

# Reporting Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

## Introduction

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This policy outlines the Institutional Review Board (IRB) requirements for reporting adverse events and unanticipated problems that occur during the course of a research project. Unanticipated problems or adverse events can occur in any type of research (medical or social/behavioral/educational research). Some events are expected (e.g., lightheadedness during blood collection), while others are unexpected (theft of devices containing data). Events also vary in seriousness and the extent to which they are related to the research. Reporting serious adverse events and unanticipated problems facilitates protection of research participants by allowing investigators and the IRB to determine whether the event/problem indicates changes are necessary to minimize risk, ensure the risk/benefit ratio remains favorable, and ensure participants are fully informed.

## Definitions

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**Unanticipated problems involving risks to subjects or others:** Any incident, experience, or outcome that meets *all* of the following criteria:

- Is 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;
- Is related or possibly related to an individual's participation in the research; **and**
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, social, economic, legal, or informational harm) than was previously known.

**Related or possibly related to the research:** An event is considered related to the research if, in the opinion of the investigator, it was more likely than not the result of the research interventions/interactions, or the result of the collection/use of identifiable private information for the research (i.e., there is a reasonable possibility that the event may have been caused by participation in the research).

**Adverse event:** Any untoward or unfavorable occurrence in a research participant that is temporally associated with the participant's involvement in the research. An adverse event encompasses physical, psychological, social, economic, legal, or informational harms. It may or may not be directly related to the individual's participation in the research.

**Serious adverse event:** Any adverse event temporally associated with the individual's participation in research that meets *any* of the following criteria:

- Results in death;
- Is life threatening (places the subject at immediate risk of death from the event as it occurs);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- Based upon appropriate medical judgment, may jeopardize the individual’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition;
- Results in a breach of confidentiality that is damaging to the participant’s rights, employment, financial standing or reputation; or
- Causes significant psychological, social, economic, or legal harm to the participant or others.

**Unexpected adverse event:** Any adverse event occurring in one or more participants when the nature, severity, or frequency is not consistent with either

- the known or foreseeable risk described in (a) the protocol-related documents (i.e., the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document) and (b) other relevant sources of information (e.g., product labeling and package inserts); or
- the expected natural progression of any underlying disease, disorder, or condition of the individual(s) experiencing the adverse event and the individual’s predisposing risk factor profile for the adverse event.

**Unanticipated adverse device effect (UADE):** For studies of medical devices, the investigational device exemption regulations define an unanticipated adverse device effect as *any serious effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects* (21 CFR 812.3(s)).

**Anticipated problem/adverse event:** Any foreseen or expected problem/event that was described in the IRB-approved research protocol, any applicable investigator brochure, and/or the current IRB-approved informed consent document.

## How to Report an Adverse Event or Unanticipated Problem

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Reporting forms are available in [IRBManager](#). On the main Study Information page for the relevant protocol, select “Start xForms” to create an Adverse Event/Unanticipated Problem form. Step-by-step instructions are available in the *Submitting Other Study-Specific Forms* section of the [Researcher’s Guide to IRBManager](#).

## Investigator Reporting Requirements and Timelines

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Investigators must promptly report to the IRB

1. any **serious adverse event** that is related or possibly related to the research; or
2. any event that meets the definition of an **unanticipated problem**.

In general, “prompt” reporting means **within one week** of an occurrence or **within one week of the principal investigator becoming aware of an occurrence**.

If applicable, reporting must also follow the requirements and timelines set forth in data safety and monitoring plans that are in place for the research.

## Immediate Risk of Serious Harm

If the problem poses an *immediate risk of serious harm to a participant or others, it must be reported immediately* to [IRB@iastate.edu](mailto:IRB@iastate.edu) or by phone (click here for a [list of staff phone numbers](#)).

## Federally Funded or Supported Research

Some federal agencies require investigators to report adverse events or unanticipated problems to the agency within specified timeframes—immediately in certain instances. Investigators should ensure they are familiar with these requirements. For additional information about agency-specific requirements, see links under Federal Regulations and Guidelines on the [IRB Policy and Guidance](#) webpage.

## Medical Devices and New Drugs

For research on medical devices, an unanticipated adverse device effect (UADE) must be reported to the IRB and the sponsor as follows:

- A report of a UADE must be submitted to the sponsor and the reviewing IRB as soon as possible but not later than **10 working days** after the investigator first learns of the event (21 CFR 812.150(a)(1)).
- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to the FDA, all reviewing IRBs, and participating investigators within **10 working days** after the sponsor first receives notice of the effect (21 CFR 812.46(b), 21 CFR 812.150 (b)(1)).

Investigators conducting clinical investigations of drug or biological products under an investigational new drug (IND) application or investigational medical devices under an FDA Investigational Device Exemption (IDE) must also report certain types of adverse events and unanticipated problems to the sponsor and/or FDA. Investigators are encouraged to carefully review the IRB's guidance [Research Involving FDA-Regulated Investigational Articles](#) and to consult with their sponsors to learn more about these requirements.

