Fred Hutch Cancer Center

Institutional Review Board

**Policy/Procedure**

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| **Title:** | Unanticipated Problems Involving Risks to Subjects or Others |
| **Version:** | 1.00 |
| **Effective Date:** | February 3, 2025 |
| **Responsible Office:** | Institutional Review Office (IRO) |
| **Responsible Official / Approved By:** | Meghan Scott, IRO Director |

## POLICY STATEMENT

Principal investigators and study staff are required to report all problems, events and information that require prompt reporting to the Institutional Review Board (IRB) within ten (10) calendar days of learning of the problem. Problems, events or information reported under this policy will be reviewed to determine whether it is an unanticipated problem involving risks to participants or others. No further action will be taken under this policy on reports determined to not represent unanticipated problems involving risks to participants or others. (Additional action may be required under *HRP-024 - POLICY - Noncompliance*).

If a problem, event or information submitted by an investigator or another source is determined by the Chair or designee to be a potential unanticipated problem involving risks to participants or others, it will be reviewed by the convened IRB. If the IRB determines the event meets the criteria for an unanticipated problem, appropriate steps will be taken, and it will be reported to appropriate institutional and governmental officials as provided under applicable law, *HRP-117 - POLICY - Requirements for Reporting to Institutional and External Officials* and this Policy.[1]

## DEFINITIONS

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

***Adverse Event***

***Principal Investigator (PI)***

***Related or Possibly Related Adverse Event***

***Serious Adverse Event***

***Third Party Safety Reports***

***Unanticipated Adverse Device Effect***

***Unexpected Adverse Event***

***Unanticipated Problems that Involve Risk to Research Participants or Others***

## INDIVIDUALS AFFECTED BY THIS POLICY

This policy applies to Institutional Review Office (IRO) staff, IRB members, Fred Hutch investigators and investigators from other institutions who submit research studies to the Fred Hutch IRB for review and approval. Instructions to investigators are posted on the IRO website. When Fred Hutch investigators are relying on an external IRB, the reporting requirements of the external IRB must be followed instead of this policy.

[1] HHS: 45 CFR 46.108(a)(4)(i); FDA: 21 CFR 56.108(b)(1), 21 CFR 312.66, 21 CFR 812.40, 21 CFR 812.150(a)(1), 21 CFR 812.150(b)(1)

## PRINCIPLES/OVERVIEW

Under the Human Subject Protection Program (HRPP) of Fred Hutch, principal investigators who conduct research involving human subjects are responsible for the safety of the research participants. Federal law requires that the IRB follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials and certain government agencies of unanticipated problems involving risks to research participants or others. This policy establishes procedures for determining which problems are unanticipated problems involving risks to research participants or others and for managing problems determined to be unanticipated problems involving risks to participants or others.

## PROCEDURES

### 1. Reporting Requirements

a. Expedited Reporting.

With respect to each research study, he or she is conducting, the principal investigator must ensure that the following problems, events, and information 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, event, or information.

i. Adverse Events. All adverse events (whether occurring on-site or off-site), which in the opinion of the principal investigator are (1) unexpected, and (2) related or possibly related to the research, and (3) serious or suggest that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized.

**Note:** Unless otherwise specified in the Protocol, therapeutic oncology protocols are not required to specify monitoring parameters for Grade I or II toxicities as described in the Common Terminology Criteria for Adverse Events published by the National Cancer Institute. These adverse events are expected and occur routinely in the subject population being studied. They should be monitored and treated in the practice of routine clinical care.

ii. Other Problems, Events, and New Information. Other problems, events, or new information that are unexpected and indicate that research participants or others are at greater risk of harm (including physical, psychological, economic, or social harm). Examples include:

- A series of related adverse events that individually may not be unexpected but indicate a trend that places research participants or others at a greater risk of harm than was previously known or recognized.
- 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.
- New information that may adversely affect the safety of participants or the conduct of the clinical trial.
- Any changes significantly affecting the conduct of the clinical trial or increasing risks to participants.
- 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.

