

	Institutional Review Board	
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Responsibility: OIRB		Page 1 of 9

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

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I. Policy

- A. Prompt reporting to the IRB is required for any “unanticipated problems involving risk to subjects or others” ([UPIRSO](#)) or “unanticipated adverse device effects” ([UADE](#)).
- B. Adverse events and UPIRSOs are also summarized in the study progress report submitted during continuing review.
- C. In addition to prompt UADE reporting, investigators or sponsors are required to report all unanticipated adverse device effects (UADE) to the IRB after evaluation by the sponsor. This requirement is in addition to required UADE reporting.
- D. Investigators must terminate all investigations or parts of investigations as soon as possible when an unanticipated adverse device effect (UADE) presents

unreasonable risk to subjects and the investigator shall report such a risk (as a UADE) to the IRB.

1. 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.
 2. An investigator may not resume a terminated investigation without FDA and IRB approval.
- E. Investigators are required to follow-up on all reports until issues are considered resolved.

II. Overview

- A. This procedure starts upon the investigator becoming aware of an [adverse event](#) or [unanticipated problem](#) (including [UADEs](#)). For the purposes of this policy, UPIRSOs also include UADEs unless otherwise specified.
- B. This procedure ends when either:
1. the PI determines the event does not meet criteria of either a UPIRSO or UADE, or;
 2. the OIRB notifies the investigator:
 - a) that the individual report of possible UPIRSO was determined not to meet UPIRSO criteria, or;
 - b) that the individual report of a possible UADE was determined not to meet UADE criteria, or;
 - c) the IRB agreed that the event was either a UPIRSO or UADE, the appropriate actions have been completed, and the issue has been resolved.

III. Procedures

- A. The Principal Investigator is responsible for:
1. **Reviewing** all incidents, experiences, and outcomes that may represent UPIRSO or UADE:
 2. **Determining** whether any reviewed incidents, experiences, and outcomes represents a possible [UPIRSO](#) or [UADE](#);
 3. Promptly reporting all possible [UPIRSOs](#) to the IRB using the Prompt Reporting Form;
 - a) Prompt reporting timeframe - report is made to the IRB within 7 days for UPIRSOs based on internal information (e.g., experienced by subjects enrolled by the investigator(s) at an institution affiliated with the UT Health San Antonio IRB) or 14 days for UPIRSOs

- based on external information (e.g., experienced by subjects enrolled by the investigator(s) at an institution not affiliated with the UT Health San Antonio IRB)
- b) Special shortened reporting timeframe for Non-VA research: All UPIRSOs based on internal information that are either life threatening or fatal events must be reported within 48 hours (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”)
 - (1) Special shortened reporting timeframe for VA research – All UPIRSOs that are fatal events must be reported verbally within 1 hour upon becoming aware of the event that is believed to be both unexpected and related or possibly related to participation in a VA non-exempt human subjects research. VA personnel must also ensure that follow-up written notification is provided to the appropriate IRB of Record within one (1) business day of becoming aware of such a death.
4. Promptly reporting all possible [UADEs](#) to the IRB using the Prompt Reporting Form;
 - a) Prompt reporting timeframe - report is made to the IRB within 10 days for UADEs based on internal events (experienced by subjects enrolled by the investigator(s) at an institution affiliated with the UT Health San Antonio IRB) or 14 days for UADEs based on external events (experienced by subjects enrolled by the investigator(s) at an institution not affiliated with the UT Health San Antonio IRB)
 - b) Special shortened reporting timeframe of UADEs involving “an unreasonable risk to subjects requiring termination by the sponsor of all investigations or parts of investigation presenting that risk”. Prompt reporting to the IRB in this situation is within 5 days after notification from the sponsor to terminate some or all of the research.
 5. **Contacting institutions** involved with the UPIRSO/UADE for recommendations or additional requirements to secure continued institutional approval of the research;
 6. **Implementing actions necessary to eliminate immediate hazard**, (if necessary, without IRB approval). Report any actions to eliminate an immediate hazard either with the initial UPIRSO/UADE report or using a follow-up report. Immediate actions that will also result in permanent modification to the research plan must be submitted for IRB approval using an amendment request;
 7. **Submitting follow-up reports** to update the information related to the event to the IRB. Follow-up reports (to correct/clarify/reassess/ or report resolution) should be submitted within 30 days of receipt of request for further information/corrections or of the date PI makes reassessment or 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 complete a new report form and address each item in the order they appear on the form;

