HUMAN RESEARCH PROTECTION PROGRAM DEPARTMENTAL GUIDANCE

9.5 REPORTABLE EVENTS GUIDANCE

RESPONSIBLE OFFICE: Human Research Protection Program Department (HRPPD) **EFFECTIVE DATE:** JUNE 1, 2021

This reportable event guidance applies to all non-exempt research conducted by or on behalf of UT Southwestern (UTSW), its affiliates, and investigators, sites, or institutions relying on the UTSW IRB.

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I. INVESTIGATOR RESPONSIBILITY

- Principal Investigators (PIs) (or their designees) are responsible for:
  - monitoring their studies in real-time for adherence to the IRB-approved investigational plan (e.g., protocol, Smartform, ICD);
  - obtaining prior IRB approval for non-emergency exceptions/waivers;
  - tracking and assessing instances of noncompliance (e.g., deviations, violations, departures);
  - promptly reporting noncompliance and UPIRSOs to the reviewing IRB (and UTSW HRPP for reliance studies); and
  - knowing and complying with all other reporting requirements (e.g., sponsor, FDA, external IRB) for their studies

II. NONCOMPLIANCE

What is Noncompliance?

Noncompliance is any failure to follow applicable federal regulations, state and local laws, or institutional policies governing human subjects protections, or the requirements or determinations of the IRB, including the requirements of the approved investigational plan (e.g., protocol, Smartform, ICD)

- Noncompliance can result from performing an act that violates these requirements ***or*** by failing to act when required.

Examples of Noncompliance

Noncompliance with IRB and/or federal requirements may involve a range of issues from relatively minor or technical deviations, which result from inadvertent errors, inattention to detail, or inadequate training and supervision of research staff to violations, which pose risks to subjects or others and/or violations of their rights or welfare. Noncompliance does not generally include individual protocol deviations; however, protocol deviations should be tracked and assessed by the investigator because they may collectively be considered noncompliance.

How to prevent noncompliance:

Sponsors and sponsor-investigators should build flexibility into their protocols and investigators should strictly adhere to the written IRB-approved protocol and investigational plan to avoid adversely affecting subject safety or science. Regulatory guidance recognizes the need to balance the protection of human subjects and scientific integrity with investigator and IRB/HRPP burden.

A. Noncompliance

- **Noncompliance** includes departures from the approved study protocol (generally intentional on the part of the investigator) without prior IRB approval that:
  - have the potential to cause harm or increase the risk of harm to one or more research participants, *or*
  - have the potential to damage the scientific integrity of the data collected for the study, *or*
  - impact a subject's rights, safety, or welfare

- **Reporting requirement**: Promptly report protocol violations to the reviewing IRB (and UTSW HRPP for reliance studies) within 5 working days of discovery.

B. Serious noncompliance

- **Serious noncompliance** includes any noncompliance that:
  - increases risk of harm to subjects; and/or
  - adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
  - adversely affects the integrity of the data and research (substantially compromises the integrity, reliability, or validity of the research)

- **Reporting requirement**: Promptly report apparent serious noncompliance to the reviewing IRB (and UTSW HRPP for reliance studies) within 5 working days of discovery.

C. **Continuing noncompliance**
- **Continuing noncompliance** includes:
  - A pattern of repeated noncompliance (in one or more protocols simultaneously or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive actions within a reasonable timeframe, which may or may not also constitute Serious Noncompliance.

- **Reporting requirement**: Promptly report apparent continuing noncompliance to the reviewing IRB (and UTSW HRPP for reliance studies) within 5 working days of discovery.

D. **Noncompliance that is neither serious nor continuing**
- **Not serious and not continuing noncompliance** includes**:**
  - Events, incidents, outcomes, etc. that do not meet the definitions of either serious noncompliance or continuing noncompliance.

- **Reporting requirement**: Noncompliance that is *neither* serious nor continuing should be tracked and summarized in the progress report at the next continuing review or notice of study closure, whichever comes first.