**Note:** In addition to submitting a Reportable New Information (RNI) submission in Hutch IRB, the **IRO Director must be notified of negative actions taken by a government oversight office within 48 hours**. See *HRP-124 - POLICY - Reporting Obligations for Principal Investigators* for more information.

- Data Safety Monitoring Board (DSMB) or Data Safety Monitoring Committee (DSMC) Reports that recommend a change in the study's status or a change to the consent form/protocol.
- A paper published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.
- A change in FDA labeling that indicates new unexpected risks or the withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- A breach of confidentiality.
- Any accidental or unintentional change to the IRB approved protocol that harmed participants or others or that indicates participants or others may be at increased risk of harm.
- Incarceration of a participant in a protocol not approved to enroll prisoners.
- Sponsor imposed suspension or termination of a study for risk.
- Complaint of a participant when the complaint indicates unexpected risks.
- Complaint of a subject that cannot be resolved by the research team.
- Changes made to the research without prior IRB approval in order to eliminate apparent immediate hazard to research subjects.
- Any other unexpected increase in the risks associated with the study.
- Unanticipated adverse device effects occurring in any study of a device, whether or not subject to an investigational device exemption.

To report problems, events, or information as described in Section 1.a, the PI must submit create and submit a Reportable New Information (RNI) submission in Hutch IRB. *HRP-255 - FORM - Reportable New Information (RNI) Supplement* and any other relevant information should be attached to the submission.

The RNI submission will be reviewed by the IRB as outlined in Section 3.

b. Third-Party Safety Reports. For research studies where there are active participants enrolled locally, only those adverse events described in third party safety reports that expressly satisfy the requirements of Section 1.a. of this Policy should be reported under Section 1.a. The PI is responsible for making the assessment as to whether the third-party safety report meets the IRB reporting criteria and if there is a need to change the protocol and/or consent. 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 safety reports do not need to be evaluated by the PI or submitted to the IRB.

Reports of adverse events described in third party safety reports that do not satisfy the requirements of Section 1.a. will **not** be reviewed by the IRB. **Adverse events that do not satisfy the expedited reporting requirements of Section 1.a should not be submitted**. However, 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.

**2. Preliminary Assessment of Reports**

The IRO staff will pre-review all RNI submissions and preliminarily assess whether the report might be an unanticipated problem involving risks to participants or others or is definitely not an unanticipated problem involving risks to participants or others. The IRO staff reviewing the report will complete *HRP-364 - Worksheet - Reportable New Information (RNI)* as appropriate. If the IRO staff determines that the report is definitely not an unanticipated problem involving risks to participants or others, no further action is required under this policy. (Additional action may be required under *HRP-024 - POLICY - Noncompliance*.)

If the IRO staff cannot determine that the subject of the report is definitely not an unanticipated problem involving risks to participants or others, IRO staff will assign the RNI to a Designated Reviewer for further assessment. Generally, the Chair of the Committee that initially approved the research affected by the report (or designee) will review the RNI; however, any Designated Reviewer may be assigned. The Designated Reviewer will review the RNI submission, including *HRP-255 - FORM - Reportable New Information (RNI) Supplement*, any supporting documentation, and *HRP-378 - WORKSHEET - IRB Chair or Designee Report Checklist for Unanticipated Problems or Noncompliance.* For reports made under Section 1a. the review by the Designated Reviewer should normally occur within 2 business days from the time the report is received by the IRO. The Designated Reviewer will determine whether the report is a potential an unanticipated problem involving risks to participants or others or is definitely not an unanticipated problem involving risks to participants or others.

