Fred Hutch Cancer Center

Institutional Review Board

Policy/Procedure

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POLICY STATEMENT

To ensure that the rights and welfare of research participants covered by the Fred Hutchinson Cancer Center (Fred Hutch) 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

See *HRP-001 - SOP - Glossary of Terms and Acronyms* for full definitions of the following:

Adverse Event

Adverse Reaction

Noncompliance ***(including Continuing, Minor, and Serious Noncompliance)***

Serious Adverse Event

Suspected Adverse Reaction

Suspension ***of IRB Approval***

Termination ***of IRB Approval***

Unanticipated Adverse Device Effect

Unanticipated Problems that Involve Risk to Research Participants or Others

Unexpected Adverse Event

Unexpected Suspected Adverse Event

INDIVIDUALS AFFECTED BY THIS POLICY

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

PROCEDURES

1. Reporting Unanticipated Problems to the IRB

When Fred Hutch is the IRB of Record:

With respect to each research study he or she is conducting, the Principal Investigator (PI) must ensure that the following unanticipated problems involving risks to research participants or others are reported to the Fred Hutch IRB not later than ten (10) calendar days after he or she first becomes aware of the problem:[1]

- 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 than was previously known or recognized. Examples include (i) unanticipated risks that although not necessarily 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;[2]
- 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) or Data Safety Monitoring Committee (DSMC) Reports. A DSMB or DSMC 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.[3]

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* (0224).

[1] HHS: 45 CFR 46.108(a)(4)(i); FDA: 21 CFR 56.108(b)(1)
[2] HHS: 45 CFR 46.116(c)(5); FDA 21 CFR 50.25(b)(5)
[3] HHS: 45 CFR 46.108(a)(4)(ii); FDA: 21 CFR 56.108(b)(3)

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 Continuing Review.

When a Fred Hutch Investigator Relies on an External IRB:

When a Fred Hutch investigator relies on an external IRB, the investigator must be familiar with the policies and procedures of the external IRB to ensure any potential unanticipated problems involving risks to research participants or others are reported in accordance with the external IRB's policies.

2. Reporting Noncompliance to the IRB

When Fred Hutch is the IRB of Record:

With respect to each research study he or she is conducting, the Principal Investigator must ensure that all potential 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.[4]

In addition, the following noncompliance events must be reported to the IRB within ten (10) calendar days of learning of the event even if the Principal Investigator or study staff does not believe the event constitutes serious or continuing noncompliance:

- The failure to obtain IRB approval of human subjects research when required under the HRPP or applicable laws and regulations;
- Enrolling a research participant who does not fit the inclusion and exclusion criteria in the protocol;
- Failing to obtain or document informed consent;
- Administering radiation, drugs, biologics, or cell products, or using devices 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 Modifications to Ongoing Activities* [025]).

The Fred Hutch IRB will determine if the event constitutes serious or continuing noncompliance. Detailed definitions, examples, and procedures for reporting noncompliance can be found at *IRB Policy 1.9 Noncompliance* (029).

When a Fred Hutch Investigator Relies on an External IRB:

When a Fred Hutch investigator relies on an external IRB, the investigator must be familiar with the policies and procedures of the external IRB to ensure any potential serious or continuing noncompliance is reported to the external IRB in accordance with the external IRB's policies.

3. Reporting Modifications to Approved Study Documents to the IRB

Modifications to study documents previously approved by the Fred Hutch 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* (025).

When a Fred Hutch investigator relies on an external IRB, the investigator must obtain IRB approval from the external IRB prior to implementing the modification, in accordance with the external IRB's policies.

4. Reporting to the IRB at Continuing Review

For research studies that require ongoing continuing review, the Principal Investigator must ensure that certain adverse events and other problems involving risks to research participants, which do not

[4] HHS: 45 CFR 46.108(a)(4)(i); FDA: 21 CFR 56.108(b)(2)

require expedited reporting under Section 1 above are reported to the Fred Hutch IRB at the time of the continuing review of a study.

Detailed definitions, examples and procedures for reporting to the IRB at the time of continuing review can be found at *IRB Policy 2.2 Continuing Review* (010)**,** *OHRP Guidance on Continuing Review* (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/index.html) and *FDA Guidance on Continuing Review* (for FDA regulated clinical investigations).

When a Fred Hutch investigator relies on an external IRB, the investigator must ensure information is submitted to the external IRB at the time of continuing review in accordance with the external IRB's policies.

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

When Fred Hutch is the IRB of Record:

With respect to each research study he or she is conducting, when there are active participants enrolled locally in the research study, 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. If the research study is permanently closed to local accrual, and there are no local participants receiving interventions or in long-term follow-up, then adverse events described in third party or sponsor safety reports do not need to be evaluated or submitted to the IRB.

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 should not be submitted and will **not** be reviewed by the IRB. .If the sponsor of a study or protocol requires documentation of these types of reports, the PI submits a Reportable New Information (RNI) submission in Hutch IRB, selecting "Sponsor/Protocol Requirement" as the category of new information. IRO staff will acknowledge the RNI. The PI, Primary Contact, and PI Proxies will receive an email notification acknowledging the submission. A formal acknowledgement letter will not be issued for reports that do not meet the IRB reporting criteria.

When a Fred Hutch Investigator Relies on an External IRB:

When a Fred Hutch investigator relies on an external IRB, the investigator must be familiar with the policies and procedures of the external IRB to ensure any reports of adverse events described in third party safety reporting forms are reported in accordance with the external IRB's policies.

