Reporting an Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) to the IRB

UPIRTSO Flowchart

Content Applies To

Mayo Clinic's Human Research Protection Program

Purpose

Federal regulations [45 CFR 46.103(b) (5) and 21 CFR 56.108(b) (1)] require the IRB to ensure that investigators promptly report “any unanticipated problems involving risk to subjects or others” (UPIRTSO) to the IRB.

The purpose of this document is to describe the requirements for reporting unanticipated problems involving risks to subjects or others to the IRB.

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 which in their opinion is a UPIRTSO.

UPIRTSO: Unanticipated **P**roblem **I**nvolving **R**isk to **S**ubjects or **O**thers is defined as any problem or event which, in the opinion of the local investigator, was unanticipated, places subjects or others at a greater risk of harm than was previously known or recognized, and was possibly related to the research procedures.

- **'Internal' UPIRTSO:** Occurs at any institution where the Mayo Clinic IRB serves as the IRB of Record.
- **'External' UPIRTSO:** Occurs at any institution which falls under the purview of an external IRB (not the Mayo Clinic IRB).

Non-UPIRTSO: A reportable event that does not meet the Mayo Clinic IRB's definition of a UPIRTSO.

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: IRB Regulatory Compliance Unit

Policy

Investigators must report a UPIRTSO to the IRB within 5 days of learning of it, using the IRB Reportable Event form.

All reportable events meeting the UPIRTSO criteria as submitted to the IRB using the Reportable Event form will be sent to an IRB Chairperson for review and determination. If the IRB Chairperson determines the event is a UPIRTSO, a convened IRB reviews it

and either confirms or does not confirm the determination. The investigator is notified and the review, determination, and investigator communication is documented in IRB electronic system.

A UPIRTSO, as confirmed by the convened IRB, is reported to the Mayo Clinic Institutional Official and other relevant Federal agencies, when required, within 30 days from the date of submission. The investigator is electronically notified of this action.

UPIRTSOs & Reportable Events

UPIRTSO: A UPIRTSO is an unanticipated problem, event or other act or omission occurring at Mayo Clinic or at a research site where the Mayo Clinic is the IRB of Record and which the investigator has determined meets all three of the following UPIRTSO 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* subject harms need not to 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 potential risks in the approved research proposal or consent document
    - Not listed in the Investigator's Brochure
    - Not part of an underlying disease
    - Occurring 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.

Occurrences which may meet UPIRTSO Criteria

Include *(but are not limited to):*

- Any change to the research protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant
- Any accidental or unintentional change to the IRB-approved research protocol that involved risks or has the potential to recur
- An event that would have implications for the conduct 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 including a new monitoring requirement, informed consent, or investigator's brochure).
- Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff
- Problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may

adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data.

- A breach of confidentiality
- A hospitalization - inpatient, new, or prolonged
- A life threatening adverse experience
- A death which cannot be attributed to underlying disease
- A disability/incapacity - persistent or significant
- A birth defect/anomaly
- Any event that requires prompt reporting to other entities according to the research protocol, monitoring plan or the sponsor
- Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research
- Any other event appropriate to the local context.
- Protocol violations: Examples of problems which violate the terms of a study and involve risks to subjects or others **include (but are not limited to):**
    - Enrolling subjects who did not meet the inclusion/exclusion criteria
    - Unauthorized (i.e. not IRB approved) persons such as faculty, staff, students or residents) participating in the conduct of a research study
    - Performing study procedures not approved by the IRB
    - Failure to obtain and/or document informed consent
    - Use of an unapproved or expired consent document
    - Changing the protocol without prior IRB approval
    - Breach of confidentiality
    - Protocol deviations/violations identified by sponsor monitor visits or study team
    - Receipt of incorrect treatment or dose by a study subject
    - Loss or destruction of samples or data
    - Over-enrollment of subjects

Investigator Responsibilities

When an unanticipated problem or event occurs, it is the responsibility of the investigator to:

1. Eliminate apparent immediate hazards to the subject or others. This can be done prior to submitting the reportable event to the IRB.

2. Determine if the reportable event meets the UPIRTSO criteria and consult, as needed, with the IRB on-call Chairperson on issues relating to the UPIRTSO determination.
3. Report any internal UPIRTSO to the IRB within five working days of learning of it. Use the IRB Reportable Event form to complete the report to IRB.
4. Indicate if the reportable event is a protocol violation.
5. Monitor subjects to detect additional risks and harm.
6. Report, when applicable, the unanticipated problem or event to other entities such as sponsors, funding agencies, or Data Safety Monitoring Boards.
7. Modify research procedures as necessary to eliminate future hazards. Report these modifications to the IRB in accordance with this procedure and with Federal regulations.
8. Put the research project on Administrative Hold if necessary and use IRB electronic system to change study status. This change automatically notifies the IRCU. See IRB document *Administrative Hold Activation by the Principal Investigator.* Modify research project procedures to eliminate future hazards.

