FRED HUTCH
Institutional Review Board

Policy/Procedure

Title:	Unanticipated Problems Involving Risks to Subjects or Others
Policy:	2.6
Version:	10.00
Effective Date:	August 1, 2021
Responsible Office:	Institutional Review Office (IRO)
Responsible Official:	Meghan Scott, IRO Director  Digitally signed by Meghan Scott Date: 2021.07.29 13:58:13 -07'00' 7/29/2021
	Signature/date

Version History	Effective Date
9.00	02-24-2020
8.00	11-15-2019
7.00	01-21-2019
6.05	06-19-2017
6.04	06-15-2015
6.03	06-01-2012
6.02	10-07-2011
6.01	03-22-2010
6.00	04-17-2009
5.02	07-24-2008
5.01	01-14-2008
4.00	08-01-2007
3.00	03-26-2007
2.00	03-09-2007
1.00	12-04-2006

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 *IRB Policy 1.9 Noncompliance* [029]).

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, *IRB Policy 2.8 IRB Requirements for Reporting to Institutional and External Officials* (021) and this Policy.[1]

DEFINITIONS

See *IRB Glossary of Terms and Acronyms* (050) for full definitions of the following:

Adverse Event

Related or Possibly Related Adverse Event

Serious Adverse Event

Unexpected Adverse Event

Unanticipated Adverse Device Effect

Third Party Safety Reports

Unanticipated Problems that Involve Risk to Research Participants or Others

Principal Investigator (PI)

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.

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.

[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)

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.
   - 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 the *Expedited Reporting Form for Reporting Unanticipated Problems or Noncompliance* (0203), the **IRO Director must be notified of negative actions taken by a government oversight office within 48 hours**. See *IRB Policy 1.11 Reporting Obligations for Principal Investigators* (032) 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.
- 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.

If the problem, event or information that must be reported under Section 1.a is an adverse event, the *Expedited Reporting Form for Reporting Unanticipated Problems or Noncompliance* (0203) accompanied by the *Adverse Event Reporting Form* (040) should be used for reporting.

If the problem, event or information that must be reported under Section 1.a is reported in a third-party safety report, the form entitled *Expedited Reporting Form for Reporting Unanticipated Problems or Noncompliance* (0203) accompanied by the *Third-Party Safety Reporting Form* (066) should be used.

If the problem, event or information that must be reported under Section 1.a is not an adverse event and is not reported in a third-party safety report, the *Expedited Reporting Form for Reporting Unanticipated Problems or Noncompliance* (0203) should be used for reporting.

These expedited reports should be submitted to the IRO with a copy of the current IRB-approved consent and will be reviewed by the IRB as outlined in Section 3.

b. Expedited Reporting of Unanticipated Problems Described in 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 Reporting Form* (066) is required 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 Reporting Form* (066) that do not satisfy the requirements of Section 1.a. will not be maintained in the IRB study file and will be returned to the PI.

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 for these types of reports, the PI must submit only the *Third-Party Safety Reporting Form* (066) noting that it is only being submitted because the sponsor or protocol required reporting to the IRB. IRB Staff will complete the *Screener: Third-Party Safety Reports Not Meeting* (0262).

2. Preliminary Assessment of Reports

The IRO staff will review all reports made under Section 1.a as well as any other reports of problems, events or new information (whether or not specifically provided under this policy) 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 the *Screener: Expedited Reporting Form for Unanticipated Problems or Noncompliance* (0296) 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 *IRB Policy 1.9 Noncompliance* [029].)

If the IRO staff cannot determine that the subject of the report is definitely not an unanticipated problem involving risks to participants or others, the Chair of the IRB that approved the research affected by the report (or designee) will review the report with any supporting documentation including the *IRB Chair or Designee Report Checklist for Unanticipated Problems or Noncompliance* (074). For reports made under Section 1a. the review by the Chair should normally occur within 2 business days from the time the report is received by the IRO. The IRB Chair (or designee) 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 IRB Chair (or designee) determines that the report is definitely not an unanticipated problem involving risks to participants or others, the result will be noted in the IRB file for the research and will be reported to the IRB on the Expedited Agenda for the next IRB meeting. No further action is required under this policy. (Additional action may be required under *IRB Policy 1.9 Noncompliance* [029].) The person making the report will also be notified.
- If the IRB Chair (or designee) determines that the report is a potential unanticipated problem involving risks to participants or others, then the report will be referred to the IRB for review as outline in Section 3. The IRB Chair 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 Reports and Action by the IRB

IRO staff will provide the following documentation to all IRB members:

- The protocol.
- The current consent document(s).
- Copy of the reported information along with any supporting documents.
- *IRB Chair or Designee Report Checklist for Unanticipated Problems or Noncompliance* (074).

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 *IRB Policy 1.9 Noncompliance* [029].)

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 (This 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
- 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 IRO staff will notify the principal investigator of the IRB's conclusions and any actions. The IRO staff will then follow *IRB Policy 2.8 IRB Requirements for Reporting to Institutional and External Officials* (021) including timelines for reporting these events.

SUPPORTING DOCUMENTS

IRB Policy 1.9 Noncompliance (029)
IRB Policy 2.2 Continuing Review (010)
IRB Policy 2.8 IRB Requirements for Reporting to Institutional and External Officials (021)
Adverse Event Reporting Form (040)
Expedited Reporting Form for Unanticipated Problems or Noncompliance (0203)
IRB Chair or Designee Report Checklist for Unanticipated Problems or Noncompliance (074)
IRB Glossary of Terms and Acronyms (050)
Screener: Expedited Reporting Form for Unanticipated Problems or Noncompliance (0296)
Screener: Third-Party Safety Report Not Meeting (0262)
Third-Party Safety Reporting Form (066)

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