SJU Saint Joseph's University

IRB Standard Operating Policy and Procedures Number:	6
Title:	Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others
Effective Date:	January 1, 2023
Responsible Office:	Office of Research Services/IRB

Purpose

Federal regulations (45CFR46.103(a) and (b)(5) & 21CFR56.108(b)) require written procedures for ensuring prompt reporting of "any unanticipated problems involving risks to subjects or others; any serious or continuing non-compliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and any suspension or termination of IRB approval" to appropriate institutional officials, supporting department or agency head (or designee), and OHRP.

This policy sets forth procedures and responsibilities of the PI, the SJU Institutional Review Board (IRB) and the Office of Research Services (ORS) associated with prompt reporting and review of adverse events and unanticipated problems that occur in IRB-approved research.

Scope and Applicability

SJU's Institutional Review Board (IRB) Standard Operating Policies & Procedures (SOPPs) apply to all research activities involving human subjects conducted by SJU faculty, staff, or students or by anyone conducting research in which the participation of SJU meets the definition of "engagement" as indicated by the Office of Human Research Protections (OHRP)*. These policies rely on and reference the Department of Health and Human Services (DHHS) Regulations pertaining to the Protection of Human Subjects in Research (hereinafter referred to as 45 CFR § 46). The guidance document on "engagement" may be found here.

Definitions

Adverse events (AE) are any untoward or unfavorable physical or psychological occurrence in a human subject, including any abnormal signs, symptoms, or diseases temporally associated with the subject's participation in the research, whether or not considered related to participation. An adverse event may also be an unanticipated problem in instances where an unexpected event is related to the research and is not consistent in nature, frequency, or severity with the current IRB protocol, consent form, or other related protocol documentation.

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.

Serious adverse events (SAE) include those resulting in death, life-threatening injury, hospitalization or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly or birth defect. Events not meeting the aforementioned criteria but requiring professional medical, psychological, or behavioral intervention to prevent one of these outcomes are also considered serious adverse events.

Policy Statement

This policy applies to research that meets Exemption criteria and research approved at the Expedited and Full Board levels. The Principal Investigator (PI) is responsible for (a) adhering to designs and procedures outlined in the IRB-approved protocol [SOPP 5], (b) providing updates at IRB-prescribed intervals via the continuing review process [SOPP 3], and (c) reporting adverse events and unanticipated problems involving risk to participants or others, in a timely manner. The PI is responsible for ensuring the IRB-approved consent documents contain accurate information for how to contact the PI should the subject have questions or research-related concerns, as well as contact information for the SJU Institutional Review Board should the subject have questions or concerns about their rights as a research subject, and for the reporting of research-related concerns. Unless the IRB has approved an alternative consent procedure, subjects should be furnished with a hard copy of the consent form. Unanticipated problems involving risks to participants or others may occur during a research study. The PI is responsible for promptly reporting such events (unanticipated problems (UPs) and serious adverse events (SAEs)) to the SJU IRB. The SJU IRB shall review such problems and reassess the balance between the risks and benefits to participants.

In response to a report or complaint received by the Research Compliance Manager (RCM) by someone other than a PI in relation to SJU IRB-approved research, the RCM will contact the PI within 24 hours of the report and request that the PI complete and submit the Reportable Event Form through IRBNet. In the case of an anonymous complaint, the complainant will be advised, if possible, that their report will be investigated but that the scope of the investigation may be affected/limited by their choice to remain anonymous. Any complaint/concern of a subject that does not indicate an unanticipated risk or a change in the risk/benefit ratio associated with the study and that can be resolved by PI, should be included as part of the continuing review/closure submission for review by the IRB [see SOPP 3].

The following serious adverse events (SAE) must be reported to the IRB within **24 hours** of the first awareness, whether by the PI or another researcher, the Office of Research Services, or a member of the IRB: **(a) Death of a research subject**, or **(b) serious injury to a research subject**. The PI must report any of the following events to the IRB within ten (10) business days of the date the investigator learns of the event:

1. An event meeting **all** of the following criteria: (a) unexpected; (b) possibly, probably, or definitely related to the research study; and (c) suggest that the research places participants or others at greater risk of harm than was previously known or recognized.
2. Any serious accidental or unintentional change to the IRB-approved protocol that increase the risk of harm to subjects or others.
3. Any deviation from the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research subject.