Investigator Reporting Criteria and Actions

Internal UPIRTSOs

When an internal UPIRTSO occurs at institutions where the Mayo Clinic IRB serves as the IRB of Record:

1. The Mayo Clinic investigator completes and submits an IRB Reportable Event form and related documentation **within five working days** after first learning of the UPIRTSO even if it is not yet resolved.
    - The investigator indicates whether the event occurred at the Mayo Clinic or at a site where the Mayo Clinic IRB is the IRB of Record.
    - The investigator confirms whether the 3 requirements for a UPIRTSO - unanticipated, serious and related - have been met.
    - The investigator indicates whether the event is a protocol violation.
2. The Mayo Clinic investigator submits a modification request to the IRB if the research project or consent document requires a revision to protect research subject/s.
3. If the IRB confirms the UPIRTSO, the investigator reports the IRB's determination to the research project sponsor, if applicable.

Internal Non-UPIRTSOs

When an internal Non-UPIRTSO occurs at institutions where the Mayo Clinic IRB serves as the IRB of Record:

1. The Mayo Clinic investigator reports problems or events that do NOT meet the criteria of an UPIRTSO to the Mayo Clinic IRB in summary format at the time of the next continuing review.

2. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs. *The IRB provides an optional event tracking worksheet for non-UPIRTSOs which is available to researchers on the IRB website.*

External UPIRTSOs

When an external UPIRTSO occurs at other institutions where Mayo Clinic is NOT the IRB of Record:

1. The Mayo Clinic investigator reports UPIRTSOs that occur at non-Mayo sites to the IRB in summary form at the time of the next continuing review.
2. If monitoring entities (e.g., an external IRB at the site where the problem or event occurred, the sponsor, or the Data Safety Monitoring Board) require modifications to the research project at all research sites or consent documents as a result of the problem, the Mayo Clinic investigator submits a modification request using the IRB electronic system.

External Non-UPIRTSOs

Non-UPIRTSOs occurring at other institutions where Mayo Clinic is NOT the IRB of Record (external) do not need to be reported to the Mayo Clinic IRB.

IRB Responsibilities

All reportable events meeting the UPIRTSO criteria are sent to an IRB Chairperson for review. If the Chairperson does not agree with the investigator's UPIRTSO assessment, the event is sent back to the investigator as a non-UPIRTSO. If the Chair agrees with the investigator assessment that the event is an UPIRTSO, the event is forwarded for review by a Convened IRB. All members of that Convened IRB receive an electronic copy of the reportable event form and relevant documents as submitted by the investigator. It is the responsibility of the IRB to:

1. Review the Reportable Event form and all related materials which have been submitted by the principal investigator.
2. Communicate directly with the investigator, as needed, to obtain more information regarding the unanticipated problem, event or other act or omission.
3. Evaluate whether the actions taken by the investigator to eliminate apparent immediate hazards are adequate and appropriate and if not, recommend further action.
4. Confirm that the problem or event meets the UPIRTSO criteria and constitutes a UPIRTSO.

   Note: Problems or events that DO NOT meet the UPIRTSO criteria or have occurred at a site where Mayo Clinic is not the IRB of Record are returned electronically to the investigator with a notification that the PI will need to summarize the problem or event at the time of next continuing review.
5. If the Reportable Event submission indicates that a Protocol Violation has occurred, the IRCU will be notified automatically by email.
6. The IRB will notify the investigator of confirmation of UPIRTSO or other results of review.

When the IRB Determination is an UPIRTSO

The IRB:

