-related toxicity is defined as fatal toxicity.
Abbreviations: CXR, chest x-ray; IV, intravenous.

ATTACHMENT A:

Reporting Unanticipated Problems and Adverse Events to IRB and DSMC

Note: This algorithm is from the following OHRP guidance document:
Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 2007

The following unanticipated problems must be reported by the Principal Investigator to the IRB and DSMC ***no later than 5 calendar days*** from the date of the event or from the date the investigator is notified of the event. Reference Table 1: City of Hope Adverse Event Reporting Timelines for the IRB and DSMC.
Use the Unanticipated Problem Reporting Form.

A. Unanticipated problems that are *not* adverse events ***(must meet all 3 of the following criteria)***.

1. ***Unexpected*** (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol-related documents; and (b) the characteristics of the subject population being studied.
2. ***Related or possibly related*** to participation in the research
3. ***Suggests that the research places subjects or others at a greater risk of harm*** (including physical, psychological, economic, or social harm) than previously known or recognized.

B. Adverse events *(both internal and external)* that are unanticipated problems ***(must meet all 3 of the above criteria) for an investigator initiated study***.

This includes, but is not limited to, adverse events that are SAEs. Use the following algorithm for determining whether an adverse event is an unanticipated problem.