IRB Policy 710  Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events

Scope

This policy defines the reporting requirements for Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and applies to all research approved by a Yale Institutional Review Board (IRB) for which a Yale IRB serves as the IRB of record, or research deemed by a Yale IRB to qualify for exemption. Incidental findings, as defined below, typically do not qualify as an Unanticipated Problem Involving Risks to Subjects or Others and are instead covered in IRB Policy 720, Incidental Findings with Possible Health and Safety Significance for Research Participants.

Policy Statement

Principal Investigators conducting research involving human subjects are required to report to the IRB all Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) (as defined below), including adverse events that meet the reporting criteria and therefore should be considered as UPIRSOs. Unanticipated problems can occur in any type of research (medical or non-medical) and may include occurrences such as adverse events, subject complaints, protocol deviations, and other untoward events involving risk. Events requiring prompt reporting by investigators and research staff may involve physical, psychological, social, legal, or economic harms. The Principal Investigator (PI) must make any changes to the protocol, informed consent documents, recruitment materials, and/or other documentation that the PI deems necessary and as may be required by the IRB in connection with such reports. In addition, the IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to subjects or others.

Reason for the Policy

The rationale for reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the IRB is to ensure that the research team and the IRB fulfill their obligations to protect human research subjects. Federal regulations require Yale (“the University”) to have written procedures for ensuring that Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) are promptly reported to the IRBs, appropriate institutional officials, and federal agencies. See 45 CFR §46.103(b)(5), 21 CFR §56.108(b)(1)

Definitions

Unanticipated Problem Involving Risks to Subjects or Others (UPIRSOs)

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND

2. Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND

3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.
Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects (see below). Please note that adverse events (as defined below) are reportable to the IRB as UPIRSOs only if they meet all 3 criteria listed above.

**Adverse Event (AE)**
Any untoward or unfavorable occurrence in a human research subject (physical or psychological harm) temporally associated with the individual’s participation in the research (whether or not considered related to participation in the research). See OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007 at [http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2](http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2).

**Serious Adverse Event (SAE)**
Any adverse event that results in any of the following outcomes:
- death,
- a life-threatening experience,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity,
- a congenital anomaly/birth defect, or
- 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.

**Related**
There is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research. See OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007 at [http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2](http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2), modified from the definition of associated with use of the drug in FDA regulations at 21 CFR §312.32(a).

**Unanticipated Adverse Device Effect**
Any serious adverse effect on health or safety, or any life-threatening problem or death caused by (or associated with) a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application; any other unanticipated, serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

**Internal Event**
An event that occurs at a study site under the jurisdiction of a Yale IRB (i.e., Yale IRB serves as the IRB of record).

**External Event**
An event that occurs at a study site NOT under the jurisdiction of a Yale IRB (e.g., at another institution in a multicenter clinical trial).

**Policy Sections**

**710.1 Events Requiring Prompt Reporting**
Principal Investigators are responsible for reporting events that meet the definition of UPIRSOs to the IRB. UPIRSOs include adverse events, if the events are unexpected, related and serious (as defined above), and may include subject complaints, protocol deviations, and other untoward events involving risk. The IRB Chair or convened IRBs are responsible for making the final determination that a reported event is a UPIRSO.

The following events may represent UPIRSOs that should be promptly reported:
- Adverse device effects that are unanticipated;
- Adverse events or injuries that are serious, unexpected, and related;
• Breaches of confidentiality involving risks;
• Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports altering the risk/benefit profile by identification of increased risks;
• Revisions to safety information, such as Investigational New Drug (IND) Safety Reports, SUSARS and MedWatch Reports, that meet the definition of a UPIRSO;
• New information indicating an unexpected increase in risks or decrease in potential benefits (e.g., literature/scientific reports or other published findings);
• Protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur;
• Unapproved changes made to the research to eliminate an apparent immediate hazard to a subject;
• Other problem or finding (e.g., loss of study data or forms) that an investigator or research staff member believes could influence the safe conduct of the research.

Timeframe for Reporting
1. Events that may require a temporary or permanent interruption of study activities by the Principal Investigator or sponsor to avoid potential harm to subjects should be reported to the IRB immediately (if possible), followed by a written report to the IRB using the UPIRSO Reporting Form (710 FR 4) no more than 5 calendar days after the Yale Principal Investigator becomes aware of the event.

2. Internal Events (defined above) should be reported to the IRB using the UPIRSO Reporting Form (710 FR 4) within 5 calendar days of the Principal Investigator becoming aware of the event.

