Purpose

This document outlines the policy and procedures for ensuring prompt reporting to the Institutional Review Board, appropriate institutional officials, any department or agency head, and the Office of Human Research Protection (OHRP) of any possible unanticipated problems, adverse events, complaints, or other events involving risk to subjects or others, as appropriate. Additionally, a description is provided of the required time frame for accomplishing these reporting requirements, and the range of possible actions the IRB may take in response to these events.

Regulatory Background

When the institution is engaged in human subjects research, HHS regulations for the protection of human subjects (45 CFR Part 46) require that institutions have in place written procedures for ensuring that unanticipated problems involving risks to subjects or others are promptly reported to the IRB, appropriate institutional officials, and federal agencies (45 CFR 46.103(b)(5)) when HHS-supported (45 CFR 46.103(a)). OHRP further specifies that these IRB procedures should provide a step-by-step description with key operational details for complying with the reporting requirements described in HHS regulations at 45 CFR 46.103(b)(5).

Scope

This applies to all investigators under the jurisdiction of Princeton University including faculty, staff and students conducting research involving human research participants.

Responsibilities

Investigators: Investigators and research staff are responsible for promptly reporting any unanticipated problems, adverse events, complaints or other problems involving risks to subjects or others to the IRB.

RIA Administrator(s): Administrators may conduct preliminary inquiry, write reports, provide regulatory guidance and make determination of the proper review procedures for unanticipated problems, adverse events, complaints or other problems involving risks to subjects or others.

IRB Member(s): Conduct expedited review and/or present assessment summary including findings of unanticipated problems, adverse events, complaints or other problems that may
heighten risks to subjects or others at convened Board meetings and votes to make the
determination as to the final disposition of the submission.

Definitions

**Unanticipated problem involving risks to subjects or others** (including researchers,
technicians, bystanders, the public, etc.): Any incident, experience, or outcome that meets all
of the following criteria:

1. unexpected (in terms of nature, 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;

2. related or possibly related to a subject's participation in the research; and

3. suggests that the research places subjects or others at a greater risk of harm (including
   physical, psychological, economic, or social harm) related to the research than was
   previously known or recognized

**Adverse event (AE):** Any untoward or unfavorable medical occurrence in a human subject,
including any abnormal sign (for example, abnormal physical exam or laboratory finding),
symptom, or disease, temporally associated with the subject's participation in the research,
whether or not considered related to the subject's participation in the research activity.

**Important Note:**

Adverse Events (FDA) versus Unanticipated Problems (OHRP)

1. While adverse events occur most commonly in the context of biomedical/clinical
   research involving physical harm; on occasion, they can also involve psychological
   harms which may occur in the context of social and behavioral research.

2. All unanticipated problems are not necessarily adverse events.

3. Some events may be both an Adverse Event and Unanticipated Problem.

**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:

1. 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

2. 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.

Possibly related to the research: There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research.

Serious adverse event (SAE): Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

1. results in death

2. is life-threatening

3. requires inpatient hospitalization or prolongation of existing hospitalization

4. results in a persistent or significant disability/incapacity

5. results in a congenital anomaly/birth defect; or

6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Policy
The Princeton IRB reviews all unanticipated problems, adverse events, complaints or other problems involving risks to subjects or others, and takes any necessary action to ensure that the rights and welfare of human research participants are protected and that these are reported to appropriate agencies as appropriate.

Procedure
Events Requiring Prompt Reporting
The following events may represent unanticipated problems or adverse events that should be promptly reported:
1. Adverse events or injuries that are serious, unexpected, and related

2. Adverse device effects that are unanticipated

3. Breaches of confidentiality that alter the risks to subjects

4. Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports which alter the risk/benefit profile

5. Any new findings or information requiring reporting according to the protocol, sponsor, or funding agency (i.e., suspension or termination of funding)

6. Investigator's brochure updates/revisions to safety information (excluding routine updates), if applicable

7. New information indicating an unexpected change in risks or potential benefits (e.g., literature/scientific reports or other published findings)

