Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

Introduction

Problems can arise in any research study. Certain types of problems associated with research—those that are unexpected or serious and harm or potentially harm research participants or others—must be reported to the IRB. This policy outlines the types of problems or incidents that must be reported, how to report them, and how the IRB reviews reported incidents. It applies to all human subjects research overseen by the Iowa State IRB.

Definitions

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

- is *unexpected* (in terms of nature, severity, or frequency) given (a) the research procedures described in the IRB-approved protocol-. and (b) the characteristics of the subject population being studied
- is *related* or *possibly related* to participation in the research
- 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 or recognized.

Related or possibly related to the research: An event is considered related or possibly related to the research if there is a reasonable possibility that the event may have been caused by the procedures involved in the research.

Adverse event: Any untoward or unfavorable medical occurrence in a research participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, that is temporally associated with the participant's involvement in the research. An adverse event encompasses both physical and psychological, 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

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 individuals(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.

Relationship Between Adverse Events and Unanticipated Problems

Adverse events may or may not constitute an unanticipated problem. An unanticipated problem is *unexpected* by definition, whereas an adverse event may be either expected or unexpected. Adverse events involve some kind of harm to participants; unanticipated problems may involve an increased risk of harm even if no actual harm occurred. An *adverse event* must be reported if is serious and related to the research, or 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).

"Others" and Unanticipated Problems

Although the primary focus of the IRB is protecting research participants, federal regulations require reporting and subsequent IRB evaluation of unanticipated problems that may pose risk to persons who are not research participants. The "others" are most likely to be researchers or participants' family members or acquaintances, but can be persons completely unassociated with the research. For example, if a research participant shared identifiable sensitive information about a third party during an interview and a confidentiality breach occurred, that third party would be at risk.

Reportable Events and Timelines

PIs must promptly report:

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

Examples of reportable events include but are not limited to

- a confidentiality breach (e.g., disclosure of confidential information, lost or stolen confidential information, etc.)
- a complaint from a participant or family member that indicates an unanticipated risk or that cannot be resolved by the research team
- threats to participants or others due to or possibly due to the research
- harm or risk of harm to others/third parties (e.g., study personnel, participants' family members, etc.) due to or possibly due to the research
- an unexpectedly unsafe research environment
- laboratory or medication errors that may involve potential risk to the participant or others
- disqualification or suspension of investigators
- deviation from the IRB-approved protocol without prior IRB review to eliminate apparent immediate hazard to a research participant
- deviation from the IRB-approved protocol that increases risk or adversely affects the participants' rights, safety, or welfare
- newly discovered information (from literature, a safety monitoring report, a revised investigator's brochure, interim results or other finding, etc.) that indicates a greater risk to subjects than expected or may adversely affect participants' safety or welfare
- loss of funding that adversely impacts participants (e.g., impedes safety-related procedures, reduces research personnel such that risk increases, etc.)
- single occurrence of a serious adverse event that is related to the research
- multiple occurrences of an adverse event that, based on *aggregate* analysis, constitutes 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.
- unanticipated adverse device effects

Reporting Timelines

Timing should reflect the urgency of the situation and need for quick interim action to prevent or rectify harm. In general, incidents should be reported ***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.

Serious events or problems

Serious adverse events that are related to the research should be reported within 24 hours of discovery.

If a problem poses an immediate risk of serious harm to a participant or others, it must be reported immediately to IRB@iastate.edu or by phone (click here for a list of staff phone numbers). Note: Investigators may implement a protocol change without prior IRB approval to eliminate a hazard to subjects or others.

Federally Funded or Supported Research

Some federal agencies require investigators to report adverse events or unanticipated problems to the agency within specified time frames—immediately in certain instances. PIs must familiarize themselves with the requirements of the agency funding their research. See links under Federal Regulations and Agency Requirements on the IRB Policies and Guidance webpage for additional information.

Medical Devices and Investigational 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.

