Title: UNANTICIPATED PROBLEMS INVOLVING RISKS TO PARTICIPANTS AND OTHERS **Version No.:** 1.8

SOP No.: RR-409 **Effective Date:** January 20, 2026

1. Purpose

This policy defines unanticipated problems (UPs) involving risks to participants or others and the associated reporting requirements, IRB review process, and how the IRB communicates its UP findings and actions to the investigator and the institution.

2. Policy

In accordance with federal regulations and MSK policy, all MSK employees or agents, who: (a) conduct non-exempt human subjects research; or (b) review or oversee such research must report UPs that are associated with non-exempt human subjects research that was or currently is reviewed and approved by the MSK IRB or Privacy Board. Such incidents should be reported to the MSK HRPP Office whether they occur during the research, as well as after study completion or subject withdrawal/completion if the incident could affect the safety and welfare of either currently or previously enrolled participants.

UP reports must be submitted to the HRPP Office within 5 calendar days of discovering the event. Incidents, experiences, or outcomes, e.g., serious adverse events and protocol deviations, not meeting the definition of an UP should be reported in accordance with IRB SOPs RR-407 and RR-408.

3. Specific Procedures

3.1 Definitions

Unanticipated problem involving risks to participants or others (UPs): Any incident, experience, or outcome that meets all the following criteria:

1. Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **and**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable probability that the incident, experience, or outcome may have been caused by procedures involved in the research); **and**
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

   Examples of UPs might include:
   - Adverse events that are unexpected, involve new or increased risks, and are related to the research;
   - Any accidental or unintentional change to the IRB-approved protocol that involved risks or has the potential to recur;
   - Any change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant;
   - Any complaint of a participant that indicates an unanticipated risk which cannot be resolved by the research staff/Principal Investigator;
   - Updated study information indicating an UP (e.g., auditing/monitoring reports, DSMC/DSMB reports, interim findings, changes in FDA labeling or withdrawal of marketing of an intervention being used in the research, etc.);

- Breach of privacy/confidentiality/data security/loss of study data/destruction of study data that may involve risk to participants or others; or
- Any other incident, experience or outcome that is related to the research and indicates participants or others might be at increased risk of harm.

Adverse event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether considered related to the subject's participation in the research.

Serious adverse event (SAE): An event that results in ANY of the following outcomes:

1. Death
2. Life-threatening adverse
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization (Note: a hospitalization for a planned procedure/disease treatment is not considered and SAE)
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
7. Any other event specified in the protocol to be an SAE

3.2 Reporting Unanticipated Problems Involving Risks to Participants and Others

Investigators must promptly report (within 5 calendar days of discovery) UPs to the HRPP Office. UPs that are SAEs are reported via PIMS SAE Report, UPs that are deviations are reported via PIMS Retrospective Deviation form, all other UPs are reported via email/memo.

3.3 Review of Reports

3.3.1 Initial Review

The individual submitting the UP is expected to make an initial assessment as to whether the event meets the UP criteria and whether the event warrants a change to the protocol and/or informed consent form/process.

The HRPP Office will review all incoming UP reports for completeness. If the submission is deemed incomplete, the HRPP Office will work with the investigator to make the report complete.

If the submission is complete, the UP report will be reviewed by HRPP management and IRB Leadership (UP Review Team) to determine whether the event constitutes an UP. The IRB Chair will determine whether suspension is necessary or other actions are required to alleviate immediate risk of harm to research participants or others. If necessary, the IRB Chair may suspend some or all the research pending review of the event at the next convened IRB meeting. Suspensions ordered by the IRB Chair will follow IRB SOP FO-310.

3.3.2 Initial Review by the UP Review Team

The UP Review Team will review the UP information submitted to the HRPP Office, along with the IRB approved applicable protocol documents. The review team will determine whether the event may constitute an UP and should be sent to a convened meeting for final adjudication.

When the UP Review Team determines that the problem does not constitute an UP, the HRPP Office will notify the investigator in writing of the UP Review Team's determination and that no further action is required. If the potential UP event was an SAE or retrospective deviation, the IRB is informed of the event at the time of continuing review.