8. Unapproved changes made to the research to eliminate an apparent immediate hazard to a subject

9. Protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur

10. Subject complaints indicating an unanticipated risk, or complaints that cannot be resolved by the research staff

11. Other problem or finding (e.g., loss of study data or forms, a subject becomes a prisoner while participating in research, etc.) that an investigator or research staff member believes could influence the safe conduct of the research

**Events Not Requiring Prompt Reporting**

Potential risks and adverse events that may be reasonably anticipated (i.e., expected) should be described in the informed consent process/form and do not require prompt reporting to the IRB by investigators and/or research staff. The following are examples of events that do not require prompt reporting:

1. Adverse events or injuries that are non-serious, expected, or unrelated

2. Adverse device effects that are non-serious, anticipated, or unrelated

3. Deaths not attributed to the research, e.g., from "natural causes," accidents, or underlying disease and the investigator has ruled out any connection between the
study procedures and the participant's death

4. DSMB reports; interim analyses; or other reports, findings, or new information that does not alter the risk/benefit profile

5. Investigator's brochure updates not involving safety information

6. Subject complaints that were resolved or complaints not involving risks

7. Protocol deviations or violations unlikely to recur or not involving risks to subjects

8. Other problems or findings not involving risk (unless the investigator or research staff member believes the information could affect participants' willingness to continue in the research).

9. PI must use sound professional judgment regarding reporting of UP, AE, etc. If the PI is unsure about the requirements for reporting, they should contact the administrators for further guidance. Those events that do not require prompt reporting should be addressed and explained during continuing review.

**Important Note:**

Often times a determination as to whether a UP or AE has occurred cannot be determined unless the IRB receives sufficient information which must be documented in the Unanticipated Problems Report Form. From a regulatory perspective, Princeton must be able to document that the IRB gave due consideration to potential UP, AE or complaints.

**Reporting Timeline**

Investigators must report possible unanticipated problems or other reportable events to the IRB promptly.

1. If the event requires immediate intervention to prevent serious harm to participants or others, the investigator must report the event within five (5) days of receiving notice of the event.

2. Investigators must report all other possible unanticipated problems or other events occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event.

3. Problems occurring within thirty (30) days after participants' active participation or treatment must be reported according to the above schedule.
Complaints:
Complaints may be submitted to the IRB office by phone, by email, in person or anonymously. RIA administrators will promptly conduct a preliminary review of all complaints, concerns, and appeals received by the IRB as appropriate.

1. All complaints, written or verbal, regardless of point of origin, are forwarded to the IRB Chair and RIA administrators.

2. Upon receipt of the complaint, the IRB Chair in consultation with RIA administrators will make a preliminary assessment of whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures below will be followed.

3. Complaints that possibly meet the definition of noncompliance, may be considered as allegations of noncompliance.

4. If the complaint meets the definition of an unanticipated problem involving risk to subjects or others, it will be handled as specified below.

5. An administrator will promptly generate a letter to acknowledge that the complaint has been received and is being investigated, providing a follow-up contact name.

Submission Requirements
Investigators must report unanticipated problems, adverse events, complaints or other problems to the IRB Office in writing using the Unanticipated Problem Reporting Form. The written report should contain the following:

1. Detailed information about the event, including relevant dates
2. Any corrective action, planned or already taken, to ensure that the event is corrected and will not occur again
3. An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences
4. Any other relevant information
5. Any other information requested by the IRB Office
Pre-review

Upon submission, the report of unanticipated problems, adverse events, complaints or other problems along with all associated documents will be initially pre-reviewed by RIA staff for completeness. RIA administrators also conduct an initial assessment and may provide follow-up recommendations including requests for revisions using the unanticipated problems pre-review checklist.

1. This checklist is also used to document recommendations to the IRB, any relevant comments or additional provisions that may be required to ensure all criteria for approval are still met, risks to subjects are minimized and to protect the rights and welfare of subjects.

2. If, based on the pre-review, the event does not meet all criteria for an unanticipated problem, RIA administrators may document this determination using the unanticipated problems checklist. An acknowledgement notice will be issued to the PI along with any requests for revisions, as appropriate. This finding along with any additional requests for revisions will be communicated to the investigator electronically in writing.

