

<b>SOP: 409</b> <b>Effective Date: 08/21/2020</b>	<b>UNANTICIPATED PROBLEMS AND ADVERSE EVENT REPORTING</b>	<b>Supersedes Document Dated: 07/01/2019</b>
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## 1. POLICY

Purdue University Investigators and Human Research Protection Program (HRPP) Staff have an obligation to report unanticipated problems involving risks to subjects or others and certain types of Adverse Events.

Investigators must report applicable Unanticipated Problems and Adverse Events to the HRPP as outlined in this SOP. The HRPP will then review the report and consider corrective actions or substantive changes, as necessary, in order to protect the safety, welfare, and rights of subjects or others. The HRPP also has an obligation to report identified Unanticipated Problems to the Office for Human Research Protections (OHRP).

These policies and procedures apply to all Human Subject Research under the jurisdiction of the IRB.

## 2. DEFINITIONS

**2.1** *Adverse Event.* Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms.

**2.2** *Serious Adverse Event.* Any Adverse Event that:

2.2.1 results in death;

2.2.2 is life-threatening (places the subject at immediate risk of death from the event as it occurred);

2.2.3 results in inpatient hospitalization or prolongation of existing hospitalization;

2.2.4 results in a persistent or significant disability/incapacity;

2.2.5 results in a congenital anomaly/birth defect; or

2.2.6 based upon appropriate medical judgment, may jeopardize the subject's health, and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not

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result in inpatient hospitalization, or the development of drug dependency or drug abuse).

**2.3** *Unanticipated Problem.* An incident, experience, or outcome that meets all of the following criteria:

2.3.1 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;

2.3.2 related or possibly related to a subject's participation in the research; and

2.3.3 suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

**2.4** *Possibly Related.* There is a reasonable possibility that the problem, event, incident, experience, or outcome may have been caused by the procedures involved in the research.

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

2.4.1 the procedures involved in the research;

2.4.2 an underlying disease, disorder, or condition of the subject; or

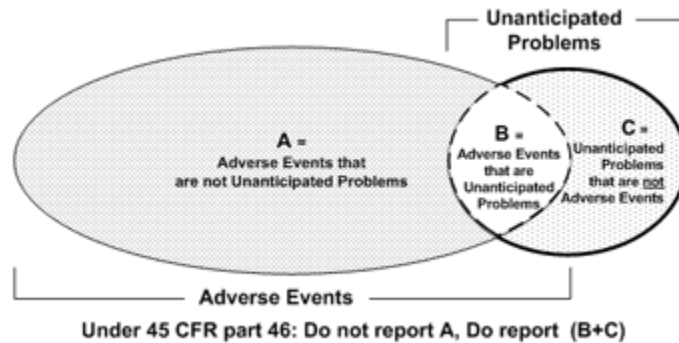
2.4.3 other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

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.

### **3. PROCEDURES**

#### **3.1 Identifying Unanticipated Problems**

3.1.1 As shown in the OHRP guidance diagram below, Investigators must report all Unanticipated Problems (including the subset that is also Adverse Events) to the HRPP.



- 3.1.2 OHRP guidance recognizes that the vast majority of Adverse Events occurring in human subjects research are not Unanticipated Problems, in light of (1) the known toxicities and side effects of the research procedures; (2) the expected natural progression of subjects' underlying diseases, disorders, and conditions; and (3) subjects' predisposing risk factor profiles for the Adverse Events. Thus, most individual Adverse Events do not meet the first criterion for an Unanticipated Problem and do not need to be reported.

