Liberty University Adverse Events Policy

## I. OBJECTIVE

**A.** This memo describes the policies and procedures for prompt research investigator reporting of the following:

- unanticipated problems or adverse events,
- problems/adverse events that do not meet the prompt reporting requirements

**B.** The memo also includes the following:

- Institutional Review Board (IRB) procedures for the review of investigator reports

## II. WHY HAVE A POLICY?

Two reasons lead to this policy's implementation:

**A.** Review of unanticipated problems or adverse events provides an important safeguard to identify concerns about a) risk to subjects or others; b) the risk/benefit ratio of the research project; c) the appropriateness of the currently approved informed consent document; and d) the need for re-consent.

**B.** Regulatory guidance provided in 45 CFR 46.103(b)(5) and 21 CFR 56.108(b) requires the IRB to have in place written procedures for ensuring prompt reporting to the IRB, appropriate Liberty University officials, and applicable regulatory agencies of any unanticipated problems involving risk to human subjects or others.

## III. DEFINITIONS

It is essential to have a good understanding of several terms in order to properly interpret this policy.

**A. Unanticipated problem -** any unforeseen or unexpected incident or experience (including an unanticipated adverse event) which is not described in the general investigational plan or elsewhere in the current IRB application or with the current investigator brochure, or in the consent document.

**B. Adverse event** – an undesirable effect detected in participants in a study. The effect may be the result of:

1. the interventions and interactions used in the research;
2. an underlying disease, disorder, or condition of the subject; and/or
3. other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

C. **Unanticipated problem involving risk to participants or others** - any unforeseen or unexpected event or experience that adversely affects the rights, safety, or welfare of subjects or others (which is not described in the general investigational plan or elsewhere in the current application or with the current investigator brochure, or in the consent document). The event or experience could involve psychological harm/risk, physical harm/risk (e.g., adverse event), social harm/risk (i.e., inappropriate breach in confidentiality, harm to a subject's reputation, or invasion of privacy), or legal harm/risk. The experience could also involve events not previously identified in severity or degree of incidence. An adverse event could be considered an "unanticipated problem involving risk to subjects or others".

D. **Anticipated problem/adverse event** – any foreseen or expected incident/experience which was described in the general investigational plan or elsewhere in the current application or with the current investigator brochure, or in the consent document.

E. **Serious problem/adverse event** - any incident that results in significant harm to or increased risk for the subject or others. Examples of events which are serious would include but are not limited to, inpatient psychiatric or medical hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject's health or welfare and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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. A disability is a substantial disruption of a person's ability to conduct normal life functions.

F. **Life-threatening event** - any experience that places the subject, in the view of the investigator, at *immediate* risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

G. **Related** - There is a reasonable possibility, in the opinion of the Principal Investigator, that the experience was likely to have been caused by the research procedures.

H. **Internal event/problem –** occurrence involves research subjects enrolled in a project approved by the LU IRB and directed by a principal investigator employed by LU or one whose project is under the purview of the LU IRB (e.g., student dissertations and theses). [Internal events/problems are reported to the IRB on the LU ADVERSE EVENT REPORTING FORM.]

I. **External event/problem -** occurrence involves research subjects enrolled in multi-center research projects that do not fall under the purview of the LU IRB. [External events/problems are reported to the IRB on the "LU EXTERNAL PROMPT

REPORTING FORM For Unanticipated Problems, Serious or Life-Threatening Events, and Related Anticipated and Unanticipated Deaths".]

The table below describes examples of whether a prompt report to the IRB is needed.

| Prompt report to IRB? | Incident | Examples |
|---|---|---|
| REQUIRED | Unanticipated problem involving risk to participants or others and related to the research procedures | Sensitive participant data stored on a computer is misplaced, lost or stolen |
| | Unanticipated serious or life threatening event related to research procedures | Participant needs psychiatric hospitalization after receiving a new psychological intervention involved in the study |
| | Anticipated or unanticipated death related to research procedures | Any death related to the procedures involved in the study. |
| NOT REQUIRED | Unanticipated problem with no harm involved to subjects | A participant talks in general terms to the press about the study. |
| | Adverse event that is anticipated | A participant in a survey on child abuse issues needs a counseling referral. This potential issue was anticipated by the researcher and appropriate referral mechanisms were described in the already-approved IRB application information. |
| | Unanticipated adverse event that is NOT related to the study procedures. | A participant in a psychotherapy study is hospitalized after receiving news that her 3 children were killed in an automobile accident. |

## IV. GENERAL DESCRIPTION

In response to the regulatory obligation, the Liberty University (LU) IRB utilizes a three category reporting system. This system facilitates review of reports and permits determination of whether the problem/event raises new concerns. The reporting categories are as follows:

**A. Prompt** (within 48 hours)Reporting of an unanticipated problem involving risk to subjects or others (including unanticipated serious or life-threatening adverse events) and anticipated or unanticipated related deaths to the IRB.

