

Unanticipated Problems Involving Risks to Subjects or Others

Also see the University of Michigan Human Research Protection Program [Operations Manual, Part 12](#)

It is a federal and university requirement that investigators of all human subjects research (whether FDA-regulated or not) report to the IRB any 'unanticipated problems involving risks to the subjects or others' (hereafter referred to as 'unanticipated problems'). The following guidance is intended to assist investigators in determining if an occurrence or other information constitutes an 'unanticipated problem' in the regulatory sense. If you need further assistance evaluating whether or not an issue constitutes an unanticipated problem, please call or email the IRB Office.

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The Three Criteria to Identify an Unanticipated Problem

For an event or information to be considered an 'unanticipated problem' three criteria must be met:

1. It must be 'unanticipated.' This means it is **not** expected in terms of its nature, severity or frequency given the:

- Procedures described in the study documents (e.g. the application, protocol, data and safety monitoring plan)
- Characteristics of the subject population being studied (the traits, behaviors, symptoms, diseases, life experiences, or other qualities typically found in the persons comprising those eligible to participate in the study)

An unanticipated problem is a problem that was expected by neither the research participants nor the investigators.

2. It must be 'related' to the research. This means there is a reasonable possibility that the event or information may have been caused by or is linked in a significant way to the research. This encompasses all aspects of the research—it is not limited to test agents or procedures. It is not necessarily limited to actions of the UM investigators (for example, labeling changes in an FDA product or an article about animal research, see additional examples below).

3. The event or information suggests that the research places subjects or others at **greater risk of harm** than was previously known or recognized. This includes physical, psychological, economic, or social harm.

The Two Types of Unanticipated Problems

An unanticipated problem may be either one of two types:

- **Type 1:** Potential harm
- **Type 2 :** Actual harm

A potential harm, a type 1 ‘unanticipated problem’, is an issue that must be reported to the IRB whenever something comes to an investigator's attention regarding the research which indicates the **possibility** that previously unsuspected harm may occur (or may occur at a higher than expected rate) even though no one has yet experienced actual harm. It is an event, development, or information that potentially increases the likelihood of harm occurring in the future. For example, a concurrent study in animals might show that the new drug being used in a UM study causes cancer in a fashion that seems to be relevant to people. This indicates a previously unrecognized risk—that the research participants will have an increased cancer risk, even if none have actually developed cancer. This type of unanticipated problem is usually reported using the IRB form for *Other Reportable Information or Occurrences (ORIO)*.

A type 2 ‘unanticipated problem’ is a recognized harmful or unfavorable outcome that has actually occurred to a research subject, a set of subjects, another individual being treated in a similar fashion in a relevant non-research setting, or another person connected to the research study (e.g. one of the researchers or the spouse of a subject).

This type of unanticipated problem is an actual event(s), not a potential risk. These kinds of unanticipated problems are *also* adverse events (AEs). A series of AEs that signal the AEs were not just isolated occurrences and were significant to subjects' rights and welfare would be considered an unanticipated problem. An expected AE that occurs at a greater frequency or severity than expected would be an unanticipated problem. ‘Type 2’ unanticipated problems should be reported to the IRB using the adverse event reporting form.

Because of their unanticipated and related nature, and because of the potential risks they suggest, these AEs require a special level of attention from investigators, IRBs, institutional officials, and others. (*Not all adverse events are ‘unanticipated problems’ because most adverse events are ‘expected’ as it is defined above. For details on how and when to report adverse events that are not unanticipated problems, refer to the IRB's adverse event reporting guidance.*)

‘Seriousness’ and Unanticipated Problems

An unanticipated problem -- because it is associated with potential risks -- is a problem that must be reported even if it is not felt to be serious. Adverse events that are unexpected and related, but *not* serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of harm than had previously been known or recognized.

