IRB Adverse Events & Unanticipated Problems

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Summary

This document applies to all non-exempt human subjects research conducted by UWL faculty, staff, or students. It provides guidance on HHS regulations for the protection of human research subjects at 45 CFR 46 and 21 CFR 312 related to the review and reporting of unanticipated problems involving risks to subjects or others. The guidance is intended to help ensure that the review and reporting of adverse events and unanticipated problems occur in a timely, meaningful way so that human subjects can be better protected from avoidable harms while reducing unnecessary administrative burden.

Definitions

Adverse Event: Any untoward or unfavorable medical 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, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms

Unanticipated Problem (UP): Any incident, experience, or outcome that meets <u>all</u> the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. related or possibly related to a subject's participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **and**
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

How to Determine What Is an Unanticipated Problem

The vast majority of adverse events occurring in human subjects are not unanticipated problems. In addition, unanticipated problems include other incidents that are not adverse events. Only unanticipated problems need to be reported to the IRB; however, the Office for Human Research Protections (OHRP) recognizes that it may be difficult to determine whether a particular event meets the definition of an unanticipated problem. Below are some guidance and examples to help researchers make this determination. However, if a PI is uncertain whether an incident or outcome meets the definition of an unanticipated problem, they should still report it to the IRB. It is always preferrable to err on the side of over-reporting than under-reporting.

To determine whether an incident is an unanticipated problem, the PI should consider each of the three questions below. If the answer is YES to all three questions, this is an unanticipated problem and must be reported to appropriate entities. (See Appendix A for a flowchart summarizing how to identify unanticipated problems.)

1. **Is the incident unexpected?**
   An incident that occurs in one or more subjects participating in a research protocol is unexpected if the nature, severity, or frequency is **not** consistent with either:

   1. the known or foreseeable risk of such incidents associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; **or**
   2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the event and the subject's predisposing risk factor profile for the event.

   For many studies, determining whether a particular event has an unexpectedly higher frequency can only be done through an analysis of appropriate data on all subjects enrolled in the research.

   Examples of unexpected events include:

- A subject experiences extreme anxiety while taking part in a research study when protocol-related documents did not identify extreme anxiety as a risk of the study, and the subject does not have an underlying anxiety condition or predisposing risk factors to experience extreme anxiety. Note: If the PI doesn't know if the subject has a related

underlying condition or risk factor, they could ask the subject a general question such as, "Do you have an underlying condition or risk factor that may predispose you to have this reaction?"

- A subject without any underlying liver disease experiences liver failure due to diffuse hepatic necrosis when the protocol-related documents and other relevant sources of information only referred to elevated hepatic enzymes or hepatitis as potential risks related to the study procedures.

  In OHRP's experience, the vast majority of adverse events occurring in the context of research are *expected* in light of (1) the known and communicated risks of the research procedures; (2) the expected natural progression of subjects' underlying diseases, disorders, and conditions; and (3) subjects' predisposing risk factor profiles for the adverse events.

  Example of an event that is NOT unexpected includes:

  - The participant was informed on the consent document that they would be exposed to psychologically concerning content that could cause emotional distress, and they experienced some emotional distress during the study.

2. Is the incident related or possibly related to participation in the research?

If the incident is caused by the procedures involved in the research, it meets this criterion. If it is caused by an underlying disease, disorder, or condition, or circumstances unrelated to the research, it does not meet this criterion. However, it can be difficult to determine for certain what caused the incident, necessitating the use of probability judgments that fall along a continuum between definitely *related* to and definitely *unrelated* to participation in the research. OHRP considers *possibly related* to participation in the research to be an important threshold for determining whether a particular event represents an unanticipated problem. *Possibly related* means there is a reasonable possibility that the incident may have been caused by the procedures involved in the research

Examples of incidents that are (possibly) related to participation in the research include:

- Subjects with cancer participating in oncology clinical trials testing chemotherapy drugs experience neutropenia and anemia, which are common side effects of these drugs.

Examples of incidents that are NOT related to participation in the research include:

- For subjects with cancer enrolled in a non-interventional, observational research study designed to collect longitudinal morbidity and mortality outcome data on the

subjects, the death of a subject from progression of the cancer would be an adverse event that is related to the subject's underlying disease.
- A participant was injured in a car accident on the way to participate in your research project.