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) ("Sponsor Investigator") must ensure the reporting of the following matters with respect to the IND:

- **Regular Reporting**. The Sponsor Investigator 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 no later than 15 (fifteen) calendar days after the Sponsor Investigator determines that reporting is required.
  - Any suspected adverse experience that is both serious and unexpected. Please note that fatal or life-threatening events are reported on an expedited basis under the subsection below entitled Expedited Reporting.
  - Increased rate of occurrence of serious suspected adverse reactions.
  - Findings from other clinical investigations that suggest a significant risk in humans (e.g., ongoing or completed clinical trials, pooled data from multiple trials).
  - Findings from animal or *in vitro* testing, whether or not conducted by the Sponsor Investigator that suggests a significant risk in humans exposed to the drug.

- Any serious adverse event that is the study endpoint and for which there is evidence suggesting a causal relationship between the drug/biologic and the event.

- **Expedited Reporting**. The Sponsor Investigator must notify the FDA by telephone or facsimile transmission as soon as possible but in no event later than 7 (seven) 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.
- **Follow-up Reporting**. The Sponsor Investigator must promptly investigate all safety information he/she receives; and, relevant follow-up information to an IND safety report must be submitted as soon as the information is available.
- **Annual Reporting**. The Sponsor Investigator 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 CFR 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.

If an adverse event is not initially determined to be reportable, but is later found to be reportable, the Sponsor Investigator must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Detailed definitions, examples and procedures for reporting and other obligations of the sponsors of INDs can be found in the FDA regulations at 21 CFR 312. See especially 21 CFR 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 IND must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event. In that case, the investigator must immediately report the event to the sponsor. 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 CFR 312. See especially 21 CFR 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 CFR 812. See especially 21 CFR 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 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 CFR 812. See especially 21 CFR 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 Fred Hutch Biological Safety Officer, the Fred Hutch 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 the Expedited Reporting of Adverse Events for Human Gene Transfer Studies 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.

12. Obtaining Prior Approval from NIH

In addition to other reporting obligations under this policy, the Principal Investigator is responsible for obtaining prior approval from NIH for any change in the originally approved grant scope. Principal Investigators should consult with their NIH project officer to determine if proposed changes to scope require prior approval. Procedures for obtaining prior approval, and examples of when prior approval is required, can be found in *NIH Notice: NOT-OD-12-129 (Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require NIH Prior Approval),* or at the Fred Hutch Office of Sponsored Research CenterNet page: https://centernet.fredhutch.org/cn/u/osr/project-management/prior-approvals/nih-change-in-scope-or-protocol.html.

13. Institutional Notification of External Audits

In the event a Principal Investigator or member of the study team receives notice of an audit by any outside regulatory agency (e.g., federal regulatory authority, funding agency, or unannounced regulatory inspector), the Principal Investigator must immediately (within 24 hours) notify the Fred Hutch Institutional Review Office (IRO) Director at 206.667.4372. The IRO Director will assure that a core group of administrative personnel representing the Office of the Director convenes to assure that proper audit coordination, Principal Investigator support, and communications are efficiently managed according to the organization's *Office of the Director Policy on Human Research Protection Program* (0280).

14. Reporting Major Events to the Institutional Review Office (IRO) (for AAHRPP reporting)

Fred Hutch was awarded full accreditation of the human research protection program by the Association for the Accreditation of Human Research Protections Programs, Inc. (AAHRPP) in March 2008. During the intervening years between accreditation site visits, the Fred Hutch IRO must submit reports to AAHRPP as applicable. The purpose of prompt reporting to AAHRPP is to ensure that AAHRPP is fully informed of compliance-related activities at Fred Hutch between regular accreditation site visits. The IRO must report Major Events to AAHRPP as soon as possible but generally within 48 hours of the organization, or any researcher, becoming aware of the event.

Therefore, with respect to each research study he or she is conducting, the Principal Investigator must ensure any of the following events are reported to the Institutional Review Office within 48 hours of becoming aware of the event:

1) Any negative actions taken by a government oversight office, including but not limited to:
    - OHRP Determination Letters;
    - FDA Warning Letters;
    - FDA 483 Inspection Reports with official action indicated;
    - FDA restrictions placed on the investigator;
    - Any corresponding compliance action taken by non-US authorities
2) Any negative press coverage (including but not limited to radio, TV, newspaper, online publications) regarding the Fred Hutch Human Research Protection Program.

Fred Hutch investigators must always notify the Institutional Review Office (IRO) Director of these major events, regardless of whether Fred Hutch is the IRB of record.

If the Fred Hutch investigator is relying on an external IRB, the investigator must be familiar with the policies and procedures of the external IRB to ensure any major events (as outlined above) are **also** reported in accordance with the external IRB's policies.

SUPPORTING DOCUMENTS

Office of the Director Policy on Human Research Protection Program (0280)

IRB Policy 1.9 Noncompliance (029)

IRB Policy 2.2 Continuing Review (010)

IRB Policy 2.5 Modifications to Ongoing Activities (025)

IRB Policy 2.6 Unanticipated Problems Involving Risks to Subjects or Others (0224)

HRP-001 - SOP - Glossary of Terms and Acronyms

REFERENCES

45 CFR 46.108

45 CFR 46.116

21 CFR 50.25

21 CFR 56.108

21 CFR 312

21 CFR 812

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

OHRP Guidance on Reporting Incidents to OHRP

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

FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies

NIH Guidelines for Research Involving Recombinant DNA Molecules

NIH Grants Policy Statement section 8.1.2.5

NIH Notice Number: NOT-OD-12-129 (Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require NIH Prior Approval)