

Federal guidance defines an *unanticipated problem involving risk to subjects or others* as any incident, experience, or outcome that meets all of the following three criteria:

- the problem is unexpected, in terms of nature, severity, or frequency, given the study procedures as described in application documents and the characteristics of study participants;
- the problem is related, or at least possibly related, to study participation;

*and*

- the problem suggests that the research places subjects or others at greater risk of physical, psychological, economic, or social harm than was previously known or recognized.

Some adverse events constitute unanticipated problems, though most do not. An adverse event—which may involve either physical or psychological harm—is any untoward or unfavorable medical occurrence in a human subject, including any sign, symptom, or disease, during the subject’s participation in the study. For an adverse event to constitute an unanticipated problem, it must be unexpected, must be either related or possibly related to the research, and must suggest that the study presents greater risk than previously recognized.

For example, suppose that subjects taking a certain investigational blood pressure drug develop gastroesophageal reflux disease—or GERD—symptoms that seem to be caused by the study drug. If the researcher hasn’t addressed GERD as a research risk, an IRB will classify these subjects’ experiences as both adverse events and unanticipated problems, since the onset of GERD symptoms was unexpected, was related to the research, and suggests an additional research risk.

Just as not all adverse events constitute unanticipated problems, not all unanticipated problems are adverse events. For example, some unanticipated problems indicate increased risk of harm, although no actual harm has occurred. Unanticipated problems may be economic or social in nature, whereas adverse events include only physical and psychological harms.

Suppose a researcher loses a laptop computer that contains individually identifiable information about study subjects’ illegal drug use. Because the occurrence was unexpected, was related to study participation, and increases social and psychological risk, an IRB should consider it an unanticipated problem. If, however, the occurrence results in no actual physical or psychological harm to subjects, it does not constitute an adverse event.

UM researchers should report any unanticipated problem in eResearch as an adverse event or ORIO. If the problem occurred in research under the direction of University faculty, staff, or students, we consider it *internal*, and a University of Michigan IRB will assess it to determine whether it meets all of the regulatory criteria for an unanticipated problem. If, on the other hand, the problem occurred at a

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non-UM site, we consider it *external*; although the UM researcher should submit an AE or ORIO to notify the IRB of an external problem report, the local principal investigator or the local IRB where the incident, experience, or outcome occurred is responsible for determining whether it meets the criteria for an unanticipated problem, unless the University of Michigan is the lead institution, in which case, once the external event has been reported here, the UM principal investigator and IRB will determine whether it constitutes an anticipated problem.

University of Michigan researchers must report serious unanticipated problems within seven days of their occurrence or of receipt of an external unanticipated problem report. Problems are considered serious if they result in or indicate increased risk of death, life-threatening circumstances, hospitalization or a prolonged hospital stay, significant or persistent disability or incapacity, or a congenital anomaly or birth defect, or if they may jeopardize a subject's health and require medical or surgical intervention in order to prevent one of these outcomes. Researchers must report non-serious unanticipated problems within 14 days. The study sponsor or the IRB that determines whether the problem meets the criteria for an unanticipated problem is also responsible for reporting it to the appropriate federal agency.

Contact the IRB for more information about unanticipated problems involving risk to subjects or others.

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