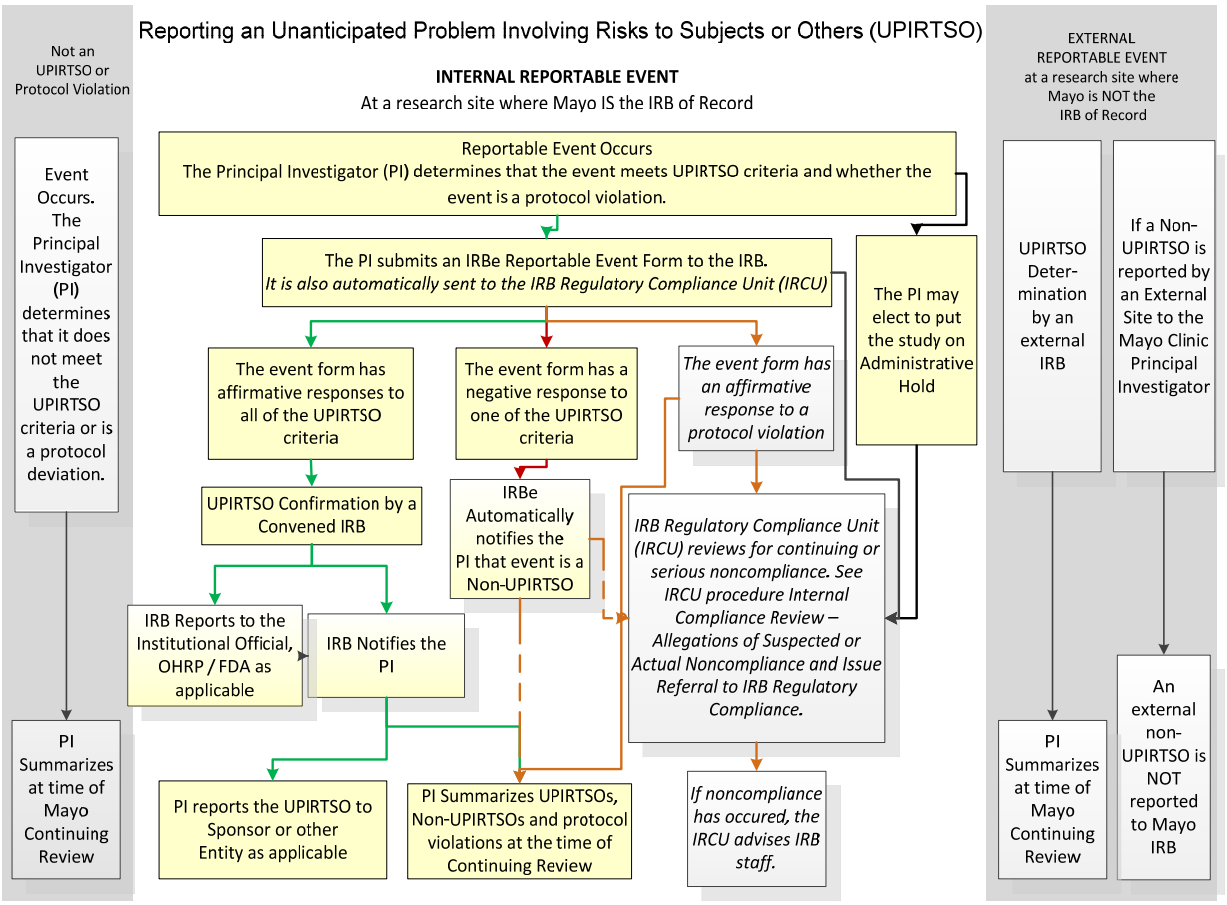
- Notifies the investigator of the UPIRTSO determination and documents the decision and communication to the investigator in the IRB electronic system.
- Reports the UPIRTSO to the Institutional Official, Federal agencies (i.e. FDA or OHRP) when required, and to any Federal agency that provides funding support for the research project per the procedure, *Reporting to the Institutional Official and Regulatory Agencies.*
- Determines whether the research project or consent document requires a modification to protect or inform research project subjects of new risks.
- The IRB may also require one or more of the following actions including but not limited to:
    - Suspension of the research
    - Termination of the research
    - Notification of current participants (required when such information might relate to participants' willingness to continue to take part in the research)
    - Additional information provided to past participants
    - Modification of the research project or plan
    - Modification of the information disclosed during the consent process
    - Require that current participants be re-consented
    - Monitoring of the research
    - Monitoring of the consent process
    - Referral to other Mayo Clinic entities (e.g., legal counsel, risk management, organizational official)
    - Recommend or require modifications to the research project protocol, consent documents, to the consent process or other research project documents.
    - Request the investigator to place the research project on administrative hold pending receipt of more information
    - Request additional information from the Data Safety Monitoring Board, or other monitoring entity
    - Require the investigator to inform past subjects of newly recognized risk(s)
    - Impose additional monitoring of the research activities or of the consent process
    - The IRB may increase the frequency of the continuing review cycle.

When the IRB determination is a Non-UPIRTSO

- The IRB notifies the investigator to summarize the problem or event at the time of next continuing review.

IRB Regulatory Compliance Unit (RCU)

When the IRB Regulatory Compliance Unit (IRCU) reviews a UPIRTSO or Non-UPIRTSO which discloses a protocol violation or other act or omission referred to them that may constitute continuing or serious non-compliance, they will investigate per applicable IRCU procedure. For IRCU procedures, see *Internal Compliance Review - Allegations of Suspected or Actual Noncompliance*; and *Issue Referral to IRB Regulatory 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

July 1, 2012