How to Report

Serious adverse events or unanticipated problems are reported by the PI or Supervising Investigator through a form in OneAegis (IRBManager). See OneAegis How-To Guide for instructions. If the PI or Supervising Investigator is unavailable or otherwise cannot report the incident, another person familiar with the incident (usually a member of the research team) should contact the IRB office for guidance (IRB@iastate.edu; staff contact information).

Collaborative/cooperative Research

For collaborative/cooperative research, incidents should be reported to the reviewing IRB, regardless of where the incident occurred. If Iowa State is reviewing IRB, the Iowa State PI is responsible for coordinating reporting. If an external IRB is handling review, the incident must be reported to the external IRB in accordance with its policies and procedures.

Information Needed

The form requests

- incident details, such as the date, a narrative description of the incident, and steps taken by the research team
- the PI's assessment of and supporting rationale for whether
    - the incident is unexpected, serious, is related to the study, or suggests participants or others are at greater risk of harm than previously known
    - the informed consent or study protocol should be revised
    - whether enrolled participants should be informed

IRB Review Process

1. The IRB Chair, Vice-Chair, and Co-Chair (Chair(s)) are notified via email when a report is submitted in OneAegis. If a report is received outside of OneAegis (e.g., by email) and the incident appears serious, IRB staff share information with the Chair(s) via email.
2. Upon receipt of a report, the IRB Chair(s) assess the incident and determine whether any immediate actions are needed to mitigate risk. The DORE is informed if necessary. The IRB Chair(s) or the DORE may temporarily suspend the study if they determine that participants or others may be at imminent risk of harm and there is insufficient time to wait for review by the convened IRB. They may also request additional information from the PI or consult with appropriate individuals (e.g., physician consultant, other IRB members, etc.) if necessary.
3. If participants or others are not at imminent risk, the report placed on the agenda for review at the next meeting of the convened IRB. An emergency IRB meeting may be convened if deemed necessary by the IRB Chair(s) or DORE.
4. The convened IRB determines whether the incident constitutes an unanticipated problem involving risks to subjects or others and specifies any corrective actions necessary to rectify the situation, protect future participants, and ensure the research continues to satisfy regulatory criteria for approval. Corrective actions may include, but are not limited to
    - requiring a corrective action plan from the PI
    - requiring protocol modifications (e.g., additional tests or visits to detect similar events in a timely fashion, changes to the confidentiality or privacy measures, changes to inclusion/exclusion criteria, etc.)
    - requiring changes to the informed consent document(s) or other study materials
    - notifying enrolled subjects and/or re-consenting when appropriate
    - increasing frequency of continuing review or status reports
    - assessing/investigating other protocols utilizing the same procedures or interventions
    - additional training for investigators and/or study personnel
    - monitoring the research procedures or informed consent process or directed post-approval monitoring

- referral to other organizational entities (e.g., General Counsel)
- suspending enrollment of new subjects
- suspending or terminating IRB approval

5. IRB staff notify the PI of the review outcome and any corrective actions or information needed. The Principal Investigator is responsible for providing information or completing corrective actions in a timely manner.

6. Adverse events or unanticipated problems that involve deviations from the IRB-approved protocol are reviewed in accordance with the *Policy on IRB Review of Noncompliance*.

Further Reporting

In accordance with federal regulations, the following will be reported by the IRB Co-Chair or DORE to applicable federal agencies (e.g., OHRP, FDA, study funder)

- incidents associated with non-exempt human subjects research deemed by the IRB to be an unanticipated problem involving risks to subjects or others, and
- any related suspension or termination of IRB approval.

The IRB Co-Chair or DORE also reports the IRB's determination to the Institutional Official.

Unanticipated problems associated with exempt research are not subject to these reporting requirements; however, the Institutional Official may be notified as needed.

Resources

Adverse Event Reporting to IRBs—Improving Human Subject Protection. Food and Drug Administration, January 2009

Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. Office for Human Research Protections. January 15, 2007.

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