

Regulations require an organization to have written procedures for ensuring prompt reporting of “unanticipated problems involving risk to subjects or others” (also referred to as UPs, UAPs, and UPIRTSOs).

This section provides definitions and procedures for the reporting of UPIRTSOs to the NJH HRPP Staff. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 8.3.

In conducting its review of protocol deviations, violations, noncompliance, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to an UPIRTSO.

18.1 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to subjects or others (UPIRTSOs) refer to any incident, experience, outcome, or new information that:

1. Is unexpected; and
2. Is at least possibly related to participation in the research; and
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized

UPIRTSOs also encompass Unanticipated Adverse Device Effects, as defined below.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by their participation in the research.

Adverse Event. For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable 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. For interventional studies, protocols can provide further definition of adverse events. Furthermore, adverse events can be determined at the investigators discretion. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Unanticipated Adverse Device Effect. An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary

plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects [21 CFR 812.3(s)].

18.2 Procedures

18.2.1 Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB for a given protocol, the NJH HRPP does not accept reports of adverse events that are not UPIRTSOs, except in summary form at the time of continuing review.

Investigators must report the following events or issues to the HRPP as soon as possible but within 7 working days after the investigator first learns of the event using the “Event Report” form. If the study is not subject FDA regulation, the report can be emailed to the HRPP office. Otherwise, hardcopy must be provided.

If investigators are uncertain but believe that the event might represent an UPIRTSO, a report should be submitted.

Examples of UPIRTSOs include:

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome);
2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy);
3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report;
4. An AE that is described or addressed in the investigator’s brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator’s brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report;
5. A serious AE that is described or addressed in the investigator’s brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report;
6. AEs involving direct harm to subjects enrolled by the local investigator which in the opinion of the investigator or sponsor, may represent an UPIRTSO;

7. IND Safety Reports from sponsors that meet the criteria for an UPIRTSO. Such reports must be accompanied by an analysis from the sponsor explaining why the report represents an UPIRTSO and whether it has been reported to the FDA as such;

8. Unanticipated adverse device effects (UADEs);

9. Any other AE or safety finding (e.g. based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.

10. Reports (including reports from DSMBs/DMCs) that indicate that risks are greater than previously known or that indicate that the research should be modified, suspended, or halted.

11. Sponsor or lead investigator/coordinating center imposed suspension or termination of some or all research activities;

12. An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects;

13. A breach of confidentiality or loss of research data (e.g., a laptop or thumb drive is lost or stolen, nonphysical harm);

14. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research subjects (e.g., investigators, research assistants, students, the public, etc.) to potential risk;

15. New information that indicates increased risk, new risk(s), or decrease to potential benefit from what was previously understood. Examples include:

a. An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits may be different than initially presented to the IRB;

b. A report or publication that indicates the risks, benefits, or merit of the research are different from what was previously understood.

18.2.2 Review Procedures

1. Upon receipt of the Event Report, the HRPP Staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information.

2. The IRB Co-Chair/HRPP staff receives and reviews the report and makes an initial determination as to whether the event represents an UPIRTSO. If needed, the Co-Chair/HRPP staff may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees).

3. If the reviewer determines that the problem does not meet the definition of an UPIRTSO, determination will be made regarding whether any additional actions are necessary to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for

review. The results of the review will be recorded in study record (and meeting minutes, if the convened IRB reviews the matter) and communicated to the investigator.

4. If the reviewer determines that the event may be an UPIRTSO, the report will be referred for review by the IRB of record. The IRB will determine whether the event is a UPIRTSO and whether any additional actions, such as those outlined below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring

boards, or steering committees). The results of the review will be recorded in the IRB minutes and communicated to the investigator.

5. Based upon the circumstances, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:

- a. Requiring modifications to the protocol or plan or procedures for implantation of the research (Research Plan) as described in the application and other materials submitted to the IRB;
- b. Revising the continuing review timetable;
- c. Modifying the consent process;
- d. Modifying the consent document;
- e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's rights, welfare, or willingness to continue participation);
- f. Providing additional information to past participants;
- g. Requiring additional training of the investigator and/or study staff;
- h. Requiring that current subjects re-consent to participation;
- i. Monitoring the research;
- j. Monitoring consent;
- k. Reporting or referral to appropriate parties (e.g., the IO, Corporate Compliance, Privacy Officer etc.);
- l. Suspending IRB approval;
- m. Terminating IRB approval;
- n. Other actions as appropriate given the specific circumstances.