4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
5. Unanticipated accident involving a research subject.
6. Display of unanticipated emotional upset or degree of emotional upset by a research subject.
7. A breach in confidentiality that may involve risk to the participant or others.
8. Any complaint of a subject that indicates an unanticipated risk and that cannot be resolved by the PI.

Federal regulations stipulate that the IRB "...must have the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects." These regulations further stipulate that "any suspension or termination. . . must be reported promptly to the investigator, appropriate institutional officials, and any supporting department or agency head" (45 CFR 46).

Procedures

Principal Investigator Reporting and IRB Review Procedures

In accordance with the policy set forth above, a PI must promptly complete and submit a Reportable Event Form to the Office of Research Services (ORS) through IRBNet upon becoming aware of a reportable event. The Reportable Event Form will be reviewed initially by the Research Compliance Manager (RCM). The RCM, in consultation with the IRB Chair, may request clarification or further information in writing from the PI and/or complainant and may consult with members of the IRB with appropriate expertise to properly evaluate the occurrence to determine if it qualifies as an unanticipated event, as defined above.

If the occurrence **does not** qualify as an unanticipated problem, no further action will be taken unless it is determined that serious or continuing non-compliance has occurred. [See SOPP 5]: Noncompliance. The IRB Chair or his/her designee will document this determination and inform the PI of the decision. If the occurrence is a Serious Adverse Event that is **not related** to the conduct of the research study, and thus, not required to be reported to OHRP, the PI is expected to submit a Reportable Event Form and to provide the IRB with documentation from an appropriate source demonstrating that the death or serious injury is not related to the research.

If the occurrence **does qualify** as an unanticipated problem, the RCM and IRB Chair will determine (a) whether the reported occurrence is a serious adverse event requiring review and modifications by the convened IRB; or (2) whether the reported occurrence is a non-serious unanticipated problem that can receive expedited review by the IRB Chair or designated reviewer(s). Furthermore, the RCM will consult with the Chair and the Director, ORS, to ensure prompt and appropriate reporting of the occurrence to the Institutional Official, OHRP, FDA, and other regulatory agencies, as appropriate, in accordance with federal regulations.

If it is determined that immediate action by the IRB is warranted (in order to protect the rights and welfare of subjects), then the IRB Chair will instruct the RCM to issue a suspension notice for the protocol until the convened IRB reviews and acts on the protocol. The RCM will place the Reportable Event on the agenda for the next meeting of the convened IRB for their discussion and resolution. The convened IRB must discuss suspensions of all protocols previously approved by the IRB. The convened IRB has the authority to suspend or terminate research activities, taking into consideration protections for participants' rights and welfare.

The review of the Reportable Event will take place in accordance with the procedures set forth in [SOPP 3: Initial and Continuing Review by the IRB, Section 2.2 (Procedures for Convened Committee Review).]

If the reported occurrence is determined to be an unanticipated problem, as defined above in Section 1.3.1, the Reportable Event Report Form will be assigned for Expedited Review. An IRB member with relevant expertise will be selected by the RCC and/or the Chair of the IRB as the Expedited Reviewer. The review may be assigned to any member with relevant experience, including the Chair and/or the RCC, in consultation with the IRB Chair may obtain consultation to obtain that expertise. The Expedited Reviewer may require corrective action with respect to the protocol at issue (See 2.5). However, the following actions require placing the Reportable Event Report on the agenda of the next meeting of the convened IRB for their discussion and resolution: (1) modification of a protocol that the convened IRB previously approved; and (2) suspension or termination of a previously approved protocol. The Expedited Reviewer may request the Chair of the IRB to suspend a protocol until the convened IRB reviews and acts on the protocol. The IRB Chair will email the Expedited Reviewer's comments, questions, and/or decisions (see below, 3.5.) to the Protocol PI. The Protocol PI will respond in writing to the IRB, and this response will be reviewed by the Expedited Reviewer and/or the Chair of the IRB. The Protocol PI, the Expedited Reviewer, or the Chair of the IRB may request that the Reportable Event Report be referred to the convened IRB for a decision. If the Reportable Event is not so referred, the next IRB agenda will notify the other IRB members of the decision(s) made by the Expedited Reviewer with respect to the Reportable Event.

