Human Research Protection Program Departmental Policy and Procedure Manual

9.2 Unanticipated Problems Involving Risk to Subjects or Others (UPIRSO) And Unanticipated Adverse Device Effects (UADE)

Responsible Office: Human Research Protection Program Department (HRPPD)

Effective Date: June 5, 2026

I. Policy Statement

a. Prompt reporting to the reviewing IRB (and UTSW HRPP for reliance studies) is required for any unanticipated problems involving risks to subjects or others (UPIRSO) or unanticipated adverse device effects (UADE). For the purposes of this policy, UPIRSOs include UADEs and death or serious injury related to a HUD unless otherwise specified.

b. Adverse events and UPIRSOs are also summarized in continuing review.

c. Investigators must report a UADE to the sponsor and reviewing IRB (and UTSW HRPP for reliance studies) within 10 working days after first learning of the UADE.

d. Sponsor-investigators must report the results of an evaluation of a UADE to FDA and all reviewing IRBs (and UTSW HRPP for reliance studies) and participating investigators within 10 working days after first receiving notice of the UADE.

e. In addition to prompt UADE reporting, investigators or sponsors are required to report all UADEs to the reviewing IRB (and UTSW HRPP for reliance studies) after evaluation by the sponsor. This requirement is in addition to required UADE reporting.

f. Investigators must terminate all investigations or parts of investigations as soon as possible when an UADE presents unreasonable risk to subjects and the investigator shall report such a risk (as a UPIRSO) to the IRB.

    i. In addition, termination must occur not later than 5 working days after a

sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

ii. An investigator may not resume a terminated investigation without FDA and IRB approval.

g. Investigators are required to follow-up on all reports until issues are considered resolved.

II. Scope

a. This policy and procedures applies to all Principal Investigators involved with human research.

III. Procedures For Policy Implementation

a. This procedure starts upon the investigator becoming aware of an adverse event or other non- AE unanticipated problem (e.g., UPIRSO or UADE).

b. This procedure ends when either the:

i. PI determines the event does not meet criteria of either a UPIRSO or UADE, or;

ii. HRPPD notifies the investigator that the:

1. Report of an apparent UPIRSO was determined not to meet UPIRSO criteria;, or

2. Report of an apparent UADE was determined not to meet UADE criteria; or

3. IRB or IO agreed that the event was either a UPIRSO or UADE, the appropriate actions have been completed, and the issue has been resolved.

c. The Principal Investigator is responsible for:

i. **Reviewing** all incidents, experiences, and outcomes that may represent UPIRSO or UADE:

ii. **Determining** whether any reviewed incidents, experiences, and outcomes represents a possible UPIRSO or UADE

iii. Promptly reporting all possible UPIRSOs and UADEs to the reviewing IRB (and UTSW HRPP for reliance studies) using the Reportable Event Smart Form in ETHOS.

1. Prompt reporting timeframe - report is made to the reviewing IRB (and UTSW HRPP for reliance studies) within 5 business days for the following:

   a. UPIRSOs based on internal information (e.g., experienced by subjects enrolled by the investigator(s) at an institution affiliated with the UT Southwestern IRB)

   b. UPIRSOs based on external information (e.g., experienced by subjects enrolled by the investigator(s) at an institution not affiliated with the UT Southwestern IRB)

   c. UPIRSOs based on internal information that are either life threatening or fatal (if the study is sponsored by the National Cancer Institutes, the shortened reporting timeframe is only applicable to UPIRSOs based on internal adverse events that are “fatal toxicities”)

iv. **Contacting institutions** involved with the UPIRSO/UADE for recommendations or additional requirements to secure continued institutional approval of the research;

v. **Implementing actions necessary to eliminate immediate hazard,** (if necessary, without IRB approval). Report any actions to eliminate an immediate hazard with the Reportable Event Smart Form in ETHOS. Immediate actions that will also result in permanent modification to the research plan must be submitted for IRB approval using an amendment request;

vi. **Submitting follow-up reports** to update the information related to the event to the reviewing IRB (and UTSW HRPP for reliance studies). Follow-up reports (to correct/clarify/reassess/ or report resolution) should be submitted within approximately 30 days of receipt of request for further information/corrections or of the date the PI makes a reassessment or an action plan is fully implemented. Follow-up reports should clarify whether previous determinations made by the investigator and recorded on the initial report form have changed. In the situation where new information may affect the answers to the items on the report form, the investigator should revise the report form and address each item in the order they appear on the form;

vii. **Submitting modification(s)** to the reviewing IRB (and UTSW HRPP for reliance studies), as necessary, to report any actions taken without prior IRB approval to eliminate an immediate hazard and to modify the research (e.g., protocol, consent form, or consent process) regardless of the source of the request for changes (i.e., external sponsor, affiliated institution, etc.)

d. All of the above actions must be taken and are ultimately the responsibility of the PI, regardless of who observed or became aware of the event.