When the IRB determines that an event is an UPIRTSO, the HRPP Staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 22. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

This section provides definitions and procedures for the reporting and review of known or suspected noncompliance for research under the oversight of the National Jewish Health IRB. Research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 8.3.

In conducting its review of protocol deviations, , unanticipated problems, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to noncompliance.

19.1 Definitions

Noncompliance is defined as the failure to follow federal, state, or local regulations governing human subject research, institutional policies related to human subject research, or the requirements or determinations of the IRB. Noncompliance may be minor or sporadic or it may be serious or continuing. Protocol deviations and violations are a form of noncompliance.

Serious Noncompliance is defined as noncompliance that, in the judgment of the convened IRB, creates an increase in risks to subjects, adversely affects the rights, welfare, or safety of subjects, or adversely affects the scientific integrity of the study. Willful violation of policies and/or federal regulations may also constitute serious noncompliance.

Continuing Noncompliance is defined as a pattern of noncompliance that, in the judgment of the convened IRB, suggests a likelihood that instances of noncompliance will continue unless the IRB or institution intervenes.

Allegation of Noncompliance. Allegation of Noncompliance is defined as an unproved assertion of noncompliance.

19.2 Reporting

Investigators and their study staff are required to report instances of possible noncompliance to the HRPP staff within 7 working days of discovery using the “Event Report” form. Reports that are for studies not under FDA regulation may e-mail the report. Reports for FDA regulated studies must be provided in hardcopy. Additionally, anyone may report concerns of possible noncompliance to the HRPP Staff verbally, by email, or other means. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and, unless reporting anonymously, cooperating with any subsequent fact-finding in relation to the report.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the Director of RRA, HRPP staff or an IRB Co-Chair directly to discuss the situation informally.

19.3 Review Procedures

1. Upon receipt of the Event Report, the HRPP Staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the report came from someone other than the investigator verbally, by email, or by other means, the Director of RRA or assigned HRPP staff will develop a written report summarizing the available information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may

have occurred, the Director of RRA, IRB Co-Chair, and, when appropriate, the IO and/or Research Integrity Officer, will be notified so that they can take any necessary steps (e.g., suspension of study etc.) to ensure the safety of subjects or investigate the matter.

2. The IRB Co-Chair/HRPP Staff receives and reviews the report and makes an initial determination as to whether the event represents noncompliance, and, if so, if the noncompliance may be serious or continuing. If needed, the IRB Chair may request additional information from the investigator or others. When circumstances warrant, the Director of RRA may bypass this step and assign the report for convened board review.

3. If the IRB Co-Chair/HRPP Staff determines that the event or issue is not noncompliance, or is noncompliance but not serious or continuing, s/he will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions are required. As warranted, the Co-Chair/HRPP Staff may refer the matter to the convened IRB for review. The results of the review will be recorded in the study file (and minutes if the convened IRB reviews the matter) and communicated to the investigator.

4. If the IRB Co-Chair/HRPP Staff determines that the event or issue may be serious or continuing noncompliance, the report will be referred for review by the IRB of record. The IRB will determine whether the event is serious or continuing noncompliance. The IRB will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions, such as those outline below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator or others. The results of the review will be recorded in the IRB minutes and communicated to the investigator.

5. When the IRB determines that an event is serious or continuing noncompliance, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:

- a. Requiring modifications to the protocol or research plan
- b. Revising the continuing review timetable
- c. Modifying the consent process
- d. Modifying the consent document
- e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
- f. Providing additional information to past participants
- g. Requiring additional training of the investigator and/or study staff
- h. Requiring that current subjects re-consent to participation
- i. Monitoring the research
- j. Monitoring consent
- k. Reporting or referral to appropriate parties (e.g., the IO, Compliance, Risk Management, Privacy)

l. Suspending IRB approval

m. Terminating IRB approval

n. Other actions as appropriate given the specific circumstances

6. When the IRB determines that an event is serious or continuing noncompliance, the HRPP Staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 22. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

7. Investigators may request that the IRB reconsider its determination by following the procedures in Section 11.4.

Complaints 20

The HRPP staff & NJH IRB will be responsive and sensitive to the complaints or concerns expressed by subjects or others and will respond to all complaints or concerns in a confidential and timely manner. The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members hear complaints or concerns from subjects, he or she will try to resolve them.