- If the Designated Reviewer determines that the RNI is definitely not an unanticipated problem involving risks to participants or others, the RNI will be acknowledged. No further action is required under this policy. (Additional action may be required under *HRP-024 - POLICY - Noncompliance*.) Once no further action is required, IRO staff will issue an acknowledgement letter. The individual that submitted the RNI as well as the PI, Primary Contact, and PI Proxies of a related study are notified of the IRB's conclusions and any actions. These individuals will receive an automated email notification from Hutch IRB that provides a link to the RNI submission, where the formal acknowledgement letter is available for download.
- If the Designated Reviewer determines that the RNI is a potential unanticipated problem involving risks to participants or others, then the RNI submission will be referred for Full Committee Review as outlined in Section 3. The Designated Reviewer will determine if an emergency meeting of the IRB is necessary or if the IRB review can occur at the next scheduled meeting of the IRB.

**3. Review of RNIs and Action by the IRB**

The following documentation will be available to all IRB members in Hutch IRB:

- The RNI submission, including *HRP-255 - FORM - Reportable New Information (RNI) Supplement* and any other relevant attachments
- The protocol
- The current consent document(s)
- *HRP-378 - WORKSHEET - IRB Chair or Designee Report Checklist for Unanticipated Problems or Noncompliance*

The IRB will first determine whether the report is an unanticipated problem involving risks to participants or others.

If the IRB determines that the report is not an unanticipated problem involving risks to participants or others, then no further actions is required under this policy. (Additional action may be required under *HRP-024 - POLICY - Noncompliance*.)

The IRB may table the report and request that additional facts be collected or that a further investigation be conducted if necessary for its determinations.

If the IRB determines that the report is an unanticipated problem involving risks to participants or others, then the IRB will consider at a minimum the following actions:

- Requiring additional information from the principal investigator with a plan for corrective action
- Monitoring or Auditing of the active protocol
- Requiring modification of the protocol
- Requiring modification of the consent

- Requiring the re-consenting of and/or providing additional information to current research participants (must occur when such information, such as new safety information, may affect the willingness of current participants to continue to take part in the research.)[2]
- Requiring the re-consenting of and/or providing additional information to past research participants
- Monitoring the consent process as described in *HRP-090 – POLICY – Informed Consent*
- Requiring more frequent continuing review of the study
- Requiring additional training of study staff
- Prohibiting use of the data collected for publication
- Suspending or terminating the protocol[3]
- Requesting that the Institutional Official (IO) (or designee) withhold funding for the study conditioned on appropriate corrective measures or informing other Fred Hutch entities about the unanticipated problem determination as appropriate.

Upon completion of the IRB's review, the individual that submitted the RNI as well as the PI, Primary Contact, and PI Proxies of the related study are notified of the IRB's conclusions and any actions. These individuals will receive an automated email notification from Hutch IRB that provides a link to the RNI submission, where the formal result letter is available for download. The IRO staff will then follow *HRP-117 - POLICY - Requirements for Reporting to Institutional and External Officials* including timelines for reporting these events.

## SUPPORTING DOCUMENTS

HRP-001 - Glossary of Terms and Acronyms

HRP-024 - POLICY - Noncompliance

HRP-090 - POLICY - Informed Consent

HRP-117 - POLICY - Requirements for Reporting to Institutional and External Officials

HRP-124 - POLICY - Reporting Obligations for Principal Investigators

HRP-255 - FORM - Reportable New Information (RNI) Supplement

HRP-364 - WORKSHEET - Reportable New Information (RNI)

HRP-378 - WORKSHEET - IRB Chair or Designee Report Checklist for Unanticipated Problems or Noncompliance

## REFERENCES

21 CFR 50.25

21 CFR 56.108

21 CFR 56.113

21 CFR 312.66

21 CFR 812.40

21 CFR 812.150

45 CFR 46.108

45 CFR 46.113

45 CFR 46.116

OHRP Compliance Activities: Common Findings and Guidance # 5

OHRP Guidance on Continuing Review

NIH Guidance: Reporting Adverse Events to IRBs supported Multicenter Clinical Trials

[2] HHS: 45 CFR 46.116(c)(5); FDA: 21 CFR 50.25(b)(5)

[3] HHS: 45 CFR 46.113; FDA 21 CFR 56.113

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

## VERSION HISTORY

| Version | Effective Date |
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