

Reporting and Reviewing Unanticipated Problems

SOP 116
Revised: January 5, 2017

Purpose and Scope

The SOP describes the procedure for reporting and reviewing Unanticipated Problems from research conducted under the approval of the University of Hawai'i (UH) Institutional Review Board (IRB).

This SOP applies to:

- all Investigators conducting human subjects research under the approval of the UH IRB; and
- all IRBs operating under the UH Federalwide Assurance (FWA).

Definitions

Per Office for Human Research Protections (OHRP)

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a study subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.¹

Serious Adverse Event (SAE): Any AE that results in any of the following to a research participant²:

1. Death,
2. A life-threatening event, which places the participant at immediate risk of death from the event as it occurred,
3. A new inpatient hospitalization or prolongation of existing hospitalization,
4. A persistent or significant disability or incapacity,
5. A congenital anomaly or birth defect, or
6. An adverse event that, based on appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (e.g., development of drug dependency or drug abuse).

Internal AE: An AE experienced by participants enrolled by UH investigators³.

External AE: An AE experienced by participants enrolled by investigators from non-UH institutions engaged in the research.

Internal Event: an event occurred in a study conducted by a UH investigator.

¹ OHRP Guidance on UPs, *supra* note Error! Bookmark not defined. at II.

² *Id.* at App. A; see 21 C.F.R. § 312.32(a).

³ "UH Investigator" means that an investigator who is affiliated with UH. See SOP 108, [Collaborative Research](#) for the definition.

External Event: an event occurred in a study conducted by an investigator from non-UH institutions engaged in the study.

Unanticipated Problem (UP): An incident, experience, or outcome that meets ALL of the following criteria⁴:

- It is unexpected (in terms of nature, severity, or frequency) given:
 - the research procedures that are described in the protocol-related documents, such as the IRB-approved protocol and consent form; and
 - the characteristics of the subject population being studied;
- It is related or possibly related to participation in the research; and
- It 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.

IND Studies

Adverse Event (AE): An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.⁵

UPs and AEs

For an AE to be a UP, the AE must be

1. unexpected,
2. serious, and
3. would have implications for the conduct of the study, e.g., requiring significant, and usually safety-related, changes in the protocol such as revising inclusion or exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure.⁶

The U.S. Food and Drug Administration (FDA) believes only the following categories of AEs should be considered as UPs and must be reported to the IRB:⁷

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure.
 - (a) e.g., 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 is uncommon in the study population.
 - (a) e.g., tendon rupture, progressive multifocal leukoencephalopathy;
3. Multiple occurrences of an AE that is determined to be a UP, based on an aggregate analysis, i.e., comparing treatment and control groups. A determination should have been made that the series of AEs were not just isolated occurrences but involve risk to human participants.
4. An AE addressed in the investigator's brochure, protocol, or consent form, but occurs at a specificity or severity inconsistent with prior observations.
 - (a) e.g., if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in participants, hepatic necrosis would be considered an unanticipated problem involving risk to human participants.

⁴ OHRP Guidance on UPs, supra note **Error! Bookmark not defined.** at I.

⁵ 21 C.F.R. § 312.32(a).

⁶ FDA Guidance on Reporting AEs, supra note **Error! Bookmark not defined.** at 3.

⁷ FDA Guidance on Reporting AEs, supra note **Error! Bookmark not defined.** at 4–5.

5. A serious AE addressed in the investigator's brochure, protocol, or consent form but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence. Here, for the AE to be a UP, there should be a credible baseline for comparison.
6. Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, protocol, or consent form, or prompt actions by the IRB to ensure the protection of participants.

IDE Studies

Unanticipated Adverse device effects (UADE)^{8 9}: Any serious adverse effect on health or safety, any life-threatening problem, or death caused by, or associated with, a device if the effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application

Or

Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Procedures

Reporting

Principal Investigator's Responsibilities

The Principal Investigator (PI) must report unanticipated problems involving risks to research participants or others to the IRB.