‘Others’ and Unanticipated Problems

Although the primary mission of an IRB is to protect the rights and welfare of research subjects, federal regulations require investigators to report, and IRBs to evaluate, any unanticipated problem that may pose risks to people who are not the actual research subjects. The 'others' are most often the researchers themselves or family members of the subjects, although they can be people not associated with the research in any way. If a research subject experienced an unexpected side effect like fainting, and fainted while driving a car, causing an accident in which a stranger was injured, this would be an unanticipated problem even if the subject was unharmed. If a laboratory reagent used in the research, but not actually administered to patients or research subjects, was found to be a potentially dangerous carcinogen, this would be an unanticipated problem posing a risk to others, namely the laboratory workers involved with the research or interacting with the research personnel in the same lab.

'External' versus 'UM' Unanticipated Problems

Investigators are required to report both internal and external unanticipated problems to the IRB.

A 'UM' unanticipated problem is one that occurs on a study that is under the direct oversight of a UM investigator or a UM IRB. The participants are UM subjects. The terms 'Internal' or 'Local' are sometimes used in referring to a 'UM' event. 'UM' includes things that happen to UM subjects anywhere, even if not on University of Michigan property. For example, a problem with a subject enrolled by a UM student conducting a study in Uganda that was approved by a UM IRB is considered a 'UM' event.

A problem that is *not* under the primary oversight of UM investigators or a UM IRB is referred to as an 'External' unanticipated problem. These are events or information about which the UM investigator received a report or read a publication rather than an event the investigator handled. Other terms used include 'Off-site' or 'at other sites.'

When an investigator receives a report of an external *unanticipated problem* it should be submitted to the IRB.

External Adverse Event Reports and Unanticipated Problems

UM investigators participating in multi-site trials and those using sponsored agents routinely receive a large volume of reports of external adverse events. The HHS Office of Human Research Protections (OHRP) has released guidance urging sponsors that individual adverse events should only be reported to investigators at all institutions when a determination has been made by the sponsor that the events meet the criteria for an unanticipated problem.

OHRP recommends that any distributed reports include: (1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and (2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

Nonetheless, investigators may continue to receive reports that have not been assessed by the sponsor. When a UM investigator receives a report of an adverse event that is unexpected and related to an agent or procedure used in the UM study, the UM investigator should review the report and assess whether it meets the criteria above for an unanticipated problem. If it does, then it should be reported to the IRB. Note that many reports labeled 'unexpected' will not meet the criteria above. It is possible

for an external adverse event report from a different study, or use of the agent or procedure in a different population or route of administration to constitute an unanticipated problem for a UM study. The UM investigator should assess whether or not the information in the report indicates a problem that affects the rights and welfare of UM subjects. If in the judgment of the UM investigator it does, then the report should be submitted.

If the report does not contain sufficient information for the UM investigator to make the needed assessment AND the source of the report (e.g. the sponsor) did not state the event is an “unanticipated problem” or an “unanticipated adverse device effect”, then a submission to the IRB is not required. Both FDA and the HHS Office of Human Research Protections have stated their expectation that an individual external adverse event will rarely meet these criteria for an unanticipated problem.

Additional Information for Investigational Device Studies

In addition to the general information above, studies involving FDA-regulated devices are required to follow the regulations at 21 CFR 812.

- The investigator must inform the sponsor of any *unanticipated adverse device effect* (UADE) during an study within 10 days.
- A ‘UADE’ is defined as any serious adverse effect on the health or safety of subjects, or any life-threatening problem or death caused by, or associated with, a device, if that problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan.
- A sponsor (the holder of the investigational device exemption (IDE)) must immediately conduct an evaluation of a UAD E and report to all investigators within 10 days.
- Investigators must send these reports to IRBs.

