Research Ethics Committee

Policy and Procedures for Reporting Adverse Events, Unanticipated Problems and Noncompliance in Human Subjects Research

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I. Introduction

A. General Policy

This policy outlines the Research Ethics Committee (REC) requirements for reporting adverse events, unanticipated problems and issues of non-compliance that occur during the course of a REC approved research project as well as issues of noncompliance. This statement of policy and procedures is intended to carry out the institution's responsibilities under the U.S. Department of Health and Human Services (HHS) and office of human research protections (OHRP) regulations at 45 CFR 46.108(a)(3)(iii) and (a)(4). Much of the information contained herein comes from the OHRP 2007 guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events.

B. Scope

The HHS regulations at 45 CFR 46.108(a)(3)(iii) and (a)(4) require that institutions have written procedures to ensure that the following incidents related to regulatory requirements pertaining to research conducted under an OHRP- approved assurance are promptly reported to OHRP:

1. **Any unanticipated problems involving risks to subjects or others;**
2. **Any serious or continuing noncompliance with this policy or the requirements or determinations of the REC; and**
3. **Any suspension or termination of REC approval**

OHRP guidance states that, in general, these reporting requirements apply to all nonexempt human subjects research that is:

1. **conducted or supported by HHS;**
2. **conducted or supported by any non-HHS federal department or agency that has adopted the Common Rule and is covered by a Federal wide Assurance (FWA) determined to be appropriate for such research; or**
3. **covered by an FWA, regardless of funding source.**

Thus, this policy applies to all University faculty, students and staff conducting human subjects research that has been approved by the REC at the level of expedited or full board review.

II. Definitions and Examples

A. General Definitions

Unanticipated problems: In 45 CFR 46.108, OHRP states there should be prompt reporting of any "unanticipated problems involving risks to subjects or others."

Though it does not specifically define unanticipated problems, OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

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 REC approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. **related or possibly related to participation in the research** (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. 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 or may not be adverse events. As described below, adverse events involved harm to participants. Unanticipated problems may involve increased risk of harm even if no actual harm occurred.

Examples of reportable unanticipated problems include, but are not limited to:

- A breach in confidentiality resulting from disclosure of confidential information that may involve risk to the subjects or others;
- Harm or risk of harm to research staff;
- Procedural errors that may involve potential risk to the subject or others;
- Disqualification or suspension of investigators
- Deviation from the REC approved protocol without prior REC review and approval of the changes;
- Newly discovered information that indicates a change in the risk / benefit ratio of the research

Adverse events (AE): There is no explicit definition of the term "adverse event" in 45 CFR 46. However, OHRP guidance uses the term broadly to include any event meeting the following definition:

> 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 (modified from the

definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Note: Adverse events encompass both **physical and psychological harms**. They occur most commonly in the context of biomedical research, although on occasion, they **can occur in the context of social and behavioral research.**

Noncompliance: Failure to comply with federal regulations, state laws, Spalding University or OHRP policies and procedures related to the protection of human subjects and / or failure to follow the approved research procedures and / or requirements or determinations of the REC.

Serious noncompliance: Noncompliance in which there is an actual or potential increased risk to the safety, rights and welfare of the human research subjects. Multiple instances of noncompliance that may be individually non-serious may be treated as serious when considered collectively.

Continuing noncompliance: Repeated instances of noncompliance indicating a lack of understanding or disregard for the regulations or requirements that protect the safety, rights and welfare of research subjects. Pattern of noncompliance suggesting noncompliance will continue without appropriate action. Failure to respond to requests from the REC regarding an instance of noncompliance.

Examples of noncompliance (Note that, depending on the circumstances, these could be considered as serious or not serious):

- *Initiating research without seeking REC approval. This includes research that may be considered exempt (considered to be serious unless determined otherwise by the REC).*
- *Delayed reporting of an unanticipated problem that warranted protocol modification.*
- *Failure to follow the approved protocol.*

DSMB / DMC: Data safety monitoring board / data monitoring committee. It is the responsibility of the investigator(s) and / or study sponsor(s), to determine the need for and establish an independent data monitoring committee as required by FDA regulation 21 CFR 56.111(a)(6).

For the purposes of this policy, the use of the term "**incident**" will hereafter refer to any unanticipated problem, adverse event or non-compliance being reported unless otherwise indicated.

B. Determination of "unanticipated problem"

The following definitions will help to determine whether or not an event meets the three aforementioned criteria of an unanticipated problem.

