

SUBJECT: Reporting Serious Adverse Events and Unanticipated Problems	Effective Date: March 30, 2018	Policy Number: 10.3.5 Version 3
		Renewal Date: October 20, 2017
	Supersedes: October 20, 2014 October 21, 2011	Page 1 of 7
	Responsible Authorities: Vice President, Research Institutional Review Board Assistant Vice President Director, Research Integrity	

I. Background

Federal regulations require researchers to promptly report to the IRB all serious adverse events (SAEs) and unanticipated problems (UPs) involving risk to human subjects or others that occur during an IRB-approved research protocol. In addition, researchers may need to report these events to the study sponsor, institutional officials, and the appropriate regulatory agencies, when applicable.

II. Purpose

This policy provides researchers with guidance on reporting serious adverse events or unanticipated problems involving risk to human subjects or others during an IRB-approved research protocol.

III. General Statement

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although they can and do occur in social-behavioral research. Many adverse events are expected based on previous studies in the literature, and are outlined in the informed consent document. These do not need to be reported to the IRB. However, if an adverse event is serious; unexpected in nature, severity, and frequency; related to the research, and a potential risk to human subjects or others, it meets the definition of a “serious adverse event.” Serious adverse events require a closer level of scrutiny and must be reported to the IRB.

Similarly, “unanticipated problems” that are not physical or medical in nature can also arise in the context of a research study. For example, a breach of confidentiality or an error in how human subjects data has been analyzed, are both unanticipated problems that do not

show up as a physical or psychological symptom in the subject. However, if they are unexpected, and can potentially pose a risk to the human subjects involved, or others, they must be reported to the IRB.

Both serious adverse events and unanticipated problems, whether they occur in a clinical trial, social/behavioral research study, or other human subjects study, may signal that risks to subjects are greater than expected. They may also trigger modifications to the research protocol, informed consent, or other information presented to the research subjects. In some cases, they may even require that a study be suspended or terminated. In order to make appropriate decisions concerning the protection of human subjects in research, the IRB requires these events to be reported appropriately. The principal investigator (PI) of any research study under the jurisdiction of the FAU IRB is responsible for reporting these events.

IV. Definitions (adapted from <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>)

Adverse Event: any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory findings), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subjects' participation in research.

Adverse events may be caused by one or more of the following:

1. the procedures involved in the research;
2. an underlying disease, disorder, or condition of the subject; or
3. other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered **related** to participation in the research, whereas adverse events determined to be solely caused by (2) or (3) would be considered **unrelated** to participation in the research.

Serious Adverse Event (SAE): Any adverse event occurring during the time period of a subject's participation in research that meets **any** of the following criteria:

- Results in death during the period of protocol defined surveillance.
- Is life threatening (defined as a subject at immediate risk of death at the time of the event).
- Requires inpatient hospitalization or prolonged hospitalization during the period of protocol-defined surveillance.
- Results in a congenital anomaly or birth defect.
- Results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a Serious Adverse Event based upon appropriate medical / psychological judgment, if the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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This definition includes *serious adverse drug or biologic experiences* and *unanticipated adverse device experiences* under FDA regulations.

Unanticipated Problem (UP) involving risks to subjects or others includes any incident, experience, or outcome that involves risks to subjects or others and meets the following criteria:

- **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 documents; and (b) the characteristics of the subject population being studied; and
- **Related or possibly related** to participation in the research (possibly related means there is some likelihood in the judgment of the investigator that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- 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**.

Unanticipated problems may be physical, psychological, economic or social.

Examples include:

- Adverse emotional reactions to study procedures, such as depression or threat of harm to self or others.
- Major complaints by subjects about the safety or ethics of research procedures.
- Breaches of confidentiality, such as the loss of a computer containing confidential information about human subjects or others.
- A finding that lab reports on blood or other samples were in error.
- A participant in a focus group on employment practices reports he has been demoted or unfavorably treated after the research study.
- Unexpected data collection on a subject for which no informed consent exists.

V. Policy

All Studies

- Serious adverse events and unanticipated problems that occur within a study that the FAU IRB has approved must be reported to FAU's IRB within the defined timeframes below.
- Not all adverse events should be reported to the IRB. They should only be reported if they meet the definition of Serious Adverse Event or Unanticipated Problem (see section IV. Definitions).
- A Serious Adverse Event or Unanticipated Problem is reportable if it occurs between the time that a subject is participating on a protocol and for 30 days following the active intervention phase of the protocol. If the event occurs more than 30 days after the active intervention has stopped, a report may be necessary if there are more stringent reporting requirements outlined in the protocol or mandated by the sponsor.

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Clinical Trials*

- The development of cancer or the identification of a congenital anomaly/birth defect in the offspring of a subject who received a study drug is always reportable, even if the event occurs more than 30 days after the end of the active intervention phase. The closing of a study does not terminate the PI's obligation to report this serious adverse event.
- All serious adverse events and unanticipated problems that occur during the performance of an investigator-initiated clinical trial (i.e., a study that originated with an FAU investigator) must be reported to the IRB and to the FDA if an IND (Investigational New Drug) or IDE (Investigational Device Exemption) has been obtained.
- If an FAU PI coordinates a multi-site clinical trial, he/she should first send any report of a serious adverse event or unanticipated problem to the Data Safety Monitoring Board (DSMB), unless otherwise stated in the IRB-approved protocol. The DSMB (or an equivalent safety monitoring committee) for an IRB-approved research protocol plays a significant part in the reporting of adverse events and unanticipated problems. Because of the volume of adverse events-- ranging from serious to relatively minor in nature--the DSMB is responsible for reviewing these events, determining their significance, and recommending changes to be made to the approved research protocol and/or consent documents. If the DSMB receives a report(s) of an adverse event or unanticipated problem that represents serious and/or unexpected events, the DSMB should send a report to the PIs and study sponsor in a prompt manner. It is the responsibility of the PI to review the report and submit a Serious Adverse Event/Unanticipated Problem report to the IRB within the appropriate timeframes listed in this policy. If there is no DSMB or equivalent monitoring committee for an IRB-approved research protocol, the PI must review the event and determine whether it represents a serious and/or unexpected event that should be reported to the IRB under this policy.

