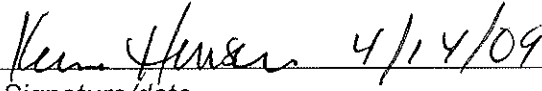


<b>Title:</b>	Unanticipated Problems Involving Risks to Subjects or Others
<b>Responsible Office:</b>	Institutional Review Office (IRO)
<b>Responsible Official:</b>	Karen Hansen, IRO Director
	 4/14/09
	Signature/date
<b>Effective Date:</b>	April 17, 2009
<b>Policy:</b>	2.6

**POLICY STATEMENT**

Principal investigators and study staff are required to report all problems, events and information that require prompt reporting to the IRB within ten (10) calendar days of learning of the problem. Problems, events or information reported under this policy will be reviewed under this policy 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*.) If a problem, event or information is determined to be an unanticipated problem involving risks to participants or others, it will be reviewed by the convened IRB, 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* and this Policy.

**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.

**Related or Possibly Related Adverse Event:** An adverse event is "related or possibly related to the research procedures" if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. Adverse events that are **solely** caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not "related or possibly related." If there is any question whether or not an adverse event is related or possibly related, the adverse event should be reported.

**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.

**Unexpected Adverse Event:** An adverse event is “unexpected” when its nature (specificity), severity, or frequency are not consistent with (a) the known or foreseeable risk of adverse events associated with the research procedures described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document and other relevant sources of information such as product labeling and package inserts; and are also not consistent with (b) the characteristics of the subject population being studied including the expected natural progression of any underlying disease, disorder or condition or any predisposing risk factor profile for the adverse event.

**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.

**Third Party Safety Reports:** A report prepared by an external sponsor or coordinating center overseeing a multi-site study describing one or more adverse events or other unanticipated problems involving risks to participants or others which have occurred at one or more of the participating sites involved in the study.

**Unanticipated Problems that Involve Risk to Research Participants 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.

**Principal Investigator or PI:** The FHCRC principal investigator for a given study.

## REFERENCES

21 CFR 50.25(b) (5)  
21 CFR 56.108(b) (1) and (3)  
21 CFR 56.113  
21 CFR 312.66  
21 CFR 812.3 (s)  
21 CFR 812.40  
21 CFR 812.150 (a) (1)  
21 CFR 812.150 (b) (1)  
38 CFR 46.103(b) (5)  
38 CFR 46.116(b) (5)  
45 CFR 46.103(b) (5)  
45 CFR 46.113  
45 CFR 46.116(b) (5)  
OHRP Compliance Activities: Common Findings and Guidance # 5  
OHRP Guidance on Continuing Review  
NIH Guidance: Reporting Adverse Events to IRBs supported Multicenter Clinical Trials  
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

## INDIVIDUALS AFFECTED BY THIS POLICY

This policy applies to IRO staff, IRB members, and FHCRC and University of Washington Consortium investigators. Instructions to investigators are posted on the IRO website.

## PRINCIPLES/OVERVIEW

Under the Human Subject Protection Program (HRPP) of FHCRC, 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.
    - An adverse event is “unexpected” when its nature (specificity), severity, or frequency are not consistent with (a) the known or foreseeable risk of adverse events associated with the research procedures described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document and other relevant sources of information such as product labeling and package inserts; and is also not consistent with (b) the characteristics of the subject population being studied including the expected natural progression of any underlying disease, disorder or condition or any predisposing risk factor profile for the adverse event.

**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.

- An adverse event is “related or possibly related to the research procedures” if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. Adverse events that are **solely** caused by an underlying disease, disorder or condition of the subject or by other

circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not “related or possibly related.” If there is any question whether or not an adverse event is related or possibly related, the adverse event should be reported.

**Note:** All serious adverse events that otherwise satisfy the requirements of Section 1.a. are reportable on an expedited basis. However, other adverse events that satisfy the requirements of this Section 1.a., but are not serious, must also be reported on an expedited basis if they suggest that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized.

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. 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.
- Data Safety Monitoring Board (DSMB) Reports that recommended 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 harm 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 this Section 1.a is an adverse event, the *Expedited Reporting Form for Reporting Unanticipated Problems or Noncompliance accompanied by the Adverse Event Reporting Form* found in the Forms Section of the FHCRC IRB website should be used for reporting. If the problem, event or information that must be reported under this Section 1.a is reported in a third party safety report, the form entitled *Expedited Reporting Form for Reporting Unanticipated Problems*

or *Noncompliance accompanied by the 3rd Party Safety Reporting Form* should be used. If the problem, event or information that must be reported under this 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* found in the Forms Section of the FHCRC IRB website should be used for reporting. These expedited reports should be filed with the IRO Director or his or her designee together with a copy of the current IRB-approved consent and will be reviewed by the IRB as provided in Section 3.

- b. Expedited Reporting of Unanticipated Problems Described in Third-Party Safety Reports. 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 *3<sup>rd</sup> Party Safety Reporting Form* is required and if there is a need to change the protocol and/or consent. Reports of adverse events described in *3<sup>rd</sup> Party Safety Reporting Form* 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 *3<sup>rd</sup> Party Safety Reporting Form* noting that it is only being submitted because the sponsor or protocol required reporting to the IRB.

## 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 and Adverse Event (AE) Reporting Forms, Screener: Expedited Reporting and 3rd Party Safety Reporting Forms or Screener: Expedited Reporting Form for Unanticipated Problem or Noncompliance 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*.)

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 Report Checklist*. For reports made under Section 1a. the review by the Chair should normally occur within forty-eight (48) hours of the time the report is received by the IRO. The IRB Chair (or designee) will determine whether the report is or might be 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 in the Expedited Reports Section of the 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*.) The person making the report will also be notified.
- If the IRB Chair (or designee) determines that the report is or might be an unanticipated problem involving risks to participants or others, then the report will be referred to the IRB for review under 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

The IRO Director (or designee) and IRB Chair (or designee) 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 Report Checklist.*

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.*)

The IRB may 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
- 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 may affect the willingness of current participants to continue to take part in the research.)
- Requiring the re-consenting of and/or providing additional information to past research participants
- Requiring more frequent review of the study
- Requiring additional training of study staff
- Prohibiting use of the data collected for publication
- Suspending or terminating the protocol
- Requesting that the President & Director (or designee) withhold funding for the study conditioned on appropriate corrective measures.

Upon completion of the IRB's review, the IRO Director (or designee) will notify the principal investigator of the IRB's conclusions and any actions. The IRO Director (or designee) will then follow *IRB Policy 2.8, IRB Requirements for Reporting to Institutional and External Officials.*

## SUPPORTING DOCUMENTS

Expedited Reporting Form for Unanticipated Problems or Noncompliance  
Adverse Event Reporting Form

Adverse Event Reporting Procedures

3<sup>rd</sup> Party Safety Reporting Form

IRB Policy 2.2 Continuing Review

Screener: Expedited Reporting and Adverse Event (AE) Reporting Forms

Screener: Expedited Reporting and 3rd Party Safety Reporting Forms

Screener: Expedited Reporting Form for Unanticipated Problems or Noncompliance

Screener: Allegation of Human Subjects Research Noncompliance Reporting Form

IRB Member Checklist

IRB Chair Report Checklist

IRB Policy 2.8 IRB Requirements for Reporting to Institutional and External Officials

IRB Policy 1.9 Noncompliance

OD Policy on Human Research Protection Program