i. In the absence of the PI, a co-investigator can fulfill these requirements to meet the reporting timeline.

ii. In the absence of either the PI or a co-investigator, a sub-investigator, coordinator, or any member of the research team must contact the HRPPD for direction.

iii. In instances where a student (graduate or undergraduate) suspects an unanticipated problem or serious adverse event, it is expected that the faculty advisor will be immediately made aware of any suspicious event that occurs during the study. After consultation with the HRPPD, a

determination should be made as to prompt reporting to the IRB.

iv. In all instances, the report must state that the reporting individual has notified or will notify the PI. If the PI has been notified, the report must include a description of the PI's analysis as well. If the PI cannot be notified prior to submission of the report, a follow-up report must be submitted identifying how and when the PI was made aware of the issue and the result of analysis by the PI.

e. In multi-site trials, one site may also take on reporting responsibilities. Local investigators at those sites would report UPIRSOs to their reviewing IRB (and UTSW HRPP for reliance studies) and to the Study Coordinating Center. The coordinating site must then also report to other participating sites, who will then report to their respective IRBs. The coordinating center will also report to FDA/OHRP as applicable.

f. The HRPP Department is responsible for:

i. Receiving the Reportable Event.

ii. Sending a summary of the initial report to the offices/officials as described in the 8.2 Reporting Policy And Procedure.

iii. Routing the report to the designated reviewer

g. Designated Reviewer is responsible for:

i. Screening Reports of Possible UPIRSO

1. The Assistant Vice President for Human Research Administration (AVPHRA), IRB Director (IRBD), or designee are designated reviewers for this process. Given their positions in the HRPP Department, these individuals are readily available to promptly review these reports and are expected to communicate with the appropriate IRB Chair, as necessary. The reviewers screen the report to determine whether they represent an apparent UPIRSO and determine whether it involves

other research review offices or committees (e.g., Office of Compliance, Privacy Office, and other affiliated groups).

2. If it is determined that the issues are pertinent to other research review entities, appropriate coordination will occur as specified in 1.5. Communication With Other Committees And Offices.
3. The reviewer utilizes the following items when reviewing the report
    a. Telephonic information
    b. Memos
    c. Amendments
    d. Progress Reports
    e. Reportable Event Smart Form in ETHOS
4. The reviewer determines whether the report should be reviewed as an initial report of possible UPIRSO/UADE or as a follow-up to a previously reported possible UPIRSO/UADE.

ii. Determining whether an Event meets Apparent UPIRSO or UADE criteria

a. The AVPHRA, IRBD, or designee reviews the report and makes one of three possible decisions:

i. The event or events meet UPIRSO criteria (i.e., finds no supporting documents or statements that contradict the defined criteria or indicate information is inadequate to determine whether any of the criteria are met). The reviewer:

ii. Considers whether the action plan provided in the report is adequate regarding:

iii. Actions taken to eliminate an immediate hazard without prior IRB approval including

iv. PI or sponsor decision to halt all or part of the study

v. PI or sponsor decision to halt enrollment

vi. Notification of currently enrolled or completed subjects

vii. Other Actions taken or planned by the PI

viii. Changes to the consent form or process (plan for re-consenting if applicable)

ix. Changes to the protocol (additional monitoring, changes in the DSMP, additional safeguards)

x. Notification of other agencies/appropriate institutional officials (e.g., FDA, HHS, DoD).

xi. Considers whether additional actions or safeguards should be taken by the investigator(s), sponsor, study coordinating center, or DSMB/DMC to protect subjects so that the study still satisfies the requirements for continued approval by the IRB.

xii. Considers whether the affected research protocol still satisfies the requirements for IRB approval under 6.2 IRB Approval Of Research and HHS regulations at 45 CFR 46.111. In particular, the reviewer considers whether risks to subjects continue to be minimized; whether risks continue to be reasonable in relation to the anticipated benefits to the subjects; and whether the risks are reasonable in relation to the importance of the knowledge that may reasonably be expected to result.

xiii. Initiates 9.4 Suspension Or Termination Of Research if the reviewer determines the report indicates the affected research protocol no longer satisfies the requirements for IRB approval under 6.2 IRB Approval Of Research and HHS regulations at 45 CFR 46.111.

xiv. Places the issue on the agenda for review by the convened IRB. The IRB is provided with a copy of the Reportable Event as well as the reviewer's

xv. recommendations concerning the PI's plan for managing the UPIRSO prior to the meeting. (See 1.1. Receiving, Routing, And Administrative Review Of IRB Submissions)

xvi. There is **insufficient information** to determine an event is either a UPIRSO or UADE. In this case the investigator/coordinator is contacted to provide additional details or clarify the information provided. If no further information is available and there continues to be insufficient information to determine that the event meets the criteria, it will not be classified as a UPIRSO or UADE.