**B. Non-Prompt** (after 48 hours) Reporting to the IRB of anticipated problems/anticipated serious adverse events or unrelated deaths;

**C. Continuation Review** Reporting if any problems/adverse events occurred within 12 months prior to the continuation review (CR) request for a written summary of all problems/adverse events involving participants since the study was initiated, whether anticipated or unanticipated, serious or non-serious, life-threatening or not life threatening, or related or not related.

The policy details the IRB requirements for reporting, including adverse events and unanticipated problems involving risks to research subjects and others. The policy applies to all research projects/clinical investigations falling under the purview of the LU IRB. In addition to the three categories noted above, there are two broad types of reports, internal and external. An *internal adverse event* is one that occurs with research participants enrolled in a project approved by the LU IRB and directed (or supervised) by an investigator employed by the University. An example of investigator supervision would be an LU faculty member's oversight of a student's dissertation or master's thesis.

An *external adverse event* is one that occurs with research subjects enrolled in multi-center research projects that do not fall under the purview of the LU IRB.

## V. PROCEDURES

**A.** *Prompt Reporting of Problems/Adverse Events: Basic Reporting Requirements (See Policy on Prompt Reporting for Definitions)*

PI = Primary Investigator below

1. The PI reports all problems/adverse events that meet these 3 conditions (a-c):

    a) The event is serious or life-threatening, AND
    b) unanticipated AND
    c) related to the study procedures

    The PI will phone or email the IRB within 2 days to report general information about the incident and will use the applicable LU Adverse Event Reporting Form in making the detailed written report. The written report should be submitted by the timeline shown below.

2. If there is insufficient information to determine whether the adverse event is related to study procedures, the PI will report the event according to the timelines in item 3 below.

3. Timeline for reporting serious and unanticipated or life-threatening events/problems using the LU Adverse Event Reporting Form:
    a) As noted above, the PI phones or emails the IRB within 48 hours to report general information about the incident.
    b) The PI reports unanticipated life-threatening experiences within 7 calendar days of his/her receipt of the information using the LU Adverse Event Reporting Form.
    c) All other serious and unanticipated events/problems are reported within 10 calendar days of his/her receipt of the information using the above form.
    d) Institutional policy requires the investigator to provide follow-up reports on serious or life-threatening and unanticipated and related events within 10 calendar days of his/her receipt of the information.

4. Timeline for reporting deaths
    a) The PI reports all deaths <u>related to study procedures</u> occurring during a study through a phone call or email to the IRB within 48 hours.
    b) If the death is related to the study procedures, the investigators report such deaths in written form (after contacting the IRB as noted in A) within 3 calendar days through using the appropriate LU Adverse Event Reporting Form
    c) If the deaths are <u>not related</u> to the study procedures (i.e., due to underlying medical disease progression), these are reported in the summary of problems/adverse events submitted at the time of IRB continuation review.

5. The IRB may request more stringent requirements for reporting events for individual research studies if the respective committee determines it to be necessary.

6. If an event does not fall under the IRB's prompt reporting requirements, but in the PI's judgment, prompt reporting of the event(s) is in the best interest of the participant(s) (e.g., because it may affect the welfare of participants; or it changes the risk level of the study; or the frequency of the same event significantly increases) the PI should submit the LU Adverse Event Reporting Form according to the applicable timeline for prompt reporting.

7. Any problems/adverse events that were initially determined to not be related to the study procedures and are subsequently determined related must be reported according to the requirements listed in items 1-3 above.

**B.** *Prompt Report: Submissions/Screening and Review of <u>Internal</u> Problems/Events*

1. The PI makes the preliminary determination if the event meets the criteria for an IRB reportable event in accordance with the LU Adverse Events Policy.

2. The PI completes the LU Adverse Event Reporting Form and submits the form to the IRB in the time period outlined above in the LU Adverse Events Policy.

