Submitting a Reportable Event to the Institutional Review Board (IRB) Policy

Scope

Applies to study personnel when reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs), Significant New Information, and Protocol Violations/Deviations (potential non-compliance) when Mayo Clinic IRB is the Reviewing IRB.

Purpose

To describe the process and requirements for reporting UPIRTSOs, Significant New Information, and Protocol Violations/Deviations (potential non-compliance) to the Mayo Clinic IRB.

Reporting Policy

UPIRTSO

The Principal Investigator (PI) must report internal UPIRTSOs to the IRB, using the IRB electronic Reportable Event form, **within five working days** of the PI or study team becoming aware of the problem or event. Refer to the guidance "Reporting Timelines for IRB Submission when Mayo Clinic is the Reviewing IRB" available at For Researchers & Study Staff – Institutional Review Board (IRB).

Reportable event submissions are initially assessed by the Office of Research Regulatory Support (ORRS) and any having the potential to meet the UPIRTSO criteria are forwarded to the IRB. The IRB Specialist may close a non UPIRTSO per internal procedure or assign the item to an IRB Chairperson. The IRB Chairperson has the authority to determine UPIRTSO criteria were not met. IRB staff close the RE in IRBe. The PI receives a system generated notice via IRBe. If the IRB Chairperson considered the event an UPIRTSO, the item must be scheduled for review by by a convened IRB. The IRB meeting minute is documented in the IRB electronic (IRBe) system. The PI is notified of the IRB determination via IRBe.

An UPIRTSO, as determined by the convened IRB, is reported to the Mayo Clinic Institutional Official and relevant federal agencies, when required, within 30 days from the date of IRB determination. The PI will be notified in writing of this action. The reporting and PI notification are described in Reporting to the Institutional Official and Regulatory Agencies Procedure

Protocol Violation/Deviation

The timing of PI reporting of protocol violation/deviations to the IRB, using the IRBe Reportable Event form, is dependent on the severity of the protocol violation/deviation.

Major protocol violations/deviations that affect the rights and welfare of subjects and others, increase risks to subjects and others, decrease potential benefits, compromise the integrity or validity of the research; or represent willful or intentional misconduct must be reported by the investigator **within five working days** of the PI or study team becoming aware of the violation/deviation. Major protocol violations and/or deviations

must be summarized and submitted to the IRB at the time of continuing review if a continuing review is required for the study.

Minor protocol violations and/or deviations must be summarized and submitted to the IRB at the time of continuing review if a continuing review is required for the study. If a continuing review is not required, the PI must keep documentation of the minor protocol violations/deviations in the study binder, but they are not reported to the IRB.

Significant New Information

Information that indicates a significant new serious risk or increased severity of known risk, or a safety issue which requires immediate action must be reported to the IRB using the IRBe Modification form, within **five working days** of the PI or study team becoming aware of the information. The modification must be titled "**Urgent Action Required"** and include the Subject Notification Form attachment.

The PI is responsible to review new information to determine if it meets the above criteria for immediate action.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A sponsor determination of a SUSAR involving a Mayo Clinic patient should be reported to the IRB whether the Mayo Clinic IRB is the Reviewing IRB or not. Submit a Reportable Event (RE) within **five working days** of the PI or study team becoming aware of the information. Submit the RE application in IRBe as *Serious* and *Related* and *Unexpected.*

Principal Investigator Responsibilities

It is the responsibility of the PI to:

- Educate the study team on how to identify reportable events.
- Eliminate apparent immediate harm to the subject or others. If needed, this can be done before submitting the reportable event to the IRB.
- Determine whether a reportable event meets the UPIRTSO or significant new information criteria and/or protocol violation/deviation definition. Consult, as needed, with the IRB on-call Chairperson on issues relating to the UPIRTSO determination.
- Report any internal UPIRTSO, significant new information and/or major protocol violations/deviations to the IRB within **five working days** of the PI or study team becoming aware of the problem/event. Monitor subjects to detect additional risks and harm.
- Report UPIRTSO determinations to the study sponsor, funding agencies, Data Safety Monitoring Boards (DSMBs), and others as appropriate.
- Modify the study plan, consent form, related materials and procedures as necessary to address newly identified risks. Submit these modifications to the IRB and obtain IRB approval.

When appropriate put the research project on a 'PI Initiated Administrative Hold' using the electronic form in IRBe. Refer to *Administrative Hold Activation by the Principal Investigator (PI) Policy*. ORRS is also notified when a PI places the research on an Administrative Hold.

Reporting Criteria and Actions

Internal UPIRTSOs

When an internal UPIRTSO occurs, and the Mayo Clinic IRB is the Reviewing IRB:

- The PI must complete and submit the Reportable Event form in IRBe **within five working days** of the PI or study team becoming aware of the problem or event even if it is not yet resolved.
- The PI submits a Modification to the IRB if the problem or event requires revision of the protocol, consent document, or other previously approved study material.
- If the convened IRB confirms the UPIRTSO, the PI reports the IRB's determination to the research project sponsor, if applicable.