## 3.2 Reporting Requirements and Procedures

- 3.2.1 The Investigator must promptly report any Unanticipated Problems to the IRB. The HRPP requires Investigators to report in accordance with the following guidelines in order to satisfy the prompt reporting requirement:
- (a) Unanticipated Problems that are Serious Adverse Events must be reported to the IRB within five (5) business days of the Investigator becoming aware of the event. The IRB strongly recommends that a preliminary report be submitted by the researcher within 48 hours of learning of the Serious Adverse Event with a formal follow-up report submitted within the above timeline. Investigators should not include identifiable information in the report(s).
  - (b) Any other Unanticipated Problem should be reported to the IRB within two (2) weeks of the Investigator becoming aware of the problem. The IRB strongly recommends that a preliminary report be submitted by the researcher within five (5) business days of learning of the Unanticipated Problem with a formal follow-up report submitted within the above timeline. Investigators should not include identifiable information in the report(s).

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- (c) All Unanticipated Problems should be reported to the Institutional Official (IO), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the Investigator.
- (d) In some cases, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB, the IO, the supporting HHS agency head (or designee), and OHRP, with a follow-up report submitted at a later date when more information is available. Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by persons knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects.
- (e) The HRPP/IRB will respond to participant complaints, Purdue hotline reports, self-disclosures, reputable reports from another source, or requirements for clarification from an investigator in the same manner as an Unanticipated Problem Report.

3.2.2 Content of Unanticipated Problem Report. When making a report to the IRB, an Investigator should include the following information:

- (a) appropriate identifying information for the research protocol, such as the title, Investigator's name, and the IRB project number;
- (b) a detailed description of the Adverse Event, incident, experience, or outcome; however, to preserve confidentiality, subject names and identifiable information should not be included in the report);
- (c) an explanation of the basis for determining that the Adverse Event, incident, experience, or outcome represents an unanticipated problem; and
- (d) a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

3.2.3 The Investigator is responsible for assessing and documenting unanticipated problems and reporting to the HRPP, as required by this policy, regardless of who observed or became aware of the event.

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- (a) The Investigator should use his or her judgment when determining if an event is considered reportable. When in doubt, the investigator should contact the HRPP for guidance.
- (b) In the absence of the Investigator, a co-researcher can fulfill these requirements to meet the reporting timeline.
- (c) In the absence of either the Investigator or a co-researcher, a student member of the research team or other research personnel must contact the HRPP for direction.

3.2.4 For collaborative research, Unanticipated Problems should be reported to the IRB of record.

- (a) When a Purdue University IRB is the IRB of record, Unanticipated Problems must be reported in accordance with this SOP, regardless of where the Unanticipated Problem occurred. The Purdue University Investigator is responsible for coordinating the reporting.
- (b) When a Purdue University Investigator is relying upon IRB review from another institution, Unanticipated Problems must be reported in accordance with the policies and procedures of that institution.

3.2.5 The IO is responsible for reporting Unanticipated Problems to OHRP and/or the Food and Drug Administration (FDA), as required.

3.2.6 The Investigator must fulfill the reporting requirements of other organizations (e.g., Sponsor), which are not satisfied nor precluded by submitting an Unanticipated Problem report to the HRPP. Likewise, submitting Unanticipated Problem or Adverse Event reports to other organizations (e.g., Sponsor) does not satisfy the reporting requirement to HRPP.

### **3.3 IRB Review and Response**

3.3.1 Initial review of Unanticipated Problems will be conducted by the IRB Chair, Associate Chair, or designee.) unless another IRB Member is specifically named by the IRB Chair or Institutional Official or a conflict of interest prevents this duty. The IRB Chair (or designee) is authorized to take the following actions in response to any incident report:

- (a) Conduct an administrative review of the report, including assessing whether the incident constitutes an Unanticipated Problem and by

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whom it should be reviewed (e.g., the IRB Chair only, IRB Associate Chair only, an IRB subcommittee, or the convened IRB).