Investigators conducting research under the auspices of NJH must report complaints to the HRPP Staff regardless of who serves as the IRB of record. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 8.3. Investigators conducting research under the oversight of the NJH IRB report complaints using the Event Report Form. Investigators are encouraged to contact the Director of RRA or IO when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (e.g., immediate attention is needed).

When the HRPP Staff is the direct recipient of complaints or concerns, the staff will do the following:

1. Document the complaint or allegation. When appropriate, the staff may request that the subject submit the complaint in writing.
2. Reassure the subject that the HRPP/IRB will take all necessary measures to inquire into the circumstances and to address the issue.
3. Provide written confirmation of receipt of the complaint to the subject, if the subject is willing to provide contact information.
4. Convey the information to the IRB of record in a timely manner.
5. When appropriate, contact the investigator for additional information or to assist with resolution.
6. When appropriate, contact other resources (e.g., Privacy Officer etc.) to assist with information-gathering or resolution.

For research under the oversight of the internal IRB, the IRB Co-Chair/HRPP Staff will consider the complaint or concern and take any reasonable steps necessary to investigate and/or resolve the issue, if appropriate, prior to review and consideration by the IRB. A report will be provided to the IRB at the

next available meeting if the research is subject to convened IRB review, or provided to the designated expedited reviewer if the research is eligible for expedited review. When reviewing complaints, the IRB will consider whether the complaint was the result of, or related to, an UPIRTSO or noncompliance, and, if so, will follow the relevant procedures. The IRB Co-Chair may refer any complaint for review by the convened IRB. The IRB minutes, or reviewer comments for expedited reviews, will reflect the action(s) taken and, if necessary, notice to the appropriate officials and/or agencies.

The HRPP Staff will maintain written copies of complaints and concerns and will document the investigation and resolution. The complainant will be notified promptly following resolution of the complaint or concern, when appropriate, and if contact information has been provided. If the HRPP Staff or IRB receives a complaint, or identifies information while investigating a complaint, that is indicative of possible misconduct in research, NJH's Research Integrity Officer will be notified immediately.

Other Reportable Information 21

When research is under the oversight of the NJH IRB, in addition to UPIRTSOs, noncompliance, and complaints, any change to the research implemented without IRB approval and any information that may impact the rights, safety, or welfare of subjects or inform the IRB's oversight of the research must be reported to the IRB within 7 working days of discovery using the Event Report Form. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 8.3.

Other reportable information includes, but is not limited to, the following:

1. Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s);
2. Monitoring, audit, and inspection reports in accordance with Section 2.1 of this SOP;
3. Sponsor or coordinating center reports;
4. Data Safety Monitoring reports, including reports from DSMBs, DMCs, and others;
5. When an existing subject becomes a member of a vulnerable population not previously approved by the IRB for inclusion in the study (e.g., incarceration, pregnancy, or change in decision-making capacity of an already enrolled subject);
6. Suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others;
7. Changes that impact the ability of the PI to conduct or supervise the study, temporarily or permanently;
8. Changes that impact the qualifications of investigators or research staff members such as actions taken by regulatory authorities, licensing boards, or credentialing committees;
9. Any other new information that may impact the rights, welfare, or willingness of subjects to continue in the research.

21.1 Review Procedures

1. Upon receipt of the report, the HRPP Staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the Director of RRA, IRB Chair, and, when appropriate, the IO and/or Research Integrity Officer, will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.
2. The IRB Co-Chair/HRPP Staff receives and reviews the report and if the report may represent an UPIRTSO or noncompliance, reviews the report as described in Section 18 or 19. When circumstances warrant, the Director of RRA may bypass this step and assign the report for convened board review.
3. If the Co-Chair/HRPP Staff determines that the event or issue is not noncompliance or an UPIRTSO, they will review the event or issue, any proposed corrective and preventative action plans, and determine if any additional actions are needed to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in the study record, and in the minutes of the convened IRB meeting in which the matter was addressed, and communicated to the investigator.