3. If the PI recognizes the problem/event involves risk to subjects or others and the information is not already in the informed consent/assent document, he/she submits a revised consent/assent form with changes underlined, if applicable. If the revised informed consent/assent form impacts the protocol/research description, the PI also submits a revised research description containing the underlined changes as well as a clean copy of both the consent/assent form and the research description.

4. IRB staff screen the report to determine whether it is complete, enter the report into the IRB database, and place the report on the IRB agenda.

5. Staff then forward the report(s) and related material(s) to the IRB Chair (or designee if the project relates to the Chair or the Chair is indisposed) who serves as the primary reviewer. The IRB Chair informs the LU Research Officer (aka Dean of the Graduate School) of the adverse event.

6. The IRB Chair (or primary reviewer designee) receives, at a minimum, the completed Adverse Event Form. Related material(s) that may be received include, but are not limited to, documents revised as a result of the problem/event or documents which provide additional assessments or summary information.

7. After review of the materials received, the IRB Chair (or primary reviewer) makes comments and returns the report to the Research Officer (aka Dean of the Graduate School) and the IRB.

8. IRB staff send copies of the adverse event materials with the IRB Chair comments in the agenda packet to each IRB member.

9. The IRB reviews internal events and problems at an online or on-campus convened IRB meeting using full review procedures.

10. If the study is federally funded (e.g., by the Department of Health and Human Services), or regulated by the Food and Drug Administration, additional IRB reporting requirements may be in effect.

11. IRB staff separate new internal reports submitted at Continuation Review (CR) from the regular CR materials and process them according to the provisions of this policy.

**C.** *IRB Review Outcome(s)*

1. For all unanticipated problems/events submitted under the IRB's prompt reporting policy, the IRB determines whether the problem/event involves risk to participants or

others. If the problem/event involves risk to subjects or others, the IRB will follow established federal reporting policies as appropriate. The IRB actions may include:

a) Acknowledgement/acceptance without further recommendation;
b) A request for further clarification from the investigator;
c) Changes in the protocol (e.g., additional test or visits to detect similar events in a timely fashion);
d) Changes in the consent/assent form(s);
e) A requirement to inform subjects already enrolled about additional risks;
f) A change in frequency of continuation review;
g) Further inquiry into other protocols utilizing the particular drug, device, or procedure in question;
h) Suspension or termination of the study; or
i) Request for quality improvement review or other actions deemed appropriate by the IRB.

2. If the IRB acknowledges/accepts without recommendation the internal problem/event, IRB staff generate and send an email and letter to the PI indicating the review outcome.

3. If the committee requests clarification(s) or additional information or revisions, IRB staff notify the PI via email and letter of the need for additional information and/or changes.

4. The PI responds to IRB requests for information or revisions in writing and sends the response to the IRB. IRB staff forward investigator responses to the IRB Chair for further review, who may forward the responses to the entire IRB for additional review, request additional information, or acknowledge/accept the response without recommendation.

5. If the PI has concerns regarding the IRB decision/ recommendations for changes in the study, he/she may submit concerns to the IRB in writing including a justification for changing the IRB decision. The IRB reviews the request and makes a final determination. IRB staff send correspondence to the PI on the IRB's final determination.

**D.** *Submissions/Screening and Review of External Problems/Events: Prompt Report*

An *external event/problem* is one that occurs with research participants enrolled in multi-center research projects that do not fall under the purview of the LU IRB.

1. The PI makes a preliminary determination if the event meets the criteria for an IRB reportable external event or unanticipated problem in accord with the Policy on Prompt Reporting.

2. The PI completes the External Prompt Reporting Form and submits it to the IRB in the time period outlined in this policy.

3. An IRB staff member screens the External Prompt Reporting Form for completeness.

4. IRB staff forward the External Prompt Reporting Form(s), any attached external reports of problems/events, and related material(s) to the IRB Chair or designee. The IRB Chair or designee serves as an expedited reviewer using expedited review procedures. Related material(s) the expedited reviewer may receive include, but are not limited to, documents revised as a result of the problem/event or documents which provide additional assessments or summary information.

5. If the expedited reviewer determines that the unanticipated event is an unanticipated problem involving risks to subjects or others, he/she makes comments on the External Prompt Reporting Form and returns the materials to the IRB. IRB staff schedule review of the unanticipated event(s) by the online or on-campus convened IRB. IRB staff send copies of each External Prompt Reporting Form with the expedited reviewer's comments in the agenda packet to each IRB member.

