THE UNIVERSITY OF IOWA

IRB Connection

HUMAN SUBJECTS OFFICE

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Reportable Events for Biomedical Research Edition

What are Reportable Events?

During the course of a research study, events or problems may occur that investigators neither expect nor anticipate. Investigators may not even be aware that certain events need to be reported to the IRB. *Reportable events* are not defined in the federal regulations, but the University of Iowa requires investigators to report incidents in which the regulations, IRB policies, and the IRB determinations related to the protection of human subjects were not followed, when unanticipated or unexpected problems occur, or when serious adverse events occur. In the conduct of biomedical research, there are five categories of reportable events at the UI that need to be reported to the IRB by the Principal Investigator (PI) via a Reportable Event Form (REF) in HawkIRB. PIs must report events that meet the UI IRB's criteria of a reportable event to the IRB within 10 working days of the incident or the PI becoming aware of the incident.

Alphabet Soup: Adverse Events (AEs), Safety Reports (SRs), and Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs)

Investigators and research team members often struggle with how to apply the criteria provided in each category and knowing whether or not to submit a REF for a specific situation. To assist investigators in their assessment of events that may qualify as reportable events, this special edition of the *IRB Connection* will provide additional information regarding the reporting criteria, as well as real examples of reportable events submitted by UI investigators that met the UI IRB's reporting criteria. Events that do not meet the IRB's reporting criteria can be summarized at the time of continuing review rather than reported in HawkIRB via a REF.

Reportable Event #1

A serious adverse drug event (either expected or unexpected) occurring in a subject enrolled by a UI investigator/research team member

UI IRB Reporting Criteria	What Does it Mean?	Examples
Serious adverse drug event (SAE) - any adverse drug experience associated with the use of the drug occurring at any dose that results in any of the following: • Death • A life-threatening adverse drug experience • Inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity • A congenital anomaly/birth defect • Important medical events that may not result in one of the above outcomes but may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above	The event must be related to the drug and NOT the subject's underlying condition or disease, or some other unrelated event (e.g. broken arm from a car accident not related to side effects from the study drug). The PI should consider the following questions in their assessment of the event: 1) Is the AE expected or unexpected? 2) Is it related or possibly related to the study or study drug? 3) Does it change the risk level to other subjects?	1) A subject enrolled in a clinical trial receiving a chemotherapy drug in a route of administration not approved by the FDA (investigational route of administration) developed a kidney infection. Risk of kidney infection was described in the protocol materials and Informed Consent Document (ICD). In this case, the IRB Chair reviewed the REF and agreed with the PI that this was an **expected serious adverse drug event**. As it was expected and already described in the ICD, subjects were not notified of the event.
Unexpected serious adverse drug event - any adverse drug experience associated with the use of the drug that was not disclosed, addressed, or noted and is not consistent with the current investigator's brochure or the risk information provided to the subjects and the IRB.	The PI was not expecting the SAE to occur. The risk was not described in the Informed Consent Document (ICD), the HawkIRB application or included in the protocol and/or Investigator's Brochure.	2) According to reports received by the FDA, 20 patients developed Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) while taking the anti-seizure drug Onfi (clobazam). While these events did not occur at the UI, the FDA issued a public warning and approved changes to the drug's labeling.
Expected adverse drug event - any adverse drug experience that is addressed and consistent with the current investigator's brochure or the risk information provided to subjects and the IRB.	The PI knew it was possible that the SAE could occur. The risk was described in the ICD, the HawkIRB application, or included in the protocol and/or Investigator's Brochure.	

Reportable Event #2

A serious adverse device effect (either anticipated or unanticipated) occurring in any subject enrolled either by the UI investigator/research team member OR enrolled by a non-UI investigator at another site

UI IRB Reporting Criteria	What Does it Mean?	Examples
Serious adverse device effect - any serious adverse 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 the frequency, specificity, or severity of which has not previously been identified in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.	Similar to assessing adverse drug events, PIs need to assess if the adverse device effect is related to the device and whether or not it is expected based on the protocol-related information and materials.	1) While a subject was being administered an investigational solution, the device with which the solution was delivered broke. As a result of the event, enrollment was halted while undergoing review by the Safety Monitoring Committee. Due to the level of risks to subjects, the REF was reviewed by the Full Board. The research team also notified the FDA of the event. The issue was resolved and enrollment restarted after a modification was submitted reporting that the device's construction had been modified to prevent the event from occurring in the future. 2) Components of a medical device implanted in a UI subject failed to work properly. This device failure led to its removal and another device to be implanted into the subject. As the risk of device failure was already described in the consent document, subjects were not notified of the event. The REF was reviewed by the Full Board, which determined that device failure in an investigational device study was to be anticipated. After the REF was reviewed, no further action was required by the IRB.