3. **Does the incident suggest that the research places subjects or others (e.g., subjects' family or friends, lab technicians, researchers) at a greater risk of harm than was previously known or recognized?**

   Risk of harm can include physical, psychological, economic, or social harm, and both serious and non-serious outcomes could increase the risk of harm. If the incident or outcome is serious, it always places the subject or others at greater risk of harm. **Serious outcomes** include those that:

   - result in death, hospitalization, or persistent or significant disability/incapacity
   - are life-threatening, **or**
   - jeopardize physical/psychological health and may require intervention (e.g., allergic reaction treated in the ER, convulsions, development of drug dependency)

   Non-serious outcomes could also place subjects or others at greater risk of harm than was previously known, such as incidents that result in:

   - temporary or moderate physical impairment (e.g., twisted ankle)
   - moderate emotional distress
   - breeches of confidentiality of sensitive information which could result in the possibility for criminal or civil liability or damage to financial standing, employability, educational advancement, or reputation

Any incident, experience, or outcome that meets the three criteria for an Unanticipated Problem described above must be reported to the IRB. If a PI is unsure whether the three criteria are met, they should report the incident anyway so the IRB can help make that determination and inform them of needed follow-up steps. Examples of incidents categorized as unanticipated problems and not unanticipated problems are provided in Appendix B of this document.

Reporting Unanticipated Problems to the IRB

Once a PI suspects or has determined that an unanticipated problem has occurred in their research, they should report it to the IRB promptly: within 7 days for serious unanticipated problems and 14 days for non-serious. The PI should complete the unanticipated problems section of Attachment C and email it to the IRB office (irb@uwlax.edu). Reports will be forwarded to the IRB Coordinator and/or the Research Integrity Officer (RIO) for evaluation in collaboration with ORSP. If the IRB determines an Unanticipated Problem has occurred, there may be additional reporting requirements (e.g., OHRP, FDA, sponsor(s)).

Any person other than the PI who witnesses or suspects an unanticipated problem has occurred in a research study, should bring this information to the PI.

Note: Unanticipated Problems occurring in research do not in and of themselves constitute IRB noncompliance or scientific misconduct. The purpose of reporting is to monitor the safety of the research protocol and make adjustments as needed when new information comes to light. However, if a PI fails to report an unanticipated problem in a timely manner to the IRB, or if an unanticipated problem is caused by a failure to follow IRB approved research protocols, these actions may represent noncompliance with IRB policy and may be subject to the IRB Noncompliance and Scientific Misconduct policies and procedures.

IRB Review Process & Timeline

When a suspected Unanticipated Problem is reported to the IRB, the report will be reviewed according to the following process and timeline:

1. The IRB Coordinator will evaluate the Unanticipated Problem information reported by the PI. If needed, the Coordinator will reach out to the PI, other investigator(s), and faculty mentor(s) when applicable to gather additional supporting information about the incident. If needed, the IRB Coordinator will consult with the IRB Chair, Research Integrity Officer (RIO), other IRB members, or other subject matter experts for technical/scientific information needed to evaluate the reported incident.
    - The IRB Coordinator will determine whether the incident meets the criteria for an Unanticipated Problem and what the associated reporting requirements are (if applicable).
2. The IRB Coordinator will notify the PI the following:
    - Determination of whether the incident meets the criteria as an Unanticipated Problem
    - Associated reporting obligations, deadlines, and who is responsible for completing the reporting
    - Any corrective actions or other required modifications to mitigate further risks during continued research (see the Corrective Actions section below)
3. In the event there are associated reporting requirements, the PI and IRB will submit the required reports according to the timelines required by the agency/sponsor. The PI will CC IRB on any report they submit and email a full copy of the submitted information for the IRB records.
4. In the event the PI discovers additional information/evidence that may change the Unanticipated Problem determination or planned corrective actions, the PI should notify the IRB, and the Coordinator will reassess and update the PI and other entities.

Corrective Actions

OHRP notes that Unanticipated Problems "generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- Changes to the research protocol [...] to eliminate apparent immediate hazards to subjects;
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring subjects;
- Suspension of enrollment of new subjects;
- Suspension of research procedures in currently enrolled subjects;
- Modification of informed consent documents to include a description of newly recognized risks; and
- Provision of additional information about newly recognized risks to previously enrolled subjects."

The IRB may require corrective actions, such as those listed above, even without an Unanticipated Problem finding. However, corrective action plans are required to be submitted to the OHRP when an Unanticipated Problem determination has been made. FDA and/or sponsor reporting requirements may apply if required by project terms and conditions or applicable regulations.

There may also be additional Corrective Actions required by OHRP, the FDA, and/or the sponsor(s), as applicable.

Completion of Corrective Actions

Upon completion of mandated corrective actions, PIs must submit an Attachment C describing the required changes made to the research protocol and documents to irb@uwlax.edu. It will be forwarded to the IRB Coordinator and RIO for review and approval. Additional information or documentation may be requested of the investigator to confirm completion. Confirmation of final approval will be sent to the PI. Documentation will be maintained in ORSP records.

