


Title:	Reporting Obligations for Principal Investigators
Responsible Office:	Institutional Review Office (IRO)
Responsible Official:	Karen Hansen, IRO Director
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	Signature/date
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POLICY STATEMENT

To ensure that the rights and welfare of participants participating in research covered by the Center's Human Research Protection Program (HRPP) are properly protected and that such research complies with applicable laws and regulations, principal investigators are required to report certain (i) adverse events, (ii) other unanticipated problems involving risks to subjects and others, (iii) matters involving certain noncompliance and (iv) other matters specified by applicable law and by the Institutional Review Board (IRB).

DEFINITIONS

Adverse Event: Any harm or untoward medical occurrence in a research participant administered a medical product, medical treatment or procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment or procedure whether or not considered to be related.

Unexpected Adverse Event: Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- a. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- b. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event

Serious Adverse Event: An adverse event that results in any of the following outcomes: Death, a life-threatening adverse event (real risk of dying), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity/or change in psychosocial status, a congenital anomaly or, requires intervention to prevent permanent impairment or damage.

Minor noncompliance: Noncompliance that is neither serious nor continuing. Unless required by the applicable protocol, instances of noncompliance that clearly constitute minor noncompliance do not need to be reported. Minor noncompliance includes, but is not limited to, individual instances of the omission or modification of research activities that are in the best interests of human research participants; provided, that the omission or modification does not materially increase the risks to or otherwise seriously jeopardize the rights and welfare of human research participants or materially impair the integrity of the study data. It is recommended that principal investigators initially prepare and, as necessary, amend protocols to minimize instances of minor noncompliance.

Noncompliance: An intentional or unintentional action or activity relating to human subjects research by a person subject to the HRPP that violates or otherwise fails to adhere to one or more of (i) the requirements or determinations of the IRB, (ii) the HRPP, or (iii) laws or regulations governing the conduct of human subjects research including applicable FDA and DHHS regulations. For purposes of this policy, noncompliance may be serious, continuing or minor. "Noncompliance" does not include protocol deviations that are beyond the control of the principal investigator and his or her study staff (e.g. delays caused by weather or by the acts or omissions of third parties such as outside labs). However, this type of protocol deviation may constitute an unanticipated problem involving risks to research subjects or others reportable under IRB Policy 2.6, *Unanticipated Problems Involving Risks to Subjects or Others*.

Continuing noncompliance: Non-compliance that while not serious evidences a pattern of behavior that, if unaddressed, might jeopardize the rights and welfare of research participants the integrity of the study data or the integrity of the HRPP. Examples include a pattern of behavior that evidences a lack of attention to or knowledge of the HRPP or the protection of research participants or that is likely to continue without intervention.

Serious noncompliance: Noncompliance that materially increases the risks to or otherwise seriously jeopardizes the rights and welfare of human research participants or materially impairs the integrity of the study data. Serious noncompliance may include, but is not limited to, (i) the failure to obtain IRB approval of human subjects research when required under the HRPP or applicable laws and regulations, (ii) enrolling a research participant who does not fit the inclusion and exclusion criteria in the protocol, (iii) Failing to obtain or document informed consent, (iv) administering a drug required by the protocol at a dose or schedule that has not been approved by the IRB except when necessary to eliminate apparent immediate hazards to the research participant (see IRB Policy 2.5).

Suspension: Study accrual is temporarily closed. This means that the treatment/intervention with previously enrolled research participants/patients ceases, as determined by the IRB. However, the investigator may request, in writing, that the IRB permit currently enrolled research participants to receive treatment and/or intervention based on their health needs The investigator provides appropriate rationale in writing in a letter addressed to the IRB Chair.

Termination: Accrual is permanently closed and treatment and intervention with previously enrolled research participants must cease, as determined by the IRB.

Unanticipated Adverse Device Effect: An unanticipated adverse device effect means any serious adverse event caused by, or associated with, a device, if that event was not previously identified in nature, severity, or degree of incidence in the investigational plan or investigational device exemption ("IDE") application, or any unanticipated serious problem associated with a device and related to the rights, safety, or welfare of research participants. If there is no IDE for the device, an unanticipated adverse device effect means any serious adverse event caused by, or associated with, a device, if that event was not previously identified in nature, severity, or degree of incidence in the study protocol or consent, or any unanticipated serious problem associated with a device and related to the rights, safety, or welfare of research participants.

Unanticipated Problems Involving Risks to Subjects or Others: Any incident, experience, or outcome that meets both of the following criteria:

- Unexpected (in terms of nature [specificity], 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;
- Indicates that the research places research participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

REFERENCES

45 CFR §46.103(b) (5)
45 CFR §46.113
38 CFR §46.103(b) (5)
38 CFR §46.113
21 CFR §56.108(b)
21 CFR §56.113
21 CFR §312.32
21 CFR §312.33
21 CFR §312.64
21 CFR §812.150(a) (1)

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

Office of Human Research Protections (OHRP) Compliance Activities: Common Findings and Guidance #71 (a)-(c) and (m)-(o), and #72

Food and Drug Administration (FDA) Information Sheets: Continuing Review After Study Approval

NIH Guidelines for Research Involving Recombinant DNA Molecules

INDIVIDUALS AFFECTED BY THIS POLICY

This policy applies to Institutional Review Office (IRO) staff, IRB members, employees of the Center and investigators from other institutions who submit research studies to the Center IRB for review and approval.