VI. Accountability

The Principal Investigator (PI) will be responsible for:

- Taking any necessary steps, as appropriate, to ensure subjects receive care or follow-up due to a Serious Adverse Event or Unanticipated Problem.
- Making immediate changes, when appropriate, at the time of testing, sampling, evaluating, etc. to eliminate apparent or immediate hazards to other subjects as a result of a Serious Adverse Event or Unanticipated Problem, even if the IRB has not yet approved the procedure.
- Analyzing the risk profile of the protocol as a result of a Serious Adverse Event or Unanticipated Problem to assess whether it should be reported to the IRB; Reporting the event to the IRB if it increases the risk of harm to subjects or others.
- Reporting to the IRB other unexpected adverse events, regardless of severity, that may alter the risk versus potential benefits of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent

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process/documents **[NOTE: Serious adverse events that are expected in some subjects but are determined to be occurring at a significantly higher frequency or severity than expected should be reported under this policy].**

- Reporting unanticipated problems to appropriate institutional officials (e.g. Division of Research) as soon as they become aware of them so that the Division can apprise supporting/funding agencies, and OHRP and FDA, as applicable, within the timelines outlined in the Code of Federal Regulations.

The IRB will be responsible for:

- Reviewing all SAE/UP reports in a timely manner and determining whether the event constitutes an unanticipated problem involving risks to subjects or others.
- Implementing immediate action, where warranted, including suspension of IRB approval to ensure the ongoing safety of research participants.
- Reviewing unanticipated problems or adverse events that do not require immediate action via an expedited review mechanism, where warranted, and deferring review to the convened IRB when deemed appropriate. Expedited review shall be limited to problems or events where only none or minimal risk changes in the study protocol or informed consent documents are required.
- Asking investigators, Data Safety Monitoring Boards or others for additional clarifying information regarding an SAE/UP, as warranted.
- Requiring the PI to implement remedial actions, as deemed appropriate, in response to an SAE/UP including:
 - a) Modifying the inclusion or exclusion criteria to mitigate the newly identified risks;
 - b) Implementing additional monitoring procedures of subjects;
 - c) Modifying informed consent documents to include a description of newly recognized risks;
 - d) Revising the protocol;
 - e) Providing additional information about newly recognized risks to previously enrolled subjects;
 - f) Suspending enrollment of new subjects;
 - g) Suspending approval of the research; or
 - h) Terminating approval of the study (via a convened IRB meeting).

The Research Integrity office will be responsible for:

- Promptly forwarding SAE/UP reports to the IRB Chair or designee.
- Communicating to the PI in writing the IRB's actions/decisions regarding an SAE/UP that he/she reports to the Board.
- Documenting the IRB protocol file appropriately.

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- Promptly communicating in writing to appropriate institutional officials, funding agencies, and regulatory agencies, the details of: a) any unanticipated problems involving risks to subjects or others; b) any serious or continuing noncompliance with 45 CFR 46, 21 CFR 56, or the requirements or determinations of the IRB; and c) any suspension or termination of IRB approval, within one month.

VII. Procedures

The PI must submit within 3 calendar days of becoming aware of the event:

- Written report of any *death or a life-threatening experience* occurring to a subject enrolled in a study approved by the FAU IRB. (Note: event must be related or possibly related to the protocol intervention; if the PI is uncertain, report it within the IRB requested timeframe until further conclusive evidence becomes available.)

The PI must submit within 1 week of becoming aware of the event:

- Written report of any other SAE or UP occurring within a study approved by the FAU IRB and occurring at an FAU site.
- Written report of an SAE or UP occurring at an **external site** of a multicenter trial approved by the FAU IRB. (*Only if the event changes the risk profile of the study and the resulting protocol or consent form*)

The PI must submit within 1 week of notification from an external sponsor:

- Changes to study materials including the protocol, consent document, or any study related materials as a result of an SAE/UP. (Use the IRB amendment form for this report.)
- Safety alert reports, data safety monitoring reports, protocol violations/ deviations, or audit reports.

** Unless specifically noted, use the IRB's Serious Adverse Event/Unanticipated Problem reporting form for these reports. If a report is submitted by the PI beyond the timelines outlined by this policy, a written explanation of the delay must accompany the adverse event form.

DO NOT SUBMIT to the IRB:

- Reports of emergency room (ER) visits *unrelated* to protocol intervention
- Reports of discontinuations from a study for medical reasons *unrelated* to a protocol intervention.
- "For Information" only reports of AEs or UPs not related to a specific FAU protocol. These reports typically occur for multi-site studies that involve the same investigational agent (e.g. drug/device/biologic) as that in an FAU study, but occur in different protocols from those that are being conducted at FAU under the oversight of the FAU IRB. ***Unless they warrant a change in the FAU protocol and/or consent document, do not submit them to the IRB for review.***

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VIII. Policy Renewal Date

As needed

IX. References

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

45 CFR §46.103 (b)(5)(i)

21 CFR 312.32, 312.66

21 CFR 56.108 (b)(1), 812.150

POLICY APPROVAL

Initiating Authority

Signature: 

Date: 3/23/2018

Name: Daniel C. Flynn, Ph.D., Vice President for Research

Executed signature pages are available in the Initiating Authority Office(s)

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