Reporting Unanticipated Problems to External Entities

Reporting Unanticipated Problems to OHRP

Unanticipated Problems are required to be reported to the Office of Human Research Protections (OHRP) (45 CFR 46.108(a)(4)(i)) if:

- It is nonexempt research (e.g., expedited, full committee reviewed) supported by US Human Health Services (HHS) or is covered by a Federalwide Assurance (FWA) (i.e., the research is conducted or supported by a US federal department or agency, unless the research is otherwise exempt from the Common Rule)

Reports should be submitted electronically and promptly by the Research Integrity Officer (RIO) according to 45 CFR 46.108(a)(4) and 45 CFR 46.113, and to any project sponsors as applicable. The criteria for reporting to OHRP includes:

- **Initial reports** may be submitted to fulfill the 'prompt' reporting requirement within one month, but subsequent reports should be submitted when new information is available, or

as the institution's evaluation of the incident progresses and a corrective plan is implemented (as applicable).

- **OHRP deliberates** and then determines if any additional interventions to mitigate risks to subjects should be included. If reports are deemed to provide insufficient information, OHRP will contact the institution for further follow-up.

Additional FDA Reporting Requirements

The US Food & Drug Administration (FDA) has different reporting requirements than OHRP.

Investigational New Drugs: For research pertaining to Investigational New Drugs (INDs), the following must be reported to the FDA(21 CFR 312.32):

1. Serious and unexpected suspected adverse reactions or an increased rate of occurrence of serious suspected adverse reactions.
    a. Serious means the reaction was fatal or life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, caused a persistent or substantial disruption of the ability to conduct normal life functions, or jeopardized the subject's health and may require medical or surgical intervention.
    b. Unexpected means not listed in investigator(s)' brochure/consent forms, not listed in general investigational plan, or not listed at the specificity or severity that has been observed.
    c. Suspected adverse reaction means there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
        i. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;
        ii. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug; or
        iii. An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a control group.
2. Any findings from epidemiological studies, pooled analysis of multiple studies, clinical studies, or animal or in vitro testing that suggest a significant risk in humans exposed to the drug.

Reports MUST be completed by the IND application sponsor. FDA regulations (21 CFR 312.3(b)) define the IND application sponsor as the individual or institution "who takes responsibility for and initiates a clinical investigation." For research projects where UWL is the IRB of record, the IRB will determine whether the IND application sponsor is UWL, the PI, or another entity and communicate reporting responsibilities accordingly. Reports can be submitted electronically to the appropriate review division, as determined. If the IND application sponsor is not the PI, it is the PI's responsibility to inform the IND application sponsor of all serious, unexpected suspected adverse reactions and findings from studies suggesting a significant risk to humans exposed to the drug.

The IND application sponsor reports must be submitted via:

- Form 3500A (if from clinical trials) or in narrative format (if from animal or epidemiological studies); and
- Form 1571

All **initial reporting** should be submitted *usually no later than 15 calendar days following the IND application sponsor's initial reception of the information.

*Unexpected fatal or life-threatening suspected adverse events must be reported to the FDA no later than 7 calendar days following the IND application sponsor's initial reception of the information.

Follow-up reporting should be submitted without delay, as soon as the information is available, but no later than 15 calendar days after the IND application sponsor receives the information.

Investigational Device Exemptions: For research pertaining to Investigational Device Exemptions (IDEs), there are separate reporting requirements for unanticipated adverse device effects that are described in FDA regulations (21 CFR 812.46).

Reporting to Research Sponsors

If research is funded by an extramural sponsor, the sponsor may have additional reporting requirements. Refer to the sponsor's regulations and award terms and conditions for detailed requirements. The PI is responsible for ensuring sponsor reporting requirements are fulfilled and must email a copy of all sponsor reports to IRB (irb@uwlax.edu) and the Office of Research & Sponsored Programs (grants@uwlax.edu) to ensure complete records.