- (b) If convened IRB review is needed, the IRB Chair or designee assigns the incident report for review at the next available regularly scheduled IRB meeting. Assignment to a convened meeting will occur by the processes found in SOP 302: Initial Review.
  - (c) Alternately, the IRB Chair may convene an emergency meeting of the IRB to review the report.
  - (d) If the IRB Chair (or designee) finds that the rights, safety, and welfare of subjects are jeopardized by the research, the IRB Chair may suspend research until such time that the full IRB can convene to review the report.
- 3.3.2 When reviewing a report of an Unanticipated Problem, the IRB should consider whether the affected research protocol still satisfies the criteria for IRB approval under regulations at 45 CFR 46.111. See SOP 302: Initial Review. In particular, the IRB should consider whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result.
- 3.3.3 When reviewing a particular incident, experience, or outcome reported as an Unanticipated Problem by the Investigator, the IRB may determine that the incident, experience, or outcome does not meet all three criteria for an Unanticipated Problem. In such cases, further reporting to appropriate institutional officials, the department or agency head (or designee), and OHRP would not be required.
- 3.3.4 After reviewing the Unanticipated Problem report, the IRB may require the following actions, in order to protect the ongoing safety of research subjects:
- (a) Modification of subject inclusion or exclusion criteria to mitigate the newly identified risks;
  - (b) Implementation of additional procedures for monitoring subjects;
  - (c) Modification of informed consent documents to include a description of newly recognized risks;
  - (d) Provision of additional information about newly recognized risks to previously enrolled subjects;

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- (e) Suspension of enrollment of new subjects;
- (f) Suspension of research procedures in currently enrolled subjects;
- (g) Suspension of the entire study; or
- (h) Termination of approval for the entire study.

3.3.5 If the response to an Unanticipated Problem requires an amendment of the research protocol and/or informed consent forms, an amendment request must be submitted to the IRB in accordance with SOP 305: Amendment Requests. If the changes are minor they may be reviewed by expedited review procedures. If the changes are more than minor, they must be reviewed and approved by the convened IRB. Any such proposed changes in response to an Unanticipated Problem must be reviewed and approved by the IRB before being implemented, except when implementation is necessary to eliminate apparent immediate hazards to subjects.

#### **4. RESPONSIBILITY**

The IRB Chair, Associate Chair, or designee is responsible for reviewing all reports of unanticipated problems and ensuring the appropriateness of all IRB decisions and actions.

The IRB Administrator is responsible for advising the IRB Chair on relevant institutional and regulatory requirements.

The IO is responsible for reporting unanticipated problems to the OHRP or other outside institutions as needed.

#### **5. PROCESS OVERVIEW**

Unanticipated Problems must be reported to the HRPP as promptly as possible, within two (2) weeks of the Investigator learning of the incident, or five (5) business days in the case of a Serious Adverse Event. All reports must be made in writing, except in the event of an emergency, in which case an initial report may be made by telephone or in person, with a formal written report to follow within the required timeframe.

In the event that HRPP Support Staff receive Unanticipated Problem Reports, they must forward to the appropriate IRB Chair for review. HRPP Support Staff also notify the IRB Administrator, Human Protections Administration, and the IO that an Unanticipated Problem report has been submitted.

The IRB Chair or designee reviews the reports. S/he evaluates the incoming report determines what actions, if any, may be needed to protect the rights, safety, and welfare of research subjects due to the nature or frequency of the reported unanticipated problem.

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If the IRB Chair finds that additional review is necessary, the IRB Chair assigns the Unanticipated Problem report for review at the next regularly scheduled IRB meeting or convenes an emergency meeting of the convened IRB. The IRB Chair may also opt to follow procedures outlined in SOP 408 if Noncompliance with an approved protocol may be a factor.

HRPP Support Staff assist the IRB Chair in communicating the results of the review, discussion, and outcome to the Investigator and other appropriate parties.

**6. APPLICABLE REGULATIONS AND GUIDELINES**

45 CFR 46.103; 46.109; 46.111; 46.113

21 CFR 56.108; 312.32; 312.64; 812.3(s); 812.46; 812.150

[OHRP Guidance, Unanticipated Problems Involving Risks & Adverse Events \(2007\)](#)

**7. REFERENCES TO OTHER SOPs**

302 Initial Review

408 Noncompliance

410 Suspension or Termination of Research