8. **Submitting amendment(s)** to the IRB, 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.).
- B. 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.
1. In the absence of the Principal Investigator, a co-PI can fulfill these requirements to meet the reporting timeline.
 2. In the absence of either the Principal Investigator or a co-PI, a sub-investigator, project coordinator, or any member of the research team must contact the OIRB for direction.
 3. 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 OIRB, a determination should be made as to prompt reporting to the IRB.
 4. 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.
- C. In multi-site trials, one site may also take on reporting responsibilities. Local investigators at those sites would report UPIRSOs to their IRB and to the Study Coordinating Center. The coordinating site must then also report to other participating sites to be reported to their respective IRBs and the coordinating center will also report to FDA/OHRP as applicable.
- D. The IRB Office is responsible for:
1. Receiving and routing the Prompt Report Form to the designated reviewer.
 2. For VA Research – Within one business day after receiving written notification of a death, the IRB Chair or another qualified IRB voting member will assess and document whether any actions are warranted to

eliminate apparent immediate hazards to subjects and if so, notifying the investigator to initiate these actions.

3. Sending a summary of the initial report to the offices/officials as described in the [Reporting Policy and Procedure](#).
4. Routing the report for the appropriate level of review. For VA, any local research death of a human subject that is believed to be both unexpected and related or possibly related to participation in a VA non-exempt human subjects research study, routing the report to the next convened IRB not to exceed 30 calendar days after the date of written notification.

E. Designated Reviewer is responsible for:

1. Screening Reports of Possible UPIRSO
 - a) The Expedited Reviewers with appropriate experience are designated by the IRB Chairs as reviewers for this process. Given their positions in the IRB Office, these individuals are readily available to promptly review these reports. The reviewers are expected to communicate with the appropriate IRB Chair and AVPRO. The reviewers screen the report to determine whether they represent unanticipated problems that meet criteria as possible unanticipated problems involving risks to participants or others and determine whether the possible UPIRSO or possible UADE raises issues pertinent to other research review offices or committees, i.e., South Texas Veterans Healthcare System R&D Office, Office of Regulatory Affairs & Compliance, Office of Clinical Research (OCR) and other affiliated groups. If it is determined that the issues are pertinent to other research review entities, appropriate coordination will be planned (see [Coordination with Other Committees and Offices Policy and Procedure](#)).
 - b) The reviewer utilizes the following items when reviewing the report
 - (1) Telephonic information
 - (2) Memos, including email correspondence
 - (3) Amendments
 - (4) Progress Reports
 - (5) UPIRSO Reports
 - c) 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.
 - (1) If the report is considered an initial report of possible UPIRSO determinations in III.E.2 below will be assessed.
 - (2) If the report is considered a follow-up to a previously reported possible UPIRSO the determinations in III.I below will be assessed.
2. Determining whether a Report of Possible UPIRSO meets criteria as UPIRSO or UADE
 - a) The IRBD or IRBAD reviews the report and makes one of three possible decisions (within 5 business days and 1 business day for VA Research where the event involves the death of a local subject):