Unexpected adverse event: OHRP definition includes any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the REC-approved research protocol, any applicable investigator brochure, and the current REC-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Event that is *related or possibly related* to participation in research: According to OHRP general guidance, adverse events that are determined to be at least partially caused by (1) below would be considered related to participation in the research, whereas adverse events determined to be solely caused by (2) or (3) below would be considered unrelated to participation in the 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.

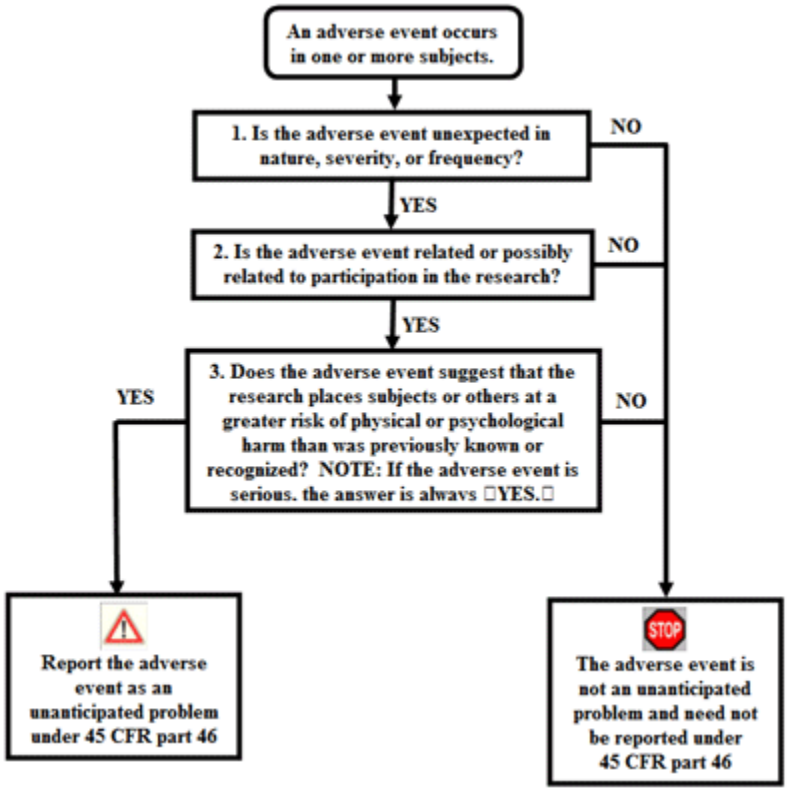
Serious adverse event (SAE): OHRP defines *serious adverse event* as any adverse event that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
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 result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Note: There are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered

adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs. Please see below a flow chart to aide in decision making and examples from OHRP guidance of unanticipated problems that require reporting.

Flow chart for determining whether an adverse event represents an unanticipated problem that needs to be reported under HHS regulations 45 CFR part 46:



Source: ***https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#Q3***

Example of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported Under the HHS Regulations at 45 CFR Part 46:

> *An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.*

Example of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR Part 46:

A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

In this example, the adverse event warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

Source: ***https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html***

III. Suspension or termination of REC approval

A. According to the HHS regulations at 45 CFR 46.113, the REC has the authority to suspend or terminate approval of research that is not being conducted in accordance with the approved protocol, REC requirements, OHRP regulations or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the REC's action and shall be promptly reported to the investigator, appropriate institutional officials, and the department or agency head.

B. Upon receipt of notification of suspension or termination of research approval, all research activities must cease immediately unless doing so would result in increased risk to subjects' safety, rights or welfare.

C. Investigators must promptly respond to REC requests for additional information regarding concerns of unanticipated problems or noncompliance. Failure to do so may result in suspension or termination of approval.

D. Research for which approval has been suspended may not resume until suspension has been lifted and approval to continue has been granted.

IV. Reporting of incident

A. Responsibility

1. It is the responsibility of the investigator(s) to ensure prompt reporting of any unanticipated problems / adverse events or non-compliance with the approved protocol. Note, it is not the responsibility of the REC to monitor study data and procedures in order to identify the occurrence of any unanticipated problems or non-compliance. Incidents should be reported to the REC (rec@splading.edu) as well as directly to the REC chair via email per the guidelines provided below in section IV.B and C.
2. The REC chair shall report findings from incident reviews to the institutional signatory official, Dr. Kurt Jefferson, Dean of Graduate Education (kjefferson@spalding.edu).
3. The REC chair and /or signatory official will ensure prompt reporting to OHPR and any other relevant agencies of any incident involving an unanticipated problem or serious or continuing noncompliance with the OHRP regulations at 45 CFR 46 or the requirements or determinations of the REC; and any suspension or termination of REC approval.
    a. It is the responsibility of the involved investigator(s) to notify the REC chair of any other relevant agencies to whom the incident should be reported
    b. The REC reserves the right to request assistance from the investigator(s) with preparation of materials for inclusion in OHRP or other regulatory agency reports.
4. The signatory official will notify, as appropriate, additional intuitional officials such as the director of the office of sponsored programs and / or university provost of incidents reported to OHRP in accordance with this policy.