xvii. The event **does not constitute** a UPIRSO/UADE. The decision will be communicated in writing to the PI describing the reasons why the report did not meet the criteria for either a UPIRSO or UADE. The PI will be given the opportunity to provide additional justification if necessary.

iii. Reviewing the report to consider whether the UPIRSO or UADE also represents Serious or Continuing Noncompliance (See 9.3 Noncompliance Review).

iv. Considers sending the report to a subcommittee for further inquiry (as described in the 9.3 Noncompliance Review).

h. Responsibilities of Institutional officials (UTSW or Affiliates) who are notified of the event (See 8.2 Reporting Policy And Procedure) include:

i. Reviewing the notices of UPIRSO / UADE;

ii. Communicating with other institutional officials, as appropriate;

Communicating with the PI to convey any additional institutional requirements necessary to resolve the event (specifying which requirements represent conditions of continued approval to conduct research at that institution and which only represent suggestions).

i. IRB responsibilities:

   i. The convened IRB considers the initial reviewer's or subcommittee's recommendation(s) and suggested management plan, determines whether the event meets criteria as an UPIRSO or UADE, and determines whether they concur with the suggested management plan.

      1. The IRB will receive access to the same items the designated reviewer reviewed as well as any notes from the designated reviewer and the entire protocol (if necessary).

      2. In making this determination the IRB considers whether the action plan provided in the report is adequate regarding:

         a. Actions taken to eliminate an immediate hazard without prior IRB approval including

            i. PI or sponsor decision to halt all or part of the study

            ii. PI or sponsor decision to halt enrollment,

            iii. Notification of currently enrolled or completed subjects

         b. Other Actions

            i. Changes to the consent form or process (plan for re-consenting if applicable)

            ii. Changes to the protocol (additional monitoring, changes in the DSMP, additional safeguards)

            iii. Notification of other agencies/appropriate institutional officials (e.g., FDA, HHS, DoD).

c. Other actions as deemed appropriate.

d. Considers whether additional actions or safeguards should be taken by the investigator(s), the sponsor, the study coordinating center, or DSMB/DMC to protect subjects so that the study still satisfies the requirements for continued approval by the IRB.

ii. The convened IRB considers whether the affected research protocol still satisfies the requirements for IRB approval under 6.2 IRB Approval Of Research and HHS regulations at 45 CFR 46.111. In particular, the reviewer considers whether risks to subjects continue to be minimized; whether risks continue to be reasonable in relation to the anticipated benefits to the subjects; and whether the risks are reasonable in relation to the importance of the knowledge that may reasonably be expected to result.

iii. The convened IRB initiates 9.4 Suspension Or Termination Of Research if the Board determines the report indicates the affected research protocol no longer satisfies the requirements for IRB approval under 6.2 IRB Approval Of Research and HHS regulations at 45 CFR 46.111.

iv. The convened IRB may take a variety of additional actions, depending on the outcome of the review, including, but not limited to, the list of actions outlined in 9.1 COMPLAINTS.

j. The Human Research Protection Program Department is responsible for reporting determinations made by designated reviewers and those made by the convened IRBs as noted in the 8.2 Reporting Policy And Procedure.

k. Determinations concerning follow-up reports

i. Reports submitted as Follow-up reports may be considered new initial reports if new information warrants (e.g., new risk, risk changed category from Non-AE to AE or an AE UPIRSO with “greater risk” was changed to “serious”). Such reports will be processed as a new

UPIRSO/UADE report as described above.

ii. Reports will be considered “follow-up” reports if submitted:

1. To identify how and when a PI was notified of a report submitted by another member of the research team so long as the PI did not disagree with the analysis in a manner that requires IRB review
2. To file the corrected report in the protocol record.
3. In response to request for further input from the appropriate UT Southwestern officials, the IRB or the Reviewer.
4. To report on actions taken by PI and research staff in response to event
5. To report implementation of action plan
6. To report on completion of action plan
7. To report additional action requirements of affiliated institutions.

iii. Follow up reports will be processed in the same manner as other Responsive Materials as described in 2.1. Initial Review Of Research.

iv. A final follow-up notice to involved institutions of internal (or external) UPIRSO determination” will be sent as described in 8.2 Reporting Policy And Procedure.

v.

IV. Definitions

a. See Glossary of Human Research Terms

V. References

a. 21 CFR 50 – Protection of Human Subjects

b. 45 CFR 46 – Protection of Human Subjects

c. 45 CFR 164 – Security and Privacy (HIPAA Privacy Rule)

d. 21 CFR 56 – Institutional Review Boards

VI. Revision and Review History

a. June 2026; HRPP; Reference to eIRB updated to ETHOS

b. June 2021; HRPP; Separated policy from P&P manual. Updated references to AVPHRA and IRB Director. Minor administrative edits.

c. November 2019; HRPP; Expanded UADE, clarified review for external IRB studies, changed possible to apparent.

d. August 2017; HRPP New Policy Development

e. March 2012; IRB OfficeIRB Written Procedures