Submitting a Reportable Event when Mayo Clinic IRB is not the IRB of Record

Content Applies To
Mayo Clinic Human Research Protection Program

Purpose
In accordance with the Authorization Agreement between the external IRB and Mayo Clinic and the Mayo Clinic Federalwide Assurance registered with the Office for Human Research Protections, Mayo Clinic commits to HHS that it will comply with the requirements set forth in the Federal regulations [45 CFR 46.103(b) (5) to ensure that investigators promptly report "any unanticipated problems involving risk to subjects or others" (UPIRTSO), or any serious or continuing non-compliance, to the Institutional Official and regulatory agencies (when appropriate).

The purpose of this document is to describe the process and requirements for reporting to the Institutional Official and regulatory agencies (when appropriate) all unanticipated problems involving risks to subjects or others (UPIRTSOs), and non-compliance involving Mayo Clinic personnel or research participants when the Mayo Clinic IRB is not the IRB of Record.

Key Terms
Reportable Event: A Reportable Event is a process (with an associated IRB form) used by an investigator to report any problem or event or other act or omission to the IRB.

Federalwide Assurance (FWA): A formal written, binding attestation in which an institution assures to Department of Health and Human Services (DHHS) that it will comply with applicable regulations governing research with human subjects.

IRB of Record: A reviewing IRB that assumes IRB responsibilities for another organization that is designated to do so through an approved Federalwide Assurance (FWA) on file with the Federal Office of Human Research Protection (OHRP), and where a formal, written IRB Authorization Agreement in which the reviewing IRB agrees to serve as the IRB of Record, has been executed.

IRCU: The IRB Compliance Unit, as part of the Mayo Clinic Human Research Protection Program (HRPP), investigates alleged non-compliance and coordinates reporting to the Institutional Official and/or external authorities as appropriate.
**UPIRTSO:** An **Unanticipated Problem Involving Risk to Subjects or Others** is defined as any problem or event which, in the opinion of the local Investigator, meets all three of the following criteria:

1. **Serious:** Serious problems or events that result in significant harm (which may be physical, psychological, financial, social, economic, or legal), or places subjects or others at a greater risk of harm than was previously known or recognized. Note that actual harm need not have occurred for there to be a change in the risk/benefit ratio.

2. **Unanticipated:** A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence and is:
   - Not already described as a potential risk in the approved informed consent
   - Not already described as a potential risk in the approved protocol
   - Not listed in the Investigator’s Brochure
   - Not part of an underlying disease
   - Occurred at an increased frequency or at an increased severity than expected

3. **Related:** A problem or event is "related" if it is possibly related to the research procedures.

**Protocol Violation/Deviation:** Any change, divergence or departure from the study design or research procedures that has not been approved by the IRB. Most protocol violations/deviations are considered non-compliance.

**Major Protocol Violation/Deviation:** Any change that affects the rights and welfare of subjects and others, increases risks to subjects and others, decreases potential benefits, compromises the integrity or validity of the research, or represents willful or knowing misconduct (see list of potential major protocol violation/deviations on page four of this document).

**Minor Protocol Violation/Deviation:** Any departure from the IRB-approved protocol procedures that was made without prior IRB approval that did not increase the risk or decrease the benefit or significantly affect the subject’s rights, safety or welfare and/or the integrity of research data (e.g. a routine lab missed at a visit and re-drawn, shortening the duration between a planned study visit, using an outdated HIPAA form or consent form when there are no differences between the two forms other than the approval date).

**Non-compliance:** An act or omission in the conduct or oversight of human subject research that represents a failure to follow: 1) federal, state or local regulations; 2) institutional policies relevant to human subject research; 3) the approved research plan; and/or 4) the determinations of the IRB.

**Serious Non-compliance:** Any non-compliance that results in, or has the potential to:
- a) substantially compromise the rights and welfare of subjects;
- b) substantially impact the integrity and validity of the study data; and/or
- c) compromise the integrity and effectiveness of the Mayo Clinic Human Research Protection Program.
Continuing Non-compliance: A pattern or multiple instances of non-compliance that, if unaddressed, could: a) compromise the rights and welfare of subjects; b) impact the integrity and validity of the study data; and/or c) compromise the integrity and effectiveness of the Mayo Clinic Human Research Protection Program.

Reporting Policy

UPIRTSO

Any UPIRTSO that involves Mayo Clinic personnel or Mayo Clinic research subjects must be reported to the Mayo Clinic IRB Compliance Unit (IRCU) **within five working days** of becoming aware of the problem or event, in addition to the reporting requirements of the external IRB.