PROCEDURES

1. Reporting Unanticipated Problems to the IRB

With respect to each research study he or she is conducting, the principal investigator must ensure that the following unanticipated problems involving risks to research participants or others are reported to the IRB not later than ten (10) calendar days after he or she first becomes aware of the problem:

- All adverse events that are (1) unexpected and (2) related or possibly related to the research and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm that was previously known or recognized. Examples include (i) unanticipated risks that although not serious require substantive changes to the consent form or (ii) a series of adverse events that individually may not be serious but indicate a trend that places research participants or others at a greater risk of harm than was previously known or recognized;
- Unanticipated problems involving risks to research participants or others that are not adverse events. These include problems involving (i) a risk of social or economic

harm as opposed to physical or psychological harm and (ii) a risk of harm, but without any actual harm occurring;

- Any other significant increase in the risks associated with the study.
- An interim analysis or safety monitoring report that may potentially impact a study's risk/benefit ratio, or is considered to place research participants at higher risk.
- Data Safety Monitory Board (DSMB) Reports. A DSMB report recommending change in the study's status or a change to the consent form/protocol.

The principal investigator must also ensure that any study termination or study suspension of any study he or she is conducting is reported to the IRB not later than ten (10) calendar days after he or she first becomes aware of the termination or suspension.

Detailed definitions, examples and procedures for reporting adverse events and other unanticipated problems involving risks to research participants or others can be found at *IRB Policy 2.6 Unanticipated Problems Involving Risks to Subjects or Others*.

For reporting requirements for adverse events or other unanticipated problems that do not meet the expedited reporting requirements described in this Section 1, see Section 4 of this policy on Reporting to the IRB at Continuation Review.

2. Reporting Noncompliance to the IRB

With respect to each research study he or she is conducting, the principal investigator must ensure that all serious or continuing non-compliance is reported to the IRB not later than ten (10) calendar days after he or she first becomes aware of the problem. If there is any question or possibility that noncompliance could constitute serious or continuing noncompliance, it should be reported.

- Serious noncompliance may include but is not limited to:
 - Failing to obtain IRB approval of human subjects research when required under the HRPP or applicable laws and regulations;
 - Enrolling research participants who do not fit the inclusion and exclusion criteria in the protocol;
 - Failing to obtain or document informed consent;
 - Administering a drug at a dose that has not been approved by the IRB; and
 - Administering a drug at a schedule not approved by the IRB.

Detailed definitions, examples and procedures for reporting noncompliance can be found at *IRB Policy 1.9 Noncompliance*.

3. Reporting Modifications to Approved Study Documents to the IRB

Modifications to study documents previously approved by the IRB require additional IRB approval before implementing the modification. Failure to obtain prior IRB approval to modify a previously approved protocol or consent constitutes noncompliance and may need to be reported under Section 2 above. Detailed definitions, examples and procedures for making modifications to approved studies including changes to the informed consent document can be found at *IRB Policy 2.5 Modifications to Ongoing Activities*.

4. Reporting to the IRB at Continuation Review

With respect to each research study he or she is conducting, the principal investigator must ensure that certain adverse events and other problems involving risks to research

participants, which do not require expedited reporting under Section 1 above are reported to the IRB at the time of the continuation review of a study.

Detailed definitions, examples and procedures for reporting to the IRB at the time of continuation review can be found at *IRB Policy 2.2 Continuing Review, OHRP Guidance on Continuation Review* (<http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm>) and *FDA Guidance on Continuation Review* (for FDA regulated clinical investigations).

5. Expedited Reporting on Unanticipated Problems Described in Third-Party Safety Reports

With respect to each research study he or she is conducting, the principal investigator must report adverse events described in third party or sponsor safety reporting form that are (1) unexpected and (2) related or possibly related to the research and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm that was previously known or recognized. The PI is responsible for making this assessment.

Reports of adverse events described in third party safety reporting forms that are **not** (1) unexpected and (2) related or possibly related to the research and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm that was previously known or recognized will **not** be maintained in the IRB study file and will be returned to the PI. If the sponsor of a study or protocol requires documentation of these types of reports, the PI must submit the *3rd Party Safety Reporting Form* noting that it is only being submitted because the sponsor or protocol required reporting to the IRB.

6. Reporting Adverse Events and other Matters as the Sponsor of an IND

In addition to any other reporting obligations under this policy, a principal investigator who is the Sponsor of an investigational new drug application (IND) must ensure the reporting of the following matters with respect to the IND:

- Regular Reporting. The sponsor must notify the United States Food and Drug Administration (FDA) and all investigators participating in the clinical investigation to which the IND relates of the following matters as soon as possible but in no event later than 15 days after the sponsor's initial receipt of the information:
 - Any adverse experience associated with the use of the drug that is both serious and unexpected. Please note that fatal or life-threatening events are reported on an expedited basis under subsection b below;
 - Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Expedited Reporting. The sponsor must notify the FDA by telephone or facsimile transmission as soon as possible but in no event later than 10 (ten) calendar days after the sponsor's initial receipt of the information of any unexpected fatal or life-threatening experience associated with the use of the drug.
- Annual Reporting. The sponsor must file an annual report with the FDA within 60 days of the anniversary of the effective date of the IND containing the information required in 21 C.F.R. Section 312.33 including a summary of serious adverse experiences by body system, a summary of IND safety reports for the last year and a list of research participants who died together with the cause of death.