3. All other events will be forwarded for review using either an expedited review procedure or full board review. Determinations regarding unanticipated problems, adverse events, complaints or other problems will be reported to the IRB in writing.

Expeditied or Full Board Review

The IRB Chair or a designee from among the board’s membership will review the submission and make a determination as to whether modifications may be needed, if the event raises new concerns about risks and whether further review by the full convened committee may be necessary.

When reports of adverse events or serious adverse events are determined to represent a possible unanticipated problem or adverse event involving risks to subjects or others, these will be forwarded to the IRB for convened review.

1. The Chair, a designee or other member with relevant expertise will serve as the primary reviewer. Secondary reviewers are assigned by administrators. Copies of the reports, all relevant information provided by the investigator, including but not limited to current consent documents or verbal scripts with any proposed changes will be included in the review materials for each IRB member prior to the meeting.

2. The complete protocol file will be available to any IRB member upon request prior to or during the convened IRB meeting.

3. A determination will be made by the full committee regarding whether the event is an unanticipated problem or adverse event involving risks to subjects or others and if further action is necessary.
4. Action(s) will be based on the nature of the event, seriousness of the event, degree to which research participants are placed at risk, occurrence or prevalence of previous problems, among other things. The IRB will also consider the rights and welfare of participants when terminating, suspending, or modifying research.

5. Additional information or an audit of the research may be requested, as appropriate. If during review the event is determined not to be an unanticipated problem involving risks to subjects or others, the reviewer will make any necessary recommendations for action (see below), which will be communicated to the principal investigator in writing.

6. Any resulting modifications proposed by the investigator or IRB reviewer will be reviewed according to the Amendment Policy.

Possible IRB Actions following review

1. Request a correction action plan from the investigator

2. Require modification of the information disclosed during the consent process or the consent form

3. Require modification of the protocol

4. Verify that participant selection is appropriate and observation of the actual informed consent

5. Increase data and safety monitoring of the research activity

6. Request a directed audit of targeted areas of concern

7. Request a status report after each participant receives intervention, if applicable

8. Modify the continuing review cycle

9. Request additional Investigator and study staff education

10. Notify current subjects, if the information about the noncompliance might affect their willingness to continue participation

11. Require current participants to re-consent to participation
12. Suspend the study or;

13. Terminate the study

The IRB's determination and action(s), including votes taken, will be recorded in the meeting minutes. Investigators (and others) will be notified in writing by Administrators of the IRB's determinations and actions as noted above. Additionally, the PI will be notified if the IRB determines that an event may be considered an unanticipated problem involving risks to participants or others.

**Final Research Disposition**

In cases where the IRB determines that the event of an unanticipated problem involving risks to subjects or others also meets the definition of noncompliance, the policy and procedure for review of such events will also be followed.

The investigator will be informed of the IRB's determination and the basis for the determination in writing and, is given a chance to respond. If the IRB determines that the noncompliance was serious or continuing, the results of the final review will be reported as described in the Noncompliance Policy.

**IRB Reporting**

If the IRB determines that an event is an unanticipated problem involving risks to subjects or others, or if the Board suspends or terminates approval of research that is associated with unexpected serious harm to subjects, the investigator(s), IRB, Institutional Official, and the investigator(s)' Dean and Department Chair (or equivalent) will be notified of the reasons for the IRB's action in writing by RIA staff within 14 days of the determination. OHRP, FDA (as applicable for FDA-regulated research), the sponsor or any other sponsoring federal Department or Agency, and others (e.g., Research and Project Administration) as necessary, in accordance with Princeton's Federalwide Assurance, will be notified in writing within 30 days. The content of the report will conform to OHRP requirements for incident reporting as specified in the procedures for IRB Incident Reporting.

**References**

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


Guidance on Reporting Incidents to OHRP
## Version History

<table>
<thead>
<tr>
<th>Version Number</th>
<th>Revision Date</th>
<th>Revisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>