Note: When an internal UPIRTSO occurs and the Mayo Clinic IRB is not the Reviewing IRB, refer to the policy/procedure entitled Submitting a Reportable Event when Mayo Clinic IRB is not the IRB of Record.

Internal Non-UPIRTSOs

When an internal non-UPIRTSO occurs on a study requiring a continuing review and the Mayo Clinic IRB is the Reviewing IRB:

- The PI must report problems or events that do NOT meet the criteria of an UPIRTSO to the Mayo Clinic IRB in a summary format at the time of the next continuing review.
- The PI must monitor the severity and frequency of subsequent adverse events that do not meet the criteria for an UPIRTSO. The IRB provides an optional event tracking worksheet for non-UPIRTSOs which is available to researchers on the IRB website.

When an internal non-UPIRTSO occurs on a study that does not require a continuing review, the investigator must keep documentation of the event in the study binder, but the event does not need to be reported to the IRB.

External UPIRTSOs

When an external UPIRTSO occurs, and Mayo Clinic is NOT the Reviewing IRB of for the external site and a continuing review is required:

- The PI must report external UPIRTSOs to the Mayo Clinic IRB in summary form at the time of the next continuing review.

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 of the protocol or consent documents at all research sites as a result of the problem, the Mayo Clinic PI must submit the modification to the Mayo Clinic IRB using IRBe

When an external UPIRTSO occurs on a study that does not require a continuing review, the investigator must keep documentation of the event in the study binder, but the event does not need to be reported to the Mayo Clinic IRB.

External Non-UPIRTSOs

Non-UPIRTSOs occurring at other institutions where Mayo Clinic is NOT the Reviewing IRB do not need to be reported to the Mayo Clinic IRB.

Major Protocol Violations/Deviations

When a major protocol violation/deviation occurs at institutions where the Mayo Clinic IRB is the Reviewing IRB:

- The PI must complete and submit the Reportable Event form in IRBe **within five working days** of the PI or study team becoming aware of the protocol violation/event.
- The PI must submit a modification application to the IRB if the problem or event requires revision of the protocol and/or consent document.
- A convened IRB may determine the major protocol violation/deviation to not constitute serious and/or continuing non-compliance. The IRB will refer potential serious and/or continuing noncompliance to the IRB Executive Committee.
- Report a determination of serious and/or continuing noncompliance to the sponsor, Data Safety Monitoring Board (DSMB), or others as appropriate.

Note: When a major protocol violation/deviation occurs and the Mayo Clinic IRB is **not** the Reviewing IRB, refer to the policy/procedure entitled Submitting a Reportable Event when Mayo Clinic IRB is not the IRB of Record.

Minor Protocol Violations/Deviations

When minor protocol violations/deviations occur at institutions where the Mayo Clinic IRB is the Reviewing IRB of Record:

- The PI must report the protocol violations/deviations in a summary format at the time of the next continuing review if a continuing review is required. If a continuing review is not required, the PI must keep documentation of violations/deviations in the study binder, but they are not reported to the IRB.

IRB Responsibilities

UPIRTSO

All reportable events meeting the UPIRTSO criteria are sent to an IRB Chairperson for review. If the Chairperson does not agree with the PI's UPIRTSO assessment, the Chairperson or delegate may contact the PI/site investigator to discuss the event and possible reasons for re-classification as a non-UPIRTSO. If the Chairperson agrees with the assessment that the event is an UPIRTSO, the event is forwarded for review by a Convened IRB. It is the responsibility of the IRB to:

- Review the Reportable Event form submitted by the PI.
- Communicate directly with the PI, as needed to obtain more information regarding the unanticipated problem, event or other act or omission.
- Evaluate whether the actions taken by the PI to eliminate apparent harms are adequate and appropriate and if not, direct further action.
- Determine whether the problem or event meets the UPIRTSO criteria and constitutes a UPIRTSO.

Significant New Information

Modifications including Significant New Information will be processed according to the IRB policy/procedure titled, Modifications to Previously Approved or Exempt Research Procedure.

Major Protocol Violations/Deviation

ORRS is notified of all reportable event (RE) submissions. ORRS processes REs per internal procedure.