If the UP Review Team determines that the event is an UP, the UP review team, and at times in collaboration with the PI/study team, will formulate a management plan. The UP Review Team will propose which of the following actions must be implemented to protect the safety, welfare or rights of research participants or others:

- No action;
- Accept/approve the proposed corrective action plan submitted along with the UP report;
- Modify the research protocol;
- Modify information disclosed during the consent process;
- Provide additional information to past participants;
- Notify current participants of the UP when such information may relate to participants' willingness to continue to take part in the research;
- Require current participants to re-consent to continue participation;
- Modify the continuing review schedule;
- Monitor the research;
- Monitor the consent process;
- Suspend the research;
- Request for more information pending final decision;
- Refer to other organizational entities (e.g. legal services, institutional official); or
- Other appropriate actions (e.g., mandatory education of research team, for cause audit, etc.).

The UP summary and management plan will be transcribed onto the incident report form. The form, along with all pertinent materials will be provided to the HRPP Office to be listed on the next available IRB meeting agenda. The HRPP Office, in consultation with the IRB Chair, will identify a UP Review team member to present the UP and the management plan at the convened IRB meeting.

3.3.3 Review by the Convened IRB

A member of the UP Review Team will present the UP report to the convened IRB. All IRB members will have access to the following documents/information:

- Incident Report Form which includes information about the UP and proposed management plan;
- The currently approved applicable protocol documents (i.e., protocol, consent)

Following presentation of the UP report to the IRB, the convened IRB will vote 1) on whether the event constitutes an UP and 2) to either accept the proposed management plan or to require additional actions that might be required to protect the safety, welfare or rights of research participants.

3.3.4 Post-Convened Board Review Procedures

HRPP Office staff will notify the principal investigator and study team in writing of the IRB UP determination and required actions. Such notifications will include:

- Date of review;
- Identification of what was reviewed;
- IRB determination regarding the UP report; and
- Required actions.

Events determined to be an UP are filed in PIMS and will be appended to the Continuing Review Report/Progress Report for informational purposes at the time of continuing review.

3.4 Reporting

Unanticipated Problems will be reported in accordance with the requirements stipulated in MSK IRB SOP CO-602.

4. Applicable Regulations and References

- 45 CFR 46.103(b)(5)(i)
- 21 CFR 56.108(b) (1)
- 21 CFR 312.32
- 21 CFR 812.3(s)
- OHRP IRB Guidance Document: Guidelines for Reporting Unanticipated Problems/Events
- FDA Guidance Document: Adverse Event Reporting to IRBs – Improving Human Subject Protections
- MSK IRB SOP CO-602
- MSK Incident Report Form

Revision History

Revision	Effective Date	Reason for Change
1.0	2/29/16	New
1.1	11/7/16	3.3.3 Clarified what the convened IRB votes on
1.2	8/15/18	3.1 Removed example of UP due to vagueness 3.2 Removed reference to CRDB and violations 3.3.1 Removed job titles
1.3	11/23/20	Updated UP reporting time frame from 5 business days to 5 calendar days throughout 3.1 Updated definition of SAE to align with IRB SOP RR-408; removed definition of local event and off-site event 3.3.3 Removed time frame to provide IRB members with access to UP documents/information 3.4 Section added
1.4	1/31/22	Grammatical revisions

		3.3.2 Updated to note that the UP review team collaborates with the PI/study team as needed to formulate a management plan; Clarified that the UP summary and management plan will be transcribed onto the OHRP incident report form and will listed on the next available IRB meeting agenda along with any other pertinent information 4 Added MSK IRB SOP CO-602
1.5	1/23/23	Added MSK OHRP Incident Report Form to the list of applicable regulations and references
1.6	2/5/24	3.3.1 Clarified members of UP Review Team as HRPP management and IRB Leadership 3.3.2 Clarified that IRB is informed of events that are not UPs at the time of continuing review if they are SAEs or retrospective deviations. 3.3.4 Added “Events determined to be an UP are filed in PIMS and will be appended to the Continuing Review Report/Progress Report for informational purposes at the time of continuing review.”
1.7	1/21/25	3.3.4 Clarified the procedures for sharing Board determinations of UPs with Principal Investigators
1.8	1/20/26	2 Updated to note this policy applies to research reviewed by the MSK IRB or Privacy Board 3.2 Updated to note UPs may be reported to the HRPP via email/memo 3.3.2 Clarified that if the UP Review Team makes the initial determination that an event may be a UP, it will send the report to a convened meeting for final adjudication 3.3.3 Clarified which documents may be reviewed by the convened board with a report of a possible UP