6. If the expedited reviewer determines it is not an unanticipated problem involving risk to subjects or others, he/she documents his/her review by signing the original report and lists any concerns/recommendations. IRB staff place the original report in the protocol file.

7. IRB staff list the external problem/event on the IRB agenda for a convened online or on-campus meeting. Any IRB member may request to review the entire IRB file and the expedited reviewer's recommendations.

8. IRB staff separate new external problem/event reports submitted at CR from the regular CR materials and process them as outlined in this policy.

**E.** *Review Outcomes*

1. The IRB actions may include:
    a) Acknowledgement/acceptance without further recommendation;
    b) A request for further clarification from the investigator;
    c) Changes in the protocol (e.g., additional tests or visits to detect similar events in a timely fashion);
    d) Changes in the consent form;
    e) A requirement to inform subjects already enrolled about additional risks;
    f) A change in frequency of continuation review;
    g) Further inquiry into other protocols utilizing the particular drug, device, or procedure in question;
    h) Recommendation for full review;
    i) Request for quality improvement program review or other actions deemed appropriate by the IRB; or
    j) Suspension of the study or termination of IRB approval.
        a.

2. If the IRB acknowledges/accepts without recommendation the external unanticipated problem/event, IRB staff generate and send a letter to the PI indicating the review outcome.

3. If the reviewer requests clarification(s) or additional information or revisions, IRB staff notify the PI in writing of the need for additional information and/or changes.

4. The PI responds to those requests for information or revisions in writing and sends the response to the IRB. IRB staff forward those responses to the IRB Chair or designee for further review. The IRB Chair or designee may request additional information, recommend full review, or acknowledge/accept the response without recommendation.

5. The IRB Chair or designee reviews any replies from the investigators on behalf of the committee unless the IRB Chair or designee determines the reply needs further review by the full committee. The IRB Chair or designee documents acknowledgement/acceptance of the report, and IRB staff notify the PI in writing in a timely manner.

6. If the PI has concerns regarding the IRB decision/ recommendations for changes in the study, he/she may submit the concerns to the IRB in writing including a justification for changing the IRB decision. The IRB reviews the request and makes a final determination. IRB staff send correspondence to the PI notifying him/her of the final IRB determination.

**F.** *Reporting of Problems/Events that do not Meet Prompt Reporting Requirements (Non-Prompt Reporting) to the IRB (Required by Sponsors; Not Required by LU IRB)*

1. If a PI recognizes that a problem/event does not meet the prompt reporting requirements, but the sponsor has requested reporting to the IRB, the PI should comply with this recommendation utilizing the LU Adverse Event Reporting Form. The PI includes comments in the report stating why the event does not meet prompt reporting guidelines.

2. Upon receipt of the above form and related materials, IRB staff enter the applicable code in the IRB database to indicate receipt of a Non-Prompt Report. IRB staff then forward the Non-Prompt Report and its attachments to the IRB Chair or designee.

3. If the IRB Chair or designee determines the problem(s)/event(s) should be reported per the prompt reporting requirements, he/she documents this on the PI's materials and returns the materials to IRB. IRB staff notify the PI that the incident falls under the prompt reporting guidelines.

4. If the IRB Chair or designee affirms the problem(s)/event(s) do not meet the prompt reporting requirements, he/she makes a notation on the PI's report to acknowledge receipt and returns the notated report and materials to the IRB.

5. IRB staff enter the applicable code in the IRB database to indicate IRB acknowledgement of the Non-Prompt nature of the report materials. IRB staff generate a letter from the IRB indicating the acknowledgment of the materials received although the problem(s)/event(s) do not meet the LU IRB's prompt reporting requirements.

6. The IRB retains a copy of the materials and IRB acknowledgement letter in the IRB protocol file.

**G.** *Continuation Review Reporting of Problems and/or Adverse Events*

1. If any problems or adverse events occurred within 12 months prior to the continuation review request, the PI provides a written summary of **all** problems/adverse events involving subjects since the study was initiated whether anticipated or unanticipated, serious or not serious, life-threatening or not life-threatening, or related or not related. The summary includes the PI's assessment of whether the problems/events warrant changes in the protocol, consent process, or risk/benefit ratio. The summary includes both a qualitative and quantitative assessment.

2. For policies and procedures for conducting continuation review, see the LU Continuation Review Policy.

**REFERENCES**

21 CFR 56.108(b)
38 CFR 16.103(b)(5)
45 CFR 46.103(b)(5)