When reporting UPs to the UH IRB, the investigator should:

- notify the IRB of each event that qualifies as a UP by contacting HSP *within 24 hours* of when the investigator becomes aware of the event,
- report the event to the IRB using the eProtocol **APP 09: Unanticipated Problem Report Form**, for reporting unanticipated problems no later than 10 working days after the investigator becomes aware of the event, and
- file a follow-up report to the HSP if appropriate.¹⁰

An investigator should not report every adverse event to the IRB unless the event qualifies as a UP. See **Guidance 614, Events and Information that Require Prompt Reporting to the IRB** for clarification on when an adverse event qualifies as a UP.

For *externally-sponsored research*, it is the responsibility of the PI to promptly report all serious adverse events and unanticipated problems to the sponsor, following sponsor policies and requirements.

For **IND Studies**, it is the responsibility of the investigator to promptly report all UPs to the IRB¹¹, and report to sponsors any AEs.¹² In a multicenter study, the investigator may rely on the sponsor's assessment of AEs and provide the IRB with a UP report prepared by the sponsor.¹³

⁸ Id. at 1.

⁹ 21 C.F.R. § 812.4(s); **IDE Definitions and Acronyms**, FDA (last updated July 29, 2013), <http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm046698.htm>.

¹⁰ See **OHRP Guidance on UPs**, *supra* note **Error! Bookmark not defined.** at V.

For **IDE Studies**, the investigator must submit to the IRB and the sponsor any unanticipated adverse device effect occurring during an investigation as soon as possible, but no later than 10 working days after the investigator first learns of the effect.¹⁴

Events and Information – Required Reporting to the IRB

Events and information that must be reported to the IRB, along with the timelines for reporting, are listed in Guidance 614, Events and Information that Require Prompt Reporting to the IRB. They should be reported to the IRB using the online IRB Report Form in the eProtocol system.

Review Procedures

UP Report Initial Assessment

1. Reports are checked for completeness by HSP staff. A report that does not satisfy initial IRB staff evaluation will be returned to the PI with an explanation.
2. The Director or the Director's designee assesses whether the reported event meets UP criteria. The Director may consult with the investigator, the Chair, or others in this determination.
3. If the reported event meets UP criteria:
 - o The Director or the Director's designee will assess whether the problem requires action prior to the next IRB meeting; and
 - o If immediate actions are required, the Director will contact the Chair, who will determine the next steps.
4. If the reported event does not meet UP criteria, the report will be returned to the Investigator.

IRB Review

- **IRB Primary Reviewer**

Reports which appear to be UPs, and reports of other reportable events and information will be assigned to an IRB member with adequate expertise for review.

- The IRB member reviews the report and materials from the protocol file, which may include the following materials:
 - o Protocol,
 - o Investigator's Brochure,
 - o Continuing Reviews,
 - o Modifications,
 - o Other Reports

- **IRB Convened Meeting Review**

¹¹ 21 C.F.R. §§ 312.66, 312.53(c)(1)(vii); and 56.108(b)(1).

¹² 21 C.F.R. § 312.64(b).

¹³ FDA Guidance on Reporting AEs, supra note **Error! Bookmark not defined.** at 5.

¹⁴ 21 C.F.R. § 812.150(a)(1).

Prior to the meeting, all voting members are given access to the report and supporting documents for review.

At the convened meeting, the IRB discusses and votes on whether the report qualifies as a UP or other reportable event. The IRB considers whether any action is necessary, and the decision and votes are documented in the meeting minutes.

- **IRB Actions**

During the IRB meeting, the IRB will review the UP report and determine actions by the IRB to address the problem.

