Submitting a Reportable Event to the IRB Policy

Scope

Mayo Clinic Human Research Protection Program

Research for which the Mayo Clinic is the IRB of Record

Purpose

The purpose of this document is to describe the process and requirements Investigators must use for reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs), Significant New Information, and Protocol Violations/Deviations (potential non-compliance) to the Mayo Clinic IRB.

Reporting Policy

UPIRTSO

The Principal Investigator 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 guidance: Reporting Timelines for IRB Submission when Mayo Clinic is serving as the IRB of Record.

Reportable events having the potential to meet the UPIRTSO criteria will be forwarded to the IRB. An IRB Chairperson has the authority to determine that the criteria were not met. If the IRB Chairperson considers the event to be a UPIRTSO it must be reviewed by a convened IRB. The investigator is notified in writing. The review, determination, and relevant communication is documented in the IRB electronic system.

A 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 investigator is notified in writing of this action.

Protocol Violation/Deviation

The timing of investigator reporting of protocol violation/deviations to the IRB, using the IRB electronic 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.

Minor protocol violations and/or deviations should be summarized and submitted to the IRB at the time of continuing review.

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 IRB electronic 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 investigator is responsible to review new information to determine if it meets the above criteria for immediate action.

Investigator Responsibilities

It is the responsibility of the investigator 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 prior to 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, when appropriate, the unanticipated problem or event to other entities such as sponsors, funding agencies, or Data Safety Monitoring Boards.
- Modify research procedures as necessary to address newly-identified risks. Submit these modifications to the IRB and obtain IRB approval.
- Put the research project on PI Initiated Administrative Hold, if necessary, using the electronic form in IRBe. This change automatically notifies ORRS. See IRB document Administrative Hold Activation by the Principal Investigator.

Investigator Reporting Criteria and Actions

Internal UPIRTSOs

When an internal UPIRTSO occurs and the Mayo Clinic IRB is the IRB of Record:

- The investigator completes the Reportable Event form within the IRB electronic system **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 investigator submits a modification to the IRB if the problem or event requires revision of the protocol and/or consent document.
- If the convened IRB confirms the UPIRTSO, the investigator 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 IRB of record, 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 and the Mayo Clinic IRB is the IRB of Record:

- The 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.

- 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 and Mayo Clinic is NOT the IRB of Record for that site:

- The investigator reports 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 investigator submits the modification to the Mayo Clinic IRB using the IRB electronic system **External Non-UPIRTSOs**

Non-UPIRTSOs occurring at other institutions where Mayo Clinic is NOT the IRB of Record 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 serves as the IRB of Record:

- The investigator completes the Reportable Event form within the IRB electronic system **within five working days** of the PI or study team becoming aware of the protocol violation/event.
- The investigator submits a modification application to the IRB if the problem or event requires revision of the protocol and/or consent document.
- If the convened IRB determines the major protocol violation/deviation to be serious and/or continuing non-compliance, the investigator reports the IRB's determination to the research project sponsor, if applicable.

NOTE: When a major protocol violation/deviation occurs and the Mayo Clinic IRB is **not** the IRB of record, 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 serves as the IRB of Record:

- The investigator reports the protocol violations/deviations in summary format at the time of the next continuing review.

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 investigator's UPIRTSO assessment, the Chairperson contacts the investigator to discuss the event and possible reasons for re-classification as a non-UPIRTSO. If the Chairperson agrees with the investigator

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 investigator.
- Communicate directly with the investigator, as needed to obtain more information regarding the unanticipated problem, event or other act or omission.
- Evaluate whether the actions taken by the investigator 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, *Modification to Previously Approved or Exempt Research*.

Major Protocol Violations/Deviation

All reportable events, including protocol violations/deviations, are sent to ORRS for review. Violations/deviations that meet the definition of a major violation/deviation may be forwarded to the IRB Executive Committee and/or a Convened IRB for further review as per the procedure *Internal Compliance Review of Allegations of Suspected or Actual Noncompliance.*

When the IRB determination is a UPIRTSO or Serious and/or Continuing non-compliance

The IRB:

- Notifies the investigator of the UPIRTSO and/or serious and/or continuing non-compliance determination and documents the decision and communication to the investigator within the IRB electronic system
- Reports the UPIRTSO and/or serious and/or continuing non-compliance to the Institutional Official, and to Federal agencies (e.g. 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 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

When the IRB determination is a non-UPIRTSO, and/or non-serious and non-continuing non-compliance, or no non-compliance

The IRB:

- Notifies the investigator of the determination.

Policy Notes

N/A

Related Procedure(s)

Administrative Hold Activation by the Principal Investigator

Reporting to the Institutional Official and Regulatory Agencies

Internal Compliance Review of Allegations of Suspected or Actual Non-compliance

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

Modifications to Previously Approved or Exempt Research

Related Document(s)

IRB Electronic Reportable Event Form

Quick Reference Guide - Reportable Events that require submission to the Mayo Clinic IRB within 5 working days (IRB 10540)

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:

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.

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

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.

IRB of Record: A reviewing 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).

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 version 10/1/2009

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

Owner

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Revision History

Date	Synopsis of Change
June 1, 2018	Revised document to remove examples of Major protocol deviations and UPIRTSOs. Added definition of Significant New Information. Added processing of Significant New Information
February 14, 2018	Updated to new template. Updated Glossary Term: Continuing non-compliance. Changed IRCU to ORRS. Changed reviewer to Nanette Bateman.
9/6/2017	Minor revision. Updated the following definitions per Glossary review: External UPIRTSO, IRB of Record, and Reportable Event.
3/3/2016	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."