Examples of Unanticipated Problems

<i>Examples of Procedures that could cause or be linked to an unanticipated problem</i>	<i>Examples of Unanticipated Problems Involving Procedures</i>
<ul style="list-style-type: none"> • Surgery required as part of the research • Storage of research data on computers or in medical records • Disclosure of genetic tests results • Completion of a survey 	<p>Type 1—Potential Harm: Newly published studies involving the heart surgery procedure in monkeys and chimps show an increased risk of early heart failure.</p> <p>Type 2—Actual Harm: A subject is denied life-insurance coverage because of a genetic test conducted solely for the purposes of the research study.</p> <p>Type 2—Actual Harm: Completed surveys about illegal drug use by a company's employees are accidentally left behind by a researcher and turned in to employees' supervisors by the janitorial staff.</p>

<p><i>Examples of Non-Procedural events or information that could cause or be linked to an unanticipated problem</i></p>	<p><i>Examples of Unanticipated Problems Involving Non-Procedural Events or Information</i></p>
<ul style="list-style-type: none"> • FDA change in labeling • Article in a journal • Internet security breach 	<p>Type 1—Potential Harm: FDA adds additional risks to a drug that is being used on label as part of a study..</p> <p>Type 1 —Potential Harm: An article in JAMA indicates that women with diabetes have a previously unknown risk of developing heart disease when taking the drug used in a research study (where having diabetes is not an exclusion criteria for the study)</p> <p>Type 2—Actual Harm: Hackers break into an internet site used by subjects to report progress in weight management. Names and contact information are stolen and sold to companies that market illegal diet drugs through email.</p>
<p><i>Examples of Agents that could cause or be linked to an unanticipated problem</i></p>	<p><i>Examples of Unanticipated Problems Involving Agents</i></p>
<ul style="list-style-type: none"> • Investigational drug • Investigation device • Biologic • Herbs or vitamins 	<p>Type 1—Potential Harm: Newly published studies involving the investigational drug in mice show a significant correlation between the drug and ovarian cancer.</p> <p>Type 2—Actual Harm: A known side effect of an investigational drug occurs at a greater frequency or severity than expected.</p>
<p><i>Examples of Persons that could cause or be linked to an unanticipated problem</i></p>	<p><i>Examples of Unanticipated Problems Involving Persons in the Research</i></p>
<ul style="list-style-type: none"> • Subject/participant • Investigator • Lab personnel 	<p>Type 1—Potential Harm: It is discovered that the study coordinator forged case report forms and falsified the results of blood tests that had been conducted for subject safety.</p> <p>Type 2—Actual Harm: A research subject holds the research team and other subjects hostage at gunpoint when he learns he received the placebo drug.</p>

When and How To Report Unanticipated Problems and Unanticipated Adverse Device Effects (UADEs) to the IRB

Serious unanticipated problems and UADEs must be reported within 7 calendar days of the problem (or within 7 calendar days of the study team becoming aware of the problem). Non-serious unanticipated problems must be reported within 14 calendar days of the problem (or within 14 calendar days of the study team becoming aware of the problem).

If the unanticipated problem involved one or more persons experiencing actual harm , report the unanticipated problem as an adverse event. Refer to the [AE Reporting](#) page and follow the instructions provided, using the external or internal form as appropriate.

If a person did not experience actual harm but an unanticipated problem entailed **potential harm** , and/or risk of harm to subjects or others, refer to the [ORIO Reporting](#) page and follow the instructions provided.

If the IRB concurs that an event is an unanticipated problem the IRB will follow the policies and procedures outlined in the University of Michigan Human Research Protection Plan [Operations Manual, part 12](#).

References:

- HHS Office of Human Research Protections (OHRP)—regulations require IRBs “have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others , or any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.” 45 CFR 46.103(b)(5)
- HHS Food and Drug Administration—regulations require “written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others ; (2) any instance of serious or continuing non-compliance with these regulations or the requirements or de terminations of the IRB; or (3) any suspension or termination of IRB approval.” 21 CFR 56.108 (b)
- OHRP– [Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#)
- FDA — [Draft Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting—Improving Human Subject Protection](#).