3. External Events (defined above) should be reported to the IRB using the UPIRSO Reporting Form (710 FR 4) within 15 calendar days of the Yale University Principal Investigator (PI) becoming aware of the event ONLY IF either of the following are true:
   (a) The Yale PI has concluded that an immediate change to the protocol is necessary to address the risks raised by the event, OR
   (b) A monitoring entity (e.g., an external IRB at the site where the problem or event occurred, the sponsor, or the Data Safety Monitoring Board) has required modifications/amendments to the research protocol or consent documents as a result of the event.

For all reports of external events, the UPIRSO Reporting Form (710 FR 4) must include the following information:
   (a) a clear explanation of why the event or series of events has been determined to meet criteria for reporting;
   (b) a description of the proposed protocol changes and any corrective actions to be taken by the PI in response to the external event; and
   (c) any aggregated data and an analysis or summary from the sponsor or DSMB, when applicable and available, sufficient to explain the significance of the event or series of events in order to ensure the information is interpretable and relevant to the IRB’s task of protecting the rights and welfare of human participants.

All internal and external events that may represent UPIRSOs should be promptly reported (in accordance with the timeframes as described above), regardless of whether they occur during the conduct of the study or after the study has closed at Yale, or whether they involve a subject who has withdrawn from or completed study participation. The IRB will make a late reporting notation to all UPIRSOs reported outside the timeframes as outlined above, and repeated incidences of late reporting may constitute continuing noncompliance. If changes to the research or consent process are proposed as a result of the event, or if additional information will be provided to current and/or past subjects, an amendment request also must be submitted for IRB review.
For a flowchart of event reporting requirements, including which events are reportable and under what timeframe, see, *Reporting of UPIRSOs, including AEs, to the IRB*, which is the last page of this Policy.

710.2 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 PIs. The following are examples of events that do not require prompt reporting:

- Adverse device effects that are non-serious, anticipated, or unrelated;
- Adverse events or injuries that are non-serious, expected, or unrelated;
- Deaths not attributed to the research (e.g., from “natural causes,” accidents, or underlying disease when the Principal Investigator has ruled out any connection between the study procedures and the subject’s death);
- DSMB reports; interim analyses; or other reports, findings, or new information not altering the risk/benefit profile;
- Protocol deviations or violations unlikely to recur or not involving risks to subjects;
- Subject complaints that were resolved or complaints not involving risks;
- Problems or findings not involving risk (unless the PI believes the information could affect subjects’ willingness to continue in the research).

All related internal and external events involving risk but not meeting the prompt reporting requirements described in Section 710.1 above should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

External events that do not meet the reporting requirements (e.g., not related or not involving risk) and that are not relevant to the protection of Yale research subjects or others should NOT be reported to the IRB.

710.3 Review Process

UPIRSO reports and accompanying information will be screened for completeness by the Yale University Human Research Protection Program (HRPP) and/or IRB staff members, who will make an initial determination confirming that the event represents a possible UPIRSO before referring them on to an IRB Chair or other qualified designee for confirmation. Reports of events determined during screening to represent possible UPIRSOs will be forwarded to the IRB for convened review, as necessary, after review by the IRB Chair or other qualified designee. Reports of events that do not meet the requirements for prompt reporting may be returned.

A. Initial Review

An IRB regulatory analyst (RA) initially assesses the report submitted by the PI and accompanying information, if any, with regard to the seriousness of the event and risks to subjects, and shall confirm that the event represents a possible UPIRSO. Such reports are evaluated on a case-by-case basis. If it is determined through clarification with the PI that the report does not in fact meet the submission criteria as defined above (i.e., concerns an adverse event that is not serious (or life-threatening), unexpected, or related to participation in the study or does not present an unexpected risk to subjects or others), then review by the IRB Chair or other qualified designee will not proceed. The PI will be notified by the IRB staff that the submission criteria was not met and educated regarding the required submission criteria.

Event reports and accompanying information that represent a possible UPIRSO will be forwarded by staff members to the appropriate IRB Chairperson, Vice-Chair, or one of the experienced members with relevant expertise. Reviewers will have access to the complete protocol file, including previously reported events, for
review. The Chairperson or designee will determine if the report raises new concerns about risks and will recommend further review by the convened IRB, as necessary, for a final determination. The IRB Chair or Vice-Chair may suspend or terminate approval of the research in accordance with IRB Procedure 700 PR4, if necessary, to assure the protection of research subjects or others. The Chair or Vice-Chair will consider the rights and welfare of subjects or others when suspending, terminating, or modifying research.