At the UI, expected and unexpected drug and device events (and houseguests) are reportable to the IRB

Reportable Events: Q & A

Question: Why do I need to submit reportable events to the IRB?

Answer: Institutions engaged in human subjects research supported by federal funding (like the UI) must have written procedures for ensuring prompt reporting to the IRB of the following:

- Unanticipated problems involving risks to subjects or others
- Any serious or continuing noncompliance
- Any suspension or termination of IRB approval

This reporting is required by the Department of Health and Human Services (45 CFR 46.103(a)(b)) and the Food and Drug Administration (21 CFR 56.108(b)).

Reportable Event #3

Receipt of new information (including risk or benefit) that may impact the willingness of subjects to participate or continue participation in the research study

UI IRB Reporting Criteria	What Does it Mean?	Examples
During the course of a study, researchers may become aware of new information, positive or negative, that would impact a subject's decision to participate, or continue participating in the study.	The information was not previously known to the investigator and is not described in the IRB-approved application or ICD. The information may affect the conduct of the study and may need to be communicated to research subjects.	1) Findings from an interim analysis supported the efficacy of a treatment relative to observation or an alternative treatment. The findings from the analysis were presented to the study's Data Safety Monitoring Board who recommended the study be stopped and all subjects notified that the data supports the efficacy of the study treatment. 2) The research team discovered an FDA warning letter was issued to the supplier of their study drug. The warning letter cited the supplier for various compliance issues and ordered the supplier to cease and desist the manufacturing and distribution of the drug. As a result, the research team reported in the REF that they would need to find a new supplier to obtain the study drug and continue enrollment.

Reportable Event #4

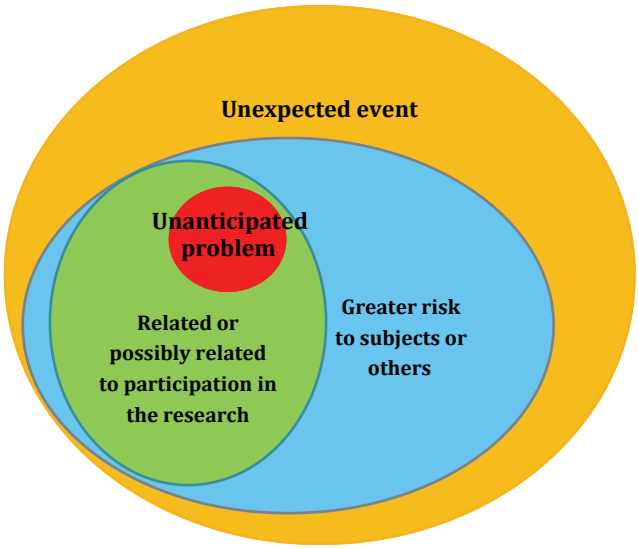
Unanticipated problem involving risks to subjects or others which occur at UI/VAMC or that impact subjects or the conduct of the study

UI IRB Reporting Criteria	What Does it Mean?	Examples
The problem is unexpected in terms of the nature, severity, or frequency given the research procedures described in the protocol-related documents, such as the IRB-approved application or the ICD.	The event is not consistent with the expected side effects, symptoms, or outcomes. "Expected" means what has been observed in past and included in the protocol-related documents. Effects are more severe, more serious, or occur more often than what has been observed in the past.	1) A nurse changed a subject's head dressing that covered her surgical wound. A catheter covered by the dressing was accidently cut in the process. The cut end of the catheter was tied in order to prevent fluid from leaking out. Because of the event, the research team was unable to collect research samples and a portion of the study was not conducted. As a result of the REF submission, the consent document was modified to reflect that the unanticipated event may occur. 2) A research team member's laptop containing subject data was stolen from his office. The data was stripped of identifiers, but a key to the code exists. If found by the individual in possession of the laptop, subject confidentiality could be breached. The REF was filed by the IRB Chair with no further required actions as the research team proposed a corrective action plan to encrypt all devices.
The problem suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.	The problem results in new circumstances that increase risk of harm to subjects. These events are unexpected in terms of the characteristics of the subject population being studied.	
The problem is related or possibly related to participation in the research.	There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.	