Protocol Violation/Deviation

Any MAJOR protocol violation/deviation that affects the rights and welfare of subjects and others, increases risks to subjects and others, decreases potential benefits, compromises the integrity or validity of the research, or represents willful or knowing misconduct, which involves Mayo Clinic personnel or Mayo Clinic research subjects is considered non-compliance and must be reported to the IRCU **within five working days** of becoming aware of the problem, Reporting requirements of the external IRB must also be followed.

Examples of problems and/or events which may meet UPIRTSO Criteria:

- Any accidental or unintentional change to the IRB-approved research protocol that increased risk to subjects or others
- An event that would have implications for the conduct or design of the research project (e.g., requiring a significant, and usually safety-related change in the research project, such as revising inclusion/exclusion criteria or a new monitoring requirement, revised informed consent or revised investigator's brochure).
- Any complaint from a subject that indicates an unanticipated risk, or that cannot be resolved by the research staff
- Problems, events, or new information (e.g. from publications, DSMB reports, interim findings, product labeling changes) that in the opinion of the investigator may adversely affect the rights, safety, or welfare of subjects or others, or which substantially compromise the research data
- Breach of confidentiality (e.g. unapproved PHI disclosure, a stolen, unencrypted laptop containing subject data and identifiers)
- An unexpected hospitalization - new or prolonged
- An unexpected life-threatening adverse experience
- An unexpected death which cannot be attributed to underlying disease
- A newly-developed disability/incapacity - persistent or significant
- An unexpected birth defect/anomaly
A processing error resulting in a subject receiving a dose of study medication significantly higher than the dose dictated by the IRB-approved protocol, even if the incorrect dosing produces no detectable adverse effect

Examples of problems or events which may meet the definition of Major Protocol Violations/Deviations (non-compliance):

- Enrolling subjects who did not meet inclusion/exclusion criteria on a greater-than-minimal risk study
- Performing study procedures not approved by the IRB
- Performing study procedures before obtaining informed consent
- Failure to obtain and/or document informed consent
- Use of an unapproved consent document
- Changing the protocol without prior IRB approval except when necessary to eliminate immediate harm to a subject
- Breach of confidentiality (i.e. any occurrence of unapproved PHI disclosure)
- Receipt of incorrect treatment or dose by a subject
- Loss or destruction of samples or data
- Over-enrollment of subjects on a greater-than-minimal risk study
- Unauthorized (i.e. not IRB-approved) persons participating in the conduct of a research study

Investigator Reporting Responsibilities

When a UPIRTSO and/or major protocol violation/deviation occurs at Mayo Clinic, but the Mayo Clinic IRB is not the IRB of Record:

1. The Investigator must complete reporting according to the requirements of the external IRB.
2. The Investigator must report the problem or event to IRCU within five working days of becoming aware of the problem or event by completing the Reportable Event form within the Mayo Clinic IRB electronic system.
3. The Investigator must, upon receipt of the external IRB’s review and determination regarding the problem or event, submit a copy of that determination to IRCU by:
   a. Completing an additional Reportable Event form within the Mayo Clinic IRB electronic system
   b. Selecting “follow-up” in section 3 of the Reportable Event form.

IRCU Responsibilities

When a UPIRTSO and/or major protocol violation/deviation occurs at Mayo Clinic, but the Mayo Clinic IRB is not the IRB of Record, IRCU will:

1. Review the submitted Reportable Event form describing the UPIRTSO and/or major protocol violation/deviation.
2. Investigate protocol violations and deviations per applicable IRCU procedure. See “Internal Compliance Review of Allegations of Suspected or Actual Noncompliance”.

3. Communicate as warranted with the designated IRB of record.

4. Notify IRB Administrative Committee, Mayo Clinic Research Compliance Officer, Mayo Clinic Institutional Official, and when required, the applicable federal agencies, as appropriate.

Related Document(s)
IRB Electronic Reportable Event Form
Internal Compliance Review of Allegations of Suspected or Actual Non-compliance

References
Association for the Accreditation of Human Research Protection Programs (AAHRPP) version 1/2012
45 CFR Part 46 Protection of Human Subjects
21 CFR Part 56 Institutional Review Boards
FDA Guidance for Clinical Investigators, Sponsors, and IRBs - Adverse Event Reporting to IRBs - Improving Human Subject Protection, January 2009

Effective Date
December 4, 2015

Revision History - newest at the top

<table>
<thead>
<tr>
<th>Date</th>
<th>Synopsis of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/18/2016</td>
<td>&quot;10 times&quot; changed to &quot;significantly&quot;</td>
</tr>
<tr>
<td>12/04/2015</td>
<td>Revised the definitions for non-compliance, serious non-compliance, and continuing non-compliance to match the definitions in the glossary</td>
</tr>
</tbody>
</table>