B. Whistleblowing

Any individual that suspects noncompliance is encouraged to report their concerns to the REC. The REC will maintain anonymity of the whistleblower and protect the person reporting from retaliation.

C. Timeframe for reporting to the REC

1. OHRP requires prompt reporting of:
   a. any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with the OHRP regulations at 45 CFR 46 or the requirements or determinations of the REC; and
   b. any suspension or termination of REC approval.

2. Unanticipated problems that are **serious adverse events** should be reported to the REC as soon as possible after the investigator becomes aware of the event to allow for REC reporting to OHRP within days of the event if needed.
   a. **If the problem poses immediate risk of serious harm to a subject or others, it must be reported immediately to REC@spalding.edu and the REC chair.**

3. Serious non-compliance should be reported to the REC as soon as possible but at least within 1 week of the investigator becoming aware of the event.

4. Any other non-compliance or unanticipated problem should be reported to the REC within 2 weeks of the investigator becoming aware of the event.

5. In general, investigators should wait until after learning the REC review outcome before making changes to the study protocol in response to an adverse event or issue of non-compliance. However, **changes may be made at the time of the incident in order to protect human subject safety or to mitigate risk** that could result from the adverse event or non-compliance. In such cases, the researcher should include this information in the incident report.

6. **The primary consideration in making judgments is the need to take timely action to prevent avoidable harm to research subjects.** This applies to both the timeframe for reporting an incident to the REC as well as adjusting study procedures.

D. Content of reports

When reporting an adverse event, non-compliance or any other incident, experience, or outcome as an unanticipated problem to the REC, the following information must be included:

1. Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number along with the number of any applicable federal award(s) (grant, contract, or cooperative agreement);

2. A detailed description of the adverse event, incident, experience, or outcome;

3. An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem; and

4. 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.
    a. Any proposed changes to a research study in response to an unanticipated problem must be reviewed and approved by the REC before being implemented, except when necessary to eliminate apparent immediate hazards to subjects.

V. REC review and response to incident reports

A. Procedures for REC review of incidents
    1. Upon receipt of an incident report, the REC chair or designated reviewer will determine whether it meets all three (3) criteria for an unanticipated problem or is an issue of non-compliance.
    2. If the incident meets the criteria for an unanticipated problem or is a report of non-compliance, the chair will review the report to determine the appropriate level of review needed.
    3. The nature of the incident and investigator(s) proposed changes to address the incident will determine:
        a. The level of review required
            i. All serious adverse events and reports of serious or continued non-compliance will undergo full board review regardless of the changes proposed by the investigator(s).
        b. The timeframe for REC review
            i. **If waiting until the next regularly scheduled REC meeting would delay prompt reporting to OHRP, a special meeting shall be called,** otherwise incident reports warranting full board review will take place at the next regularly scheduled meeting.
    4. Whether following expedited or full board review procedures, consideration shall be given to determine whether the affected research protocol still satisfies the requirements for REC approval under HHS regulations at 45 CFR 46.111. **Specifically, it is the responsibility of the reviewer / committee to 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.**
    5. In the event a full board review is required, the REC chair must be in attendance and quorum must be met in order to review the report and determine the REC's response.

B. REC response to incident reports
    1. The REC determines the response to the incident, which may include, but is not limited to the following:
        a. Acknowledgement/acceptance of the proposed changes without further recommendation;

   b. Submission of more detailed information by the investigator(s), the sponsor, the study coordinating center, or DSMB/DMC about any adverse event, unanticipated problem or non-compliance occurring in a research protocol;
   c. Recommendation of (additional) corrective action(s)
   d. Suspension or termination of the research
2. The REC determines any corrective action(s) necessary in response to unanticipated problems. Corrective actions may include, but are not limited to the following:
   a. requiring notification and / or reconsenting of current participants, when such information might be related to their willingness to continue to take part in the study
   b. requiring modifications to the protocol and/or consent documents
   c. increase in frequency of continuing review
   d. imposition of additional monitoring requirements
   e. requiring additional training of some or all members of the research team
3. The REC shall notify the primary investigator of its response to incident reports in a timely manner.
4. The REC chair reports the REC's determination to the signatory official and ensures, together with the signatory official, prompt reporting to other institutional officials and federal agencies as outlined in section IV. A.