- (1) The event or events **meets 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:
 - (a) Considers whether the action plan provided in the report is adequate regarding:
 - (i) Actions taken to eliminate an immediate hazard without prior IRB approval including
 - (a) PI or sponsor decision to [halt](#) all or part of the study
 - (b) PI or sponsor decision to halt enrollment
 - (c) Notification of currently enrolled or completed subjects
 - (ii) Other Actions taken or planned by the PI
 - (a) Changes to the consent form or process (plan for re-consenting if applicable)
 - (b) Changes to the protocol (additional monitoring, changes in the DSMP, additional safeguards)
 - (c) Notification of other agencies/appropriate institutional officials (e.g., FDA, VA R&D).
 - (b) 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.
 - (c) Considers whether the affected research protocol still satisfies the requirements for IRB approval under [IRB Approval of Research Policy and Procedure](#) 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.
 - (d) Initiates the [Suspension or Termination Policy and Procedure](#) if the reviewer determines the report indicates the affected research protocol no longer satisfies the requirements for IRB approval under [IRB Approval of Research Policy and Procedure](#) and HHS regulations at 45 CFR 46.111.
 - (e) Places the issue on the agenda for review by the convened IRB. The IRB is provided with a copy of the Report of Possible UPIRSO/UADE as well as the reviewer's recommendations concerning the PI's plan for managing the unanticipated problem involving risks to participants or others and if applicable, the Notice to Involved Institutions/OHRP containing the action plan when applicable are provided to the members as part of the review packet prior to the meeting. (See [Receiving,](#)

[Routing, and Administrative Review of Submissions Policy and Procedure](#))

- (2) 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.
 - (3) 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.
3. Reviewing the report to consider whether the UPIRSO or UADE also represents Serious or Continuing Noncompliance (See [Noncompliance Policy and Procedure](#))
 4. Considers sending the report to a subcommittee for further inquiry (as described in the [Noncompliance Policy and Procedure](#)).
- F. Responsibilities of Institutional officials (HSC or Affiliates) who are notified of the event (See [Reporting Policy and Procedure](#)) include:
1. Reviewing the notices of UPIRSO / UADE;
 2. Communicating with other appropriate institutional officials as appropriate;
 3. Communicating with the PI and institutions 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). Institutions may follow-up with the PI where appropriate when the IRB has resolved all regulatory issues.
- G. IRB responsibilities:
1. 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.
 - a) 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).
 - b) In making this determination the IRB considers whether the action plan provided in the report is adequate regarding:
 - (1) Actions taken to eliminate an immediate hazard without prior IRB approval including

- (a) PI or sponsor decision to [halt](#) all or part of the study
 - (b) PI or sponsor decision to halt enrollment,
 - (c) Notification of currently enrolled or completed subjects
 - (2) Other Actions
 - (a) Changes to the consent form or process (plan for re-consenting if applicable)
 - (b) Changes to the protocol (additional monitoring, changes in the DSMP, additional safeguards)
 - (c) Notification of other agencies/appropriate institutional officials (e.g., FDA, VA R&D).
 - (3) Other actions as deemed appropriate.
 - (4) 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.
 - (5) For VA research involving the death of a subject:
 - (a) whether the death was both unexpected and related or possibly related to participation in the research; and
 - (b) what, if any, protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.
2. The convened IRB considers whether the affected research protocol still satisfies the requirements for IRB approval under [IRB Approval of Research Policy and Procedure](#) 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.
3. The convened IRB initiates the [Suspension or Termination Policy and Procedure](#) if the Board determines the report indicates the affected research protocol no longer satisfies the requirements for IRB approval

under [IRB Approval of Research Policy and Procedure](#) and HHS regulations at 45 CFR 46.111.

4. 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 the [Complaints Policy and Procedure](#).
- H. The Office of the IRB is responsible for reporting determinations made by designated reviewers and those made by the convened IRBs as noted in the [Reporting Policy and Procedure](#).
- I. Determinations concerning follow-up reports
1. 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.
 2. Reports will be considered “follow-up” reports if submitted:
 - a) 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
 - b) To file the corrected report in the protocol record.
 - c) In response to request for further input from the appropriate HSC officials, the IRB or the Reviewer.
 - d) To report on actions taken by PI and research staff in response to event
 - e) To report implementation of action plan
 - f) To report on completion of action plan
 - g) To report additional action requirements of affiliated institutions.
 3. Follow up reports will be processed in the same manner as other Responsive Materials as described in the [Initial Review of Research Policy and Procedure](#).
 4. A final “Follow-up notice to Involved Institutions of Internal (or External) UPIRSO Determination” letter will be sent as described in the [Reporting Policy and Procedure](#).

IV. References

- A. Definitions (see [Glossary](#))
- B. Regulatory (see [Policy on Policies Policy and Procedure](#))