When the IRB determination is an UPIRTSO

The IRB will:

- Notify the PI of the UPIRTSO determination and documents the decision and communication to the investigator in IRBe
- Report the UPIRTSO to the Institutional Official, and to Federal agencies like the Food and Drug Administration (FDA) or Office of Human Research Protection (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.
- Determine whether a study modification is required to address newly identified risks.
- May also require additional actions such as, but not limited to:
    - Suspension of the research
    - Termination of the research
    - Notification of current subjects (required when such information might relate to subjects' willingness to continue to take part in the research)
    - Additional information provided to subjects who have completed study procedures
    - Modification of the research study
    - Modification of the information disclosed during the consent process
    - Re-consenting of current subjects
    - Monitoring of the research
    - Monitoring of the consent process
    - Referral to other Mayo Clinic entities (e.g., legal counsel, risk management, Institutional Official)
    - Request for additional information from the Data Safety Monitoring Board, or other monitoring entity
    - Shortening of the continuing review cycle

Note: When the IRB determination is a non-UPIRTSO, and/or non-serious and non-continuing non-compliance, or no non-compliance, the IRB will notify the PI of the determination via IRBe.

The IRB

Policy Notes

N/A

Related Procedures

Reporting to the Institutional Official and Regulatory Agencies

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

Modifications to Previously Approved or Exempt Research

Related Documents

Administrative Hold Activation by the Principal Investigator

Quick Reference Guide - Events that Require Submission to the Mayo Clinic IRB within 5 working days

Reporting Timelines for IRB submission when Mayo Clinic is serving as the IRB of Record

Definitions

Reportable Event: A type of event that requires reporting to the IRB within 5 working days.

UPIRTSO: An Unanticipated **P**roblem **I**nvolving **R**isk **t**o **S**ubjects or **O**thers 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:
    a. Not already described as a potential risk in the approved informed consent
    b. Not already described as a potential risk in the approved protocol
    c. Not listed in the Investigator's Brochure
    d. Not part of an underlying disease
    e. 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.

Internal UPIRTSO: A UPIRTSO that involves subjects, data, or specimens for which the Mayo Clinic IRB serves as the Reviewing IRB.

External UPIRTSO: A problem or event involving research subjects enrolled by other institutions in multicenter research projects that fall under the purview of an external IRB, that is, not the Mayo Clinic IRB.

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

Reviewing IRB: An IRB that assumes IRB responsibilities for another organization and is designated to do so through an approved Federal-wide Assurance (FWA) on file with the Office for Human Research Protections (OHRP).

Note: Commercial IRBs will not have FWAs, but must be registered with OHRP.

ORRS: Office of Research Regulatory Support (ORRS), 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.

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 intentional misconduct (for a list of potential major protocol violation/deviations see the Quick Reference Guide: Reportable Events that Require Submission to the Mayo Clinic IRB within 5 working days).
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> **Minor Protocol Violation/Deviation:** Any change 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).

Significant New Information: Information that indicates a significant new serious risk or increased severity of known risk, or a safety issue which requires immediate action

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 of non-compliance that continues to occur after a report of non-compliance and a corrective action plan have been reviewed and approved by the IRB. Continuing non-compliance may also be a pattern of non-compliance that continues to occur after the IRB has directed the investigator to correct the issue(s).

References

Association for the Accreditation of Human Research Protection Programs (AAHRPP) Standards

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

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Revision History

Date	Synopsis of Change
05/31/2023	Outside of scheduled review. Additional information added under UPIRTSO.
09/12/2022	Scheduled review. Transferred to standardized template. Updated Owner and Contact. Other minor updates.
06/012018	Revised document to remove examples of Major protocol deviations and UPIRTSOs. Added definition of Significant New Information. Added processing of Significant New Information
02/14/2018	Updated to new template. Updated Glossary Term: Continuing non-compliance. Changed IRCU to ORRS. Changed reviewer to Nanette Bateman.
09/06/2017	Minor revision. Updated the following definitions per Glossary review: External UPIRTSO, IRB of Record, and Reportable Event.
03/03/2016	Added a link to Related Document item ‘Submitting a Reportable Event when Mayo Clinic IRB is not the IRB of Record’.
01/20/2016	Changed "10 times higher" to "significantly."
Unknown	Approval for need to establish document: IRB

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Applicable Sites

Arizona Sites:
Arizona

Florida Sites:
Florida

Rochester Sites:
Duluth, Kasson, Litchfield, Little Falls, Minneapolis, Northfield, Rochester, St. Cloud, Superior

NW WI Region:
Barron, Bloomer, Chetek, Chippewa Falls, Eau Claire, Glenwood City, Menomonie, Mondovi, Osseo, Rice Lake

SE MN Region:
Adams, Albert Lea, Austin, Cannon Falls, Ellsworth, Faribault, Lake City, Lake Mills, New Richland, Owatonna, Plainview, Red Wing, Wells, Zumbrota

SW MN Region:
Belle Plaine, Fairmont, Janesville, Le Sueur, Mankato, Montgomery, New Prague, St. James, St. Peter, Waseca, Waterville

SW WI Region:
Arcadia, Caledonia, Holmen, La Crosse, Onalaska, Prairie du Chien, Sparta, Tomah

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