Detailed definitions, examples and procedures for reporting and other obligations of the sponsors of INDs can be found in the FDA regulations at 21 C.F.R. Chapter 1, Part 312. See especially 21 C.F.R. Sections 312.32 and 312.33.

7. Reporting Adverse Events to the Sponsor as an Investigator under an IND

In addition to any other reporting obligations under this policy, an investigator for a clinical investigation subject to an investigational new drug application (IND) must promptly report any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug being studied. If the adverse effect is alarming, the investigator must report the adverse effect immediately. The investigator must also provide the sponsor with an adequate report shortly after completion of the investigator's participation in the clinical investigation.

Detailed definitions, examples and procedures for reporting and other obligations of investigators INDs can be found in the FDA regulations at 21 C.F.R. Chapter 1, Part 312. See especially 21 C.F.R. Section 312.64.

8. Reporting Adverse Events and other Matters as the Sponsor of an IDE

In addition to any other reporting obligations under this policy, a principal investigator who is the Sponsor of an investigational device exemption (IDE) must conduct an evaluation of any unanticipated adverse device effect relating to the IDE, and must report the results of that evaluation to the FDA, all reviewing IRBs, and participating investigators within ten (10) calendar days after the sponsor first receives notice of the effect.

Detailed definitions, examples and procedures for reporting and other obligations of the sponsors of IDEs can be found in the FDA regulations at 21 C.F.R. Chapter 1, Part 812. See especially 21 C.F.R. Sections 812.46(b) and 812.150(b) (1).

9. Reporting Adverse Events to the Sponsor as the Investigator under an IDE

In addition to any other reporting obligations under this policy, an investigator for a clinical investigation subject to an investigational device exemption (IDE) must submit to the reviewing IRB and the sponsor a report of any unanticipated adverse device effect occurring during the investigation as soon as possible, but in no event later than ten (10) calendar days after the investigator first learns of the effect.

Detailed definitions, examples and procedures for reporting and other obligations of the sponsors of IDEs can be found in the FDA regulations at 21 C.F.R. Chapter 1, Part 812. See especially 21 C.F.R. Sections 812.46(b) and 812.150(b) (1).

10. Reporting Adverse Events and other Matters for Studies Involving Recombinant DNA Experiments

In addition to any other reporting obligations under this policy, the principal investigator of any human subject's research involving experiments using recombinant DNA must ensure that the following matters relating to such research are reported:

- General Reporting Requirements. The principal investigator must ensure that the following matters are reported to the Center's Biological Safety Officer, the Center's Institutional Biosafety Committee (IBC), NIHs Office of Biotechnology Activities (OBA), and other appropriate authorities (if applicable) within 30 days:
 - Any significant problems;
 - Violations of the *NIH Guidelines for Research Involving Recombinant DNA*;
 - Any significant research-related accidents and illnesses.
- Regular Reporting of Adverse Events for Human Gene Transfer Studies. For research involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human subjects (human gene transfer research), the principal investigator must ensure that OBA and the IBC are notified

of the following matters as soon as possible but in no event later than 15 days after the investigator's initial receipt of the information:

- Any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators should not await definitive proof of association before reporting such events). If, after further evaluation, an adverse event initially considered not to be associated with the use of the gene transfer product is subsequently determined to be associated, then the event must be reported within 15 days of the determination. Please note that fatal or life-threatening events are reported on an expedited basis under subsection c below;
- Any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Expedited Reporting of Adverse Events for Human Gene Transfer Studies. The principal investigator must ensure that OBA and the IBC are notified by telephone or facsimile transmission as soon as possible but in no event later than ten (10) calendar days after the principal investigator learns of the information of any serious adverse event that is fatal or life-threatening, unexpected, and associated with the use of the gene transfer product.

Detailed definitions, examples and procedures for reporting requirements for human gene transfer research and other research using recombinant DNA can be found in the *NIH Guidelines for Research Involving Recombinant DNA*. See especially Section IV-B-7-a-(3) and Appendix M-I-C-4.

11. Protocol Reporting Requirements

In addition to any other reporting obligations under this policy, the principal investigator is responsible for ensuring that any reporting obligations required by the protocol or the sponsor of the research or clinical investigation for which he or she is the principal investigator are satisfied.

SUPPORTING DOCUMENTS

IRB Policy 2.6 Unanticipated Problems Involving Risks to Subjects or Others
IRB Policy 2.8 IRB Requirements for Reporting to Institutional and External Officials
IRB Policy 1.9 Noncompliance
IRB Policy 2.2 Continuing Review
3rd Party Safety Reporting Form