The actions taken to correct reportable events vary and depend on the nature and seriousness of the event. The IRB may take any of the following actions:

1. No action
2. Request protocol and/or consent form/process modification
3. Require that all participants be re-consented
4. Require previous participants to be informed of any changes to the protocol and/or consent procedures
5. Require observation of consent procedures
6. Require more frequent review of the conduct of the research
7. Require additional training for the research team
8. Require follow-up audit(s) of the research
9. Suspend the research
10. Terminate the research
11. Referral to other institutional entities (e.g., Institutional Official, Dean, General Counsel)
12. Any other action deemed appropriate by the IRB to protect the rights and welfare of research subjects.

The IRB will convene to determine the following: (1) any required modifications; (2) determine if modifications may be reviewed through an Expedited process or by the Full IRB; and (3) the time frame for submission of required modifications. Following a determination by the IRB of necessary actions, if any, the IRB Chair or his/her designee will draft a letter to the Protocol PI, to be published in IRBNet, setting forth the IRB determinations, any required modifications and

the time frame within which such modifications must be made. The Protocol PI will provide written notification to the IRB through IRBNet when s/he has made any required modifications.

Upon full implementation of the corrective plan, the IRB Chair (or designee) will draft a final report for review by the IRB Committee at the next available meeting. If the IRB finds that the corrective action plan has been appropriately implemented, the IRB Chair (or designee) will report the outcome of the review of the reported event to the Director of Research Services in order to facilitate necessary institutional reporting procedures. Failure of the PI to complete modifications as required by the IRB within the IRB prescribed time fame may result is suspension or termination of the research, and the PI may be subject to noncompliance actions (See SOPP 5).

Institutional Reporting Procedures

The Director of Research Services (ORS) will ensure compliance with federally mandated reporting requirements concerning unanticipated problems, noncompliance, and suspensions and terminations involving human subject research protocols previously approved by the IRB.

Final Reports

A final report should include the following information: (1) the name of the Protocol PI; (2) the IRB's OHRP registration number, SJU's FWA number; (3) protocol title; (4) sponsor of the study; (5) any applicable grant numbers; (6) the dates(s) and nature of the event(s); (7) details concerning how the event was discovered; (8) the IRB's response to the event; (9) the Protocol PI's response to the event; (10) investigatory/audit findings; (11) IRB's actions and rationale and any response by the Protocol PI; (12) details of the corrective plan; (13) any pertinent details concerning the Protocol PI's implementation of the corrective plan; (14) participants' response to corrective measures; (15) IRB plan for monitoring the outcome of the event; (16) certification of destruction of data resulting from un-approved research activities, if applicable; (17) outcomes of withdrawal and follow-up of participants, if applicable; and (18) any general educational activities inspired by the incident.

Initial Reports

While this information is being compiled for the final report and the corrective plan is being implemented, the IRB and the Director of ORS may elect to have ORS submit an initial report to OHRP and/or FDA in order to ensure prompt reporting. An initial report should include as much of this information as is available.

ORS will draft initial and final reports, and the Director of ORS will be responsible for signing and finalizing them. After initial and final reports are signed, ORS will distribute them to appropriate institutional officials and government agencies.

Regulation and Guidance
1. 45 CFR 46.103: Requirement for written assurance of compliance with 45 CFR 46; in particular, 45 CFR 46.103(5): Requirement for written procedures for ensuring, in part, "prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of any unanticipated problems involving risks to subjects or others." 2. 21 CFR 56.108: IRB Functions and Operations; in particular 21 CFR 56.108(b): Requirement for written procedures for ensuring "prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of any unanticipated problems involving risks to human subjects or others."

3. OHRP Guidance on Unanticipated Problems Involving Risks and Adverse Events: mailto:https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/