Reportable Events: Q & A

Question: How do I know when an unexpected event is an unanticipated problem that should be reported to the IRB?

Answer: When the event falls within <u>all</u> three circles, depicted in the red circle, in the illustration below



Remember to provide a corrective action plan in your REF submission. You should inform the IRB how the research team is going to prevent the event from occurring again in the future (whenever possible). Also consider if you need to submit a modification to update your Informed Consent Document(s).

Reportable Event #5

Noncompliance with federal regulations or the requirements or determinations of the IRB

UI IRB Reporting Criteria	What Does it Mean?	Examples
Failure to follow the federal regulations (45 CFR 46; 21 CFR 50) with respect to the protection of human subjects in research or failure to follow the determinations of the IRB with respect to conduct of the research as approved by the IRB. For studies conducted using Veterans Affairs Health Care System (VAHCS) resources, this includes failure to follow the requirements of the VHA Handbook 1200.5.	The PI or members of the research team conduct human subjects research without IRB review or continuing review of the research. Noncompliance can also involve (but is not limited to): 1) Failure to appropriately carry out study procedures as described in the HawkIRB application as approved by the IRB 2) Adding procedures or eliminating procedures designed to monitor subject safety 3) Failure to appropriately document the informed consent process	1) The subject signed an expired Informed Consent Document (ICD). A modification was recently approved by the IRB that changed the content of the ICD. A subject signed an older version of the IRB-approved ICD that did not include the content changes after the modification was approved and released. The REF was filed by the IRB Chair with no required actions as the research team proposed a corrective action plan to contact the subject and obtain consent using the correct ICD. 2) An investigator had IRB approval to review 250 medical records in Epic as part of an IRB-approved retrospective data review. At the time of the continuing review for the study, the PI reported reviewing 300 records. The REF was filed by the IRB Chair with no required actions as the event did not rise to the level of serious or continuing noncompliance. 3) Subjects completed study procedures before signing the ICD. The research team proposed a corrective action plan to verify subjects are consented before beginning study procedures. 4) A group of enrolled subjects were contacted for follow-up interviews for the incorrect protocol. The REF was filed by IRB Chair with no required actions as the research team proposed a corrective action plan to implement changes to data collection and follow-up procedures to prevent future events.
Continuing noncompliance - Noncompliance that occurs repeatedly to the point of suggesting a pattern or an underlying problem. Continuing noncompliance may occur due to a lack of knowledge (unintentional) or due to deliberate choice to ignore regulations or determinations of the IRB (intentional).	The IRB chair will determine if the reported noncompliance is potentially serious or continuing noncompliance. If so, the REF may then may be scheduled to a Full Board IRB meeting for review which can result in further reporting to federal regulatory agencies by the IRB. The following instance(s) of noncompliance, as defined by the Office of Human Research Protections (OHRP), will always be determined as serious noncompliance: • Non-exempt human subjects research being carried out without IRB review and approval or without appropriate informed consent • Substantive modifications to IRB-approved research without IRB approval	
Serious noncompliance - Noncompliance that materially increases risks or that results in unexpected substantial harm to subjects or others.		

Reportable Events: Fast Fact

Reportable events happen...

In 2012, 259 REFs were submitted to IRB-01/03

Some Reportable Events are Preventable

The most common REFs fall under the noncompliance category and report the over-enrollment of subjects. You can prevent this by remembering to submit a modification to the HawkIRB application to increase the enrollment number BEFORE enrolling additional subjects or reviewing additional medical records.

Human Subjects Office

Office of the Vice President for Research and Economic Development
105 Hardin Library for the Health Sciences
600 Newton Rd.
Iowa City, IA 52242-1098

Phone: (319) 335-6564
Fax: (319) 335-7310
E-mail: irb@uiowa.edu

hso.research.uiowa.edu

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Content edited by Cena Jones-Bitterman