B. Convened Review

Events reported to the IRB via the UPIRSO Reporting Form (710 FR 4) that are determined during screening to represent possible UPIRSOs will be forwarded, as necessary, to the IRB for convened review. Modifications proposed by the PI or IRB reviewer that represent more than minor changes will also be reviewed by the convened IRB. The Chair, Vice-Chair, or other member with relevant expertise will serve as the primary reviewer. Copies of the reports, all other information provided by the PI, and current consent documents (or verbal scripts) with any proposed changes will be included in the review materials for each IRB member. Sections from the protocol, previous event reports, and other relevant information or reference materials will also be included, as applicable. The complete protocol file will be available to any IRB member upon request prior to or during the convened IRB meeting.

The IRB will determine by convened review whether the event is an Unanticipated Problem Involving Risks to Subjects or Others and if further action is necessary. Action(s) will be based on the nature of the event, degree to which research subjects or others are placed at risk, occurrence of previous problems, etc. The IRB will consider the rights and welfare of subjects or others when suspending, terminating, or modifying research.

710.4 IRB Actions

The types of actions that the IRB may consider for any event include, but are not limited to:

- Modification(s) of the research protocol or procedures;
- Modification(s) of the consent process or consent form;
- Providing additional information to current research subjects (required when such information may relate to their willingness to continue in the research);
- Providing additional information to past research subjects;
- Reconfirming consent of current research subjects;
- Requiring additional follow-up/monitoring for current and/or past research subjects;
- Monitoring of the research (including audits) or consent process;
- Education or mentoring for the Principal Investigator, co-investigators and/or research staff;
- Additional reporting, including modification of the continuing review schedule;
- Requiring additional resources to support the Principal Investigator’s research activities;
- Placing limitations (e.g., restriction to co-investigator status) on the Principal Investigator’s research activities or use of research data;
- Suspending or terminating the research;
- Referral to other appropriate University process (e.g., Responsible Conduct of Research Review or other Faculty, Department, School or Center based inquiries).

The IRB’s determination and action(s), including votes taken, will be recorded in the meeting minutes. The requirements for quorum and majority apply. PIs will be notified in writing of IRB decisions regarding events determined not to represent UPIRSOs following approval of the meeting minutes by the IRB Chair or Vice-Chair. Suspended IRB approval may be reinstated, as appropriate, based on the outcome of the convened review. PIs (and others) will be notified of IRB actions regarding events determined to be UPIRSOs as described below.

710.5 Institutional Reporting

If the IRB determines that an event is a UPIRSO, or if the Board suspends or terminates approval of research that is associated with unexpected serious harm to subjects or others, the PI will be notified of the reasons for the IRB’s action in writing. The Institutional Official, the PI’s Dean and/or Department Chair (or equivalent), the Office for Human Research Protections (OHRP), the U.S. Food and Drug Administration (FDA) (as applicable for FDA-regulated research), the sponsor or any federal department or agency funding the research, and others (e.g.,
Office of Grant & Contract Administration), will also be notified in writing within 30 days of the determination, as necessary or required, in accordance with Yale University’s Federal Wide Assurance.

Principal Investigators with other regulatory (e.g., FDA) or contractual reporting requirements related to adverse events or Unanticipated Problems Involving Risks to Subjects or Others (e.g., the National Institutes of Health (NIH) and study sponsors) are responsible for providing any reports required under those regulations/agreements in addition to the reporting requirement described here. See Policy 600: Use of Investigational New Drugs (INDs) and Investigational New Device Exemptions (IDEs) in Human Research

## Related Information
IRB Policy 420: Data and Safety Monitoring
IRB Policy 600: Use of Investigational New Drugs (INDs) and Investigational New Device Exemptions (IDEs) in Human Research
Form 710 FR4: UPIRSO, Including AEs Reporting Form
IRB Policy 720: Findings with Possible Health and Safety Significance for Research Participants

For electronically-submitted protocols, see Huron/Click Quick Guide on Notifying the IRB of a specific event.

## Applicable Regulatory References/Guidance
DHHS regulations: 45 CFR 46.103(b)(5) and 45 CFR 46.116(b)(5)
OHRP “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events” (01/15/07), OHRP “Guidance on Reporting Incidents to OHRP” (06/20/11)

FDA “Guidance on Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection (January 2009)

## Contacts

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<th>Subject</th>
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<tr>
<td>Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including Adverse Events</td>
<td>Human Investigation Committee or Human Subjects Committee</td>
<td>203.785.4688 <a href="mailto:hrpp@yale.edu">hrpp@yale.edu</a> <a href="mailto:human.subjects@yale.edu">human.subjects@yale.edu</a></td>
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## Roles and Responsibilities

**Human Investigation Committee (HIC)**
The HIC I, HIC II, HIC III and HIC IV serve as the four Institutional Review Boards or IRBs for biomedical human subjects research conducted at Yale University.

**Human Subjects Committee (HSC)**
The HSC serves as the Institutional Review Board for social, behavioral and educational research involving human subjects conducted at Yale University.

## Revision History