III. Events submitted via the Reportable Event pathway, but do not constitute noncompliance

A. **Exceptions**
- Exceptions are also called single-subject exceptions or single-subject waivers
- Exceptions include any changes to the IRB-approved investigational plan that is ***not due to an emergency*** and is:
  - intentional on part of the investigator;
  - in the investigator's control;
  - not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria); or
  - in rare instances, intended as a systemic change, but the change has not yet been IRB-approved

- **Reporting requirement for studies relying on the UTSW IRB**: Exceptions require ***prospective*** IRB approval before being implemented. Call the HRPP at 214-648-3060 if your request is urgent.
  - **NOTE**: Failure to obtain prior IRB approval for exceptions is considered noncompliance . If the noncompliance meets the definition of a protocol violation, of serious noncompliance and/or continuing noncompliance, promptly report it to the IRB within 5 working days of discovery. Otherwise, if a minor deviation (e.g., out of window visit that doesn't impact safety) report the deviation at the next continuing review or notice of study closure, whichever comes first.

- **Reporting requirement for studies relying on non-UTSW IRBs**:

The UTSW HRPP cannot approve exceptions for studies relying on non-UTSW IRBs. Study teams should contact their reviewing IRBs for exception/waiver requests and approval. Exceptions/waivers approved by non-UTSW IRBs should be reported to the UTSW HRPP at the next continuing review or notice of study closure, whichever comes first.

B. **Emergency deviations**

- **Emergency deviations** include any changes to the IRB-approved investigational plan without prior IRB approval intended to:
  - eliminate an apparent immediate hazard to subjects, or
  - protect the life or physical well-being of a subject in an emergency (for IDE studies).

- **Reporting requirement**: Promptly report emergency deviations to the reviewing IRB (and UTSW HRPP for reliance studies) within 5 working days of occurrence.

IV. UNANTICIPATED PROBLEMS

- Unanticipated problems involving risks to subjects or others (UPIRSOs) are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure (IB), protocol, or informed consent document),

AND

2. Probably or definitely related to participation in the research,

AND

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic/financial, legal, or social harm) than was previously known or recognized.

- For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

- **NOTE**: UPIRSOs require changes to the research documents/investigational plan (e.g., protocol, IB, and/or informed consent document/process) or corrective actions to protect the integrity of the research or the rights, safety, or welfare of subjects or others. Therefore, if no changes to the research or corrective actions are being made as a result of the event, it is *probably not* a UPIRSO.

- **Reporting requirement**: Promptly report apparent UPIRSOs to the reviewing IRB (and UTSW HRPP for reliance studies) within 5 working days of discovery.

- **NOTE:** Some instances of noncompliance may also be UPIRSOs, and vice versa. For example, administering a subject 100 mg of study drug vs. the protocol-required dosage of 10 mg, even if the subject experiences no adverse effects, is both noncompliance and a UPIRSO.

V. COMPLAINTS

- Research-related complaints can be made by a subject, subject's family, or others. Refer to HRPP Policy 9.1 Complaints.

- **Reporting requirement**: Promptly report research-related complaints affecting subjects' rights, safety, or welfare to the reviewing IRB (and UTSW HRPP for reliance studies) within 5 working days of receiving the complaint.

VI. OTHER RESEARCH-RELATED INCIDENTS AND REPORTS

- The following other research-related incidents or reports should NOT be promptly reported to the UTSW IRB (or HRPP for reliance studies) unless they contain events, incidents, or outcomes that appear to constitute protocol violations, serious noncompliance, continuing noncompliance, or UPIRSOs:
  - Events, problems, or reports that are required by the sponsor to be submitted to the UTSW IRB/HRPP
  - Data safety monitoring (DSMB/DMC/DSC) reports
  - Safety (i.e., IND/IDE, MedWatch/Form FDA 3500, CIOMS) reports
  - Monitoring reports
  - Audit reports
  - Instances of noncompliance (e.g., deviations) that do not meet the UTSW HRPP definition of protocol violation, serious noncompliance, or continuing noncompliance
  - AEs/SAEs that do not meet ALL 3 UPIRSO criteria
  - Any new information since the last IRB review

- **Reporting requirement**: Other research-related incidents and reports that do NOT appear to constitute protocol violations, serious noncompliance, continuing noncompliance, or UPIRSOs should be tracked, evaluated, and submitted to the IRB (and UTSW HRPP for reliance studies) in summary form at the next continuing review or notice of study closure, whichever comes first.