Possible IRB actions are:

- accepting the report as submitted;
- requesting additional information from the investigator;
- requiring modifications to the risk section of the consent form;
- requiring that a written communication be sent to all enrolled subjects about the newly-recognized risk;
- requiring provision of additional information to past participants;
- requiring current subjects to re-consent to participation;
- modifying the schedule of continuing review;
- requiring changes to the protocol initiated by the investigator before obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- requiring a change in the study inclusion or exclusion criteria;
- requiring additional training for the research team;
- requiring the research site to develop procedures designed to prevent the reoccurrence of the UP;
- requiring changes to the protocol designed to reduce or eliminate the risk;
- requiring temporary or permanent suspension of enrollment of participants;
- requiring more than one review annually;
- suspension or termination of the research;
- requiring that the investigator report the event to the sponsor, regulatory agency, or both; or other action determined to be appropriate by the IRB.

- **Decision**

The IRB decision is communicated in writing to the investigator and documented in the protocol file. Further reporting to external and/or internal entities (see below) may be required if the convened IRB

- Determines that an unanticipated problem involving risks to participant or others has occurred;
- Determines some other reportable event has occurred; or
- Suspends or terminates the approval of a protocol.

Internal/ External Reporting

Although it is the responsibility of the PI to promptly report all serious adverse events and unanticipated problems to the sponsor for externally-sponsored research, the UH IRB may determine that it will independently report the problem and its concerns to any sponsor of a study.

Institutional Official and Other Institutional Leaders

The Human Studies Program will promptly report unanticipated problems involving risk to subjects or others to the Institutional Official, other institutional leaders, as appropriate, and the appropriate federal regulatory agency (e.g., OHRP and/or FDA).

It is expected that UPs occurring at external (to UH) participating institutions will be reported by the institution experiencing the UP.

Federal Agencies

UPs occurring within all research funded by a federal agency that has adopted the Common Rule must be promptly reported to OHRP. UPs occurring within all FDA-regulated research must be promptly reported to the FDA

UP Report submitted to either OHRP or the FDA should include:

- Name of the institution conducting the research,
- Title of the research project in which the UP occurred,
- The research sponsor,
- Name of the PI on the protocol,
- Number of the research project assigned by the IRB and the federal *award* number (not the protocol number),
- A detailed description of the problem, and
- Actions the institution has taken or plans to take to address the problem.
- For reports to the FDA, also include:
 - The IND or IDE number, and
 - The complete title of the research protocol

Federal regulations do not specify time limits for submitting UP reports. However, OHRP offers the following guidance:

- i. For serious incidents, submit the UP report within a few days and, for less serious incidents, submit the UP report within a few weeks.
- ii. It may be appropriate to send an initial report advising OHRP of the problem and to submit a follow-up report when an investigation has been completed or a corrective action plan has been implemented.
- iii. UP reports should be submitted to federal agencies, using the following contact information.
 - Send reports to OHRP (PDF or Word documents preferred) to the following email address: IRPT.OS@hhs.gov
 - Send reports involving investigational drugs to the FDA at:

Ms. Dana Walters at Dana.Walters@fda.hhs.gov
U.S. Food & Drug Administration
Division of Scientific Investigations (HFD-45)
Office of Compliance
Center for Drug Evaluation and Research

White Oak Campus
10903 New Hampshire Ave.
Bldg 51, Rm 5341
Silver Spring, MD 20993
Phone (301) 796-3150
Fax (301) 847-8748

- Send reports involving investigational devices to:

Ms. Sheila Brown (sheila.brown@fda.hhs.gov)
Center for Devices and Radiological Health
U.S. Food & Drug Administration
10903 New Hampshire Ave.
WO66 Rm 1651
Silver Spring, MD 20993
Phone (301) 796-6563
Fax (301) 847-8120

Reporting Timeframe for Unanticipated Problems

The maximum time allowed between the recognition of an unanticipated problem event that involves risks to participants or others and fulfilling its reporting requirements should not exceed more than thirty (30) business days.

Materials

- APP 09: Unanticipated Problem Report Form
- WKSH 314 Unanticipated Problem/ Adverse Event Reviewer Worksheet
- TMP 435 Letter of Acknowledgement – Unanticipated Problem
- GUIDE 614 Events and Information that Require Prompt Reporting to the IRB

References

- The IRB has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate. (**AAHRPP Element II.2.F**)