References

Code of Federal Regulations: 21 CFR 312.3: Definitions & Interpretations. (2008). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-A/section-312.3

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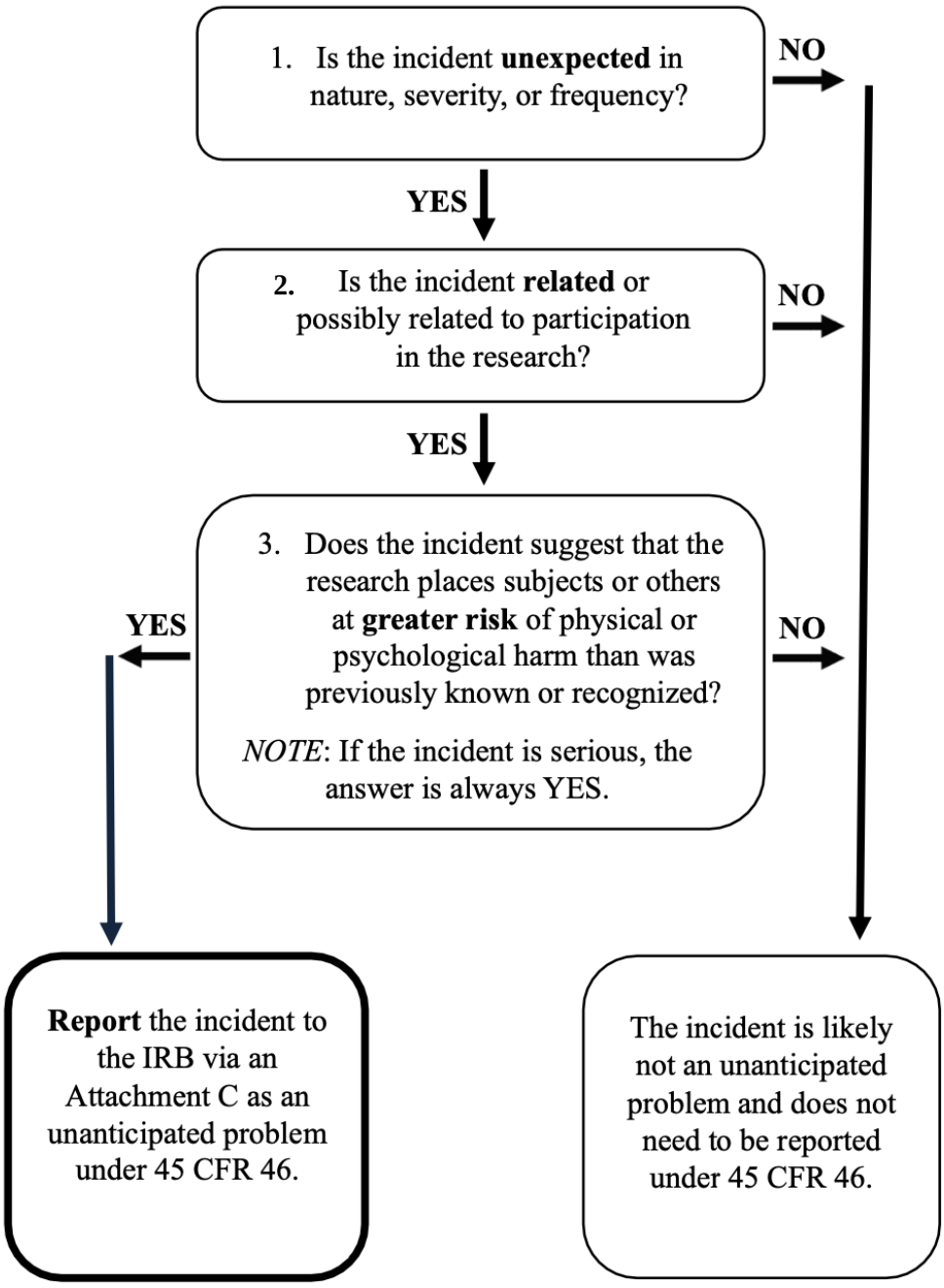
Reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events: OHRP guidance. (2007). US Department of Health & Human Services (HHS), Office of Human Research Protections (OHRP). https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

Appendix A: Identifying Unanticipated Problems



Flowchart to determine if an incident is also an unanticipated problem AND if it is reportable under 45 CFR 46. Adapted from flowchart created by HHS. If you are unsure if the incident meets any of these criteria, please submit an Attachment C.

Appendix B: Examples of Unanticipated Problems

Examples of Unanticipated Problems

1. An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work.
    - This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.
2. A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia. Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent.
    - This is an example of an unanticipated problem that must be reported because the hematologic toxicity was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) serious.

Examples that Are Not Unanticipated Problems

1. An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research.
    - This example is not an unanticipated problem because the occurrence of the claustrophobic reactions – in terms of nature, severity, and frequency – was expected.
2. A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject's initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, presumed related to the underlying renal cell carcinoma. The investigator concludes that the subject's death is unrelated to participation in the research.
    - This example is not an unanticipated problem because the subject's pulmonary embolus and death were attributed to causes other than the research interventions.

Additional examples of incidents that would represent and not represent unanticipated problems are available in Appendix B, C, and D of this HHS document.