## Relationship between Adverse Events and Unanticipated Problems

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An unanticipated problem is by definition unexpected, whereas an adverse event may be either expected or unexpected. Unanticipated problems may or may not be adverse events. Adverse events relate to harm to participants; unanticipated problems may involve an increased risk of harm even if no actual harm occurred.

Examples of reportable *unanticipated problems* (which may or may not be adverse events) include, but are not limited to:

- A breach in confidentiality resulting from disclosure of confidential information or from lost or stolen confidential information that may involve risk to the subjects or others;
- Complaint of a participant or family member that indicates an unanticipated risk;
- Harm or risk of harm to research staff;
- Laboratory or medication errors that may involve potential risk to the individual or others;
- Disqualification or suspension of investigators;

- Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;
- Deviation from the IRB-approved protocol without prior IRB review to eliminate apparent immediate hazard to a research participant;
- Any deviation from the IRB-approved protocol that increases risk or affects the participants' rights, safety, or welfare; or
- Newly discovered information (publication in literature, a safety monitoring report, a revised investigator's brochure, interim results, or other finding) that indicates a change in the risk/benefit ratio of the research.

Any *adverse event* must be reported (whether or not it is serious) if it meets the definition of an unanticipated problem (i.e., unexpected, related to the research, suggests increased risk of harm to subjects or others). In general, the following types of adverse events are considered to be unanticipated problems that must be reported to the IRB:

- Single occurrence of a serious, unexpected event that is strongly associated with the research;
- Multiple occurrences of an adverse event that, based on *aggregate* analysis, is determined to be an unanticipated problem. There should be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups in the drug treatment arm versus a control).;
- An expected adverse event (that is described in the investigator's brochure, protocol, or informed consent documents) that occurs at a severity or rate/frequency that is inconsistent with prior observations.

## IRB Process for Handling Reported Problems

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1. Upon review of the report, the IRB Chair(s) or Director of the Office of Research Ethics (DORE) will (a) determine if the report includes the necessary information, (b) perform an initial evaluation, and (c) consult with appropriate individuals (e.g., physician consultant, other IRB members, etc.) if necessary.
2. If, in the judgment of the IRB Chair(s) or the DORE, participants or others may be at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the IRB Chair(s) or the DORE will require the principal investigator to suspend the study pending review by the convened IRB.
3. If participants or others are not at immediate risk, the report is scheduled for review at the next meeting of the convened IRB.
4. The convened IRB determines whether the incident constitutes an unanticipated problem involving risks to subjects or others, and specifies any corrective actions. Corrective actions may include, but are not limited to the following:
  - Acknowledgement/acceptance without further recommendation;
  - A request for further clarification or a corrective action plan from the investigator;
  - Changes in the protocol (e.g., additional tests or visits to detect similar events in a timely fashion; changes to the confidentiality measures employed in the study, changes to inclusion/exclusion criteria);
  - Changes to the informed consent document(s);
  - Notification to enrolled subjects and/or re-consenting when appropriate;

- A change in frequency of continuing review;
  - Further inquiry into other protocols utilizing particular dietary supplements, devices, or procedures in question;
  - Additional training for investigators and/or research staff;
  - Monitoring of the research procedures or informed consent process;
  - Referral to other organizational entities (e.g., University Counsel);
  - Suspension or termination of IRB approval for the study; and
  - Post-approval monitoring or other monitoring actions deemed appropriate by the IRB.
5. If the IRB acknowledges/accepts the report and deems that no further follow-up is required, ORE staff notify the PI of the review outcome.
  6. If the committee requests clarification(s), additional information or revisions to the approved protocol, ORE staff notify the PI of the need for additional information and/or changes.
  7. Adverse events or unanticipated problems that also involve deviations from the IRB-approved protocol are reviewed in accordance with the [\*IRB Review of Protocol Deviations and Noncompliance\*](#).
  8. If the IRB determines the problem/event to be an unanticipated problem involving risks to subjects or others, the DORE reports the IRB's determination to federal agencies or sponsors in accordance with federal regulations. The DORE also reports the IRB's determination to the Institutional Official.

## Resources

[Protection of Human Subjects, 45 CFR part 46](#)

[Protection of Human Subjects, 21 CFR part 50](#)

[Institutional Review Board, 21 CFR part 56](#)

[Investigational New Drug Application, 21 CFR part 312](#)

[Investigational Device Exemptions, 21 CFR part 812](#)

[Adverse Event Reporting to IRBs—Improving Human Subject Protection](#). Food and Drug Administration, January 2009

[International Conference on Harmonization E-6 Guidelines for Good Clinical Practice](#), 2016

[Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events Guidance](#). Office for Human Research Protections. January 15, 2007.

### Document History

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