- **Progress Report at Continuing Review**
  - The progress report should include a summarization (not a listing) of the investigator's overall assessment of any adverse events, noncompliance, UPIRSOs, and any other new information that has become available in order for the IRB to determine if the risk/benefit ratio has changed. Examples of appropriate summaries:
    - "There were several out-of-window visits due to the participants' schedules and two participants failed to bring their medication diary to their follow-up visits. No systemic issues were identified."
    - "We obtained prior IRB approval for exceptions on two subjects who were taking the same excluded medication, XYZ. After reviewing the safety profile of the medication, the sponsor decided to modify the eligibility criteria to allow subjects to use XYZ at its lowest dose while participating in the study. We submitted the revised protocol documents to the IRB/HRPP in MOD #4, which was approved on 1/15/2017."
    - "Since the last reporting period, 5 SAEs and 35 AEs occurred. All were expected or not related to the study interventions or procedures."

VII. RESEARCH RELYING ON A NON-UTSW (EXTERNAL, CENTRAL, OR SINGLE) IRB

- Investigators relying on a non-UTSW IRB who are conducting research on behalf of UTSW or its affiliates are responsible for reporting events to the reviewing IRB as required by the reviewing IRB policies. **Please note: the reviewing IRB's reporting requirements may differ substantially from the UTSW HRPP reporting policies. You must be familiar with the reporting policies of the reviewing IRB.**
- In addition to reporting to the reviewing IRB, the following **LOCAL** events must be submitted to the UTSW HRPP:
  - **LOCAL** emergency deviations
  - **LOCAL** events that appear to constitute protocol violations or serious or continuing noncompliance
  - **LOCAL** UPIRSOs
  - **LOCAL** research-related complaints affecting subjects' rights, safety, or welfare

- **Reporting requirement**: Promptly report the **LOCAL** events listed above to the Reviewing IRB **and** to the UTSW HRPP within 5 working days of discovery. In addition, submit the external IRB's responses or determinations on these local events to the UTSW HRPP within 10 working days of receipt.

VIII. QUESTIONS

For questions on how to classify an event or whether an event should be reported promptly, at continuing review, or at all, please contact the Human Research Protection Program's IRB Office at 214-648-3060 or HRPP@utsouthwestern.edu.

IX. DEFINITIONS

SEE GLOSSARY OF HUMAN RESEARCH TERMS

X. REFERENCES

Resource
21 CFR 50 – PROTECTION OF HUMAN SUBJECTS
45 CFR 46 – PROTECTION OF HUMAN SUBJECTS
45 CFR 164 – SECURITY AND PRIVACY (HIPAA PRIVACY RULE)
21 CFR 56 – INSTITUTIONAL REVIEW BOARDS
Food and Drug Administration (FDA) ADVERSE EVENT REPORTING TO IRBS – IMPROVING HUMAN SUBJECT PROTECTION
NIH Office of Biotechnology Activities (OBA) - REPORTING OF INCIDENTS RELATED TO RESEARCH SUBJECT TO THE NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT OR SYNTHETIC NUCLEIC ACIDS TO THE NIH OBA
Office of Human Research Protections (OHRP) REVIEWING AND REPORTING UPIRSOS AND ADVERSE EVENTS

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XI. REVISION AND REVIEW HISTORY

Revision Date	Author	Description
June 2021	HRPP	Separated Guidance from P&P Manual; renumbered to 9-1 to reflect guidance numbering; revised to reflect all noncompliance should be reported.
November 2019	HRPP	Updated definitions and reporting requirements for serious/continuing noncompliance
August 2017	HRPP	New Policy Development, standardized reporting timeframes
August 2016	HRPP Office	Revised reporting requirements to be consistent with Federal Requirements
March 2012	IRB Office	IRB Written Procedures