

15.0 INVESTIGATORS' REPORTING of UNANTICIPATED PROBLEMS and or ADVERSE EVENTS

15.1 OBJECTIVE

To describe the policies and procedures guiding investigators' prompt reporting of unanticipated problems and or adverse events, reporting of problems/adverse events that do not meet the prompt reporting requirements, and the procedures guiding the review of such reports by the IRB.

15.2 GENERAL DESCRIPTION

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 University officials, and applicable regulatory agencies of any unanticipated problems involving risk to human subjects or others. In response to the regulatory obligation, the HU IRB, in conjunction with the Institutional Biosafety Committee (IBC), utilizes a three-category reporting system to facilitate review of reports and determinations about whether the problem/event raises new concerns about 1) risk to subjects or others; 2) the risk/benefit ratio; 3) the approved informed consent document; and the 4) need for re-consent.

- The HU reporting categories are as follows:
 - Prompt 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 and IBC.
 - Non-Prompt Reporting of anticipated problems/anticipated serious adverse events or unrelated deaths (required by sponsor but not by HU) to the IRB;
 - 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 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 policy on prompt reporting, non-prompt reporting, and CR reporting of problems/events is the basis for the SOPP. The policy details the IRB and IBC requirements for reporting, including adverse events and unanticipated problems involving risks to research subjects and others. In addition to the three categories, there are two broad types of reports, internal and external.

15.3 DEFINITIONS

An *internal event/problem* is one that occurs with research subjects enrolled in a project approved by the HU IRB and directed by an investigator employed by the University or one whose project is under the purview of the HU IRB.

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

See HU Policy on Prompt Reporting for additional definitions.

15.4 RESPONSIBILITY

Execution of SOPP: IRB Chair, IRB, Office of Regulatory Research Compliance (ORRC) Staff, Principal Investigator (PI)/Study Personnel, Institutional Biosafety Committee

15.5 PROCEDURES

HU Basic Reporting Requirements for Prompt Reporting of Problems/Adverse Events.

- The PI reports all problems/adverse events that are serious or life-threatening, AND unanticipated AND which are related to the study procedures, using the applicable HU Reporting Form.
- The PI reports unanticipated life-threatening experiences within 7 calendar days of his/her receipt of the information and all other serious and unanticipated events/problems within 14 calendar days of his/her receipt of the information. Institutional policy requires the investigator to provide follow-up reports on serious or life-threatening and unanticipated and related events within 14 calendar days of his/her receipt of the information.
- The PI reports all deaths related to study procedures occurring during a study using the appropriate HU Internal/External Prompt Reporting Form. Institutional policy requires investigators to report deaths that are related to the study procedures immediately upon investigator receipt of the information (i.e., within 48 hours). The PI includes reports of deaths that are not related to the study procedures (i.e., due to underlying disease progression) in the summary of problems/adverse events submitted at the time of IRB continuation review.
- The IRB and IBC may request more stringent requirements for reporting events for individual research studies if the respective committee determines it to be necessary.

Submissions/Screening and Review of Internal Problems/Events: Prompt Report

- The PI makes the preliminary determination if the event meets the criteria for an IRB reportable internal problem/event in accordance with the HU Policy on Prompt Reporting.

- The PI completes the HU Internal Prompt Reporting Form and submits the form to the ORRC in the time period outlined in the Policy on Prompt Reporting.
- If the PI recognizes the problem/event involves risk to subjects or others and the information is not already in the consent/assent document, he/she submits a revised consent/assent form with changes underlined, if applicable. If the revised 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.
- ORRC staff screen the report to determine whether it is complete, enter the report into the ORRC protocol-tracking database, and place the report on an IRB agenda.
- Staff then forwards the report(s) and related material(s) to the IRB Chair or designee who serves as the primary reviewer.
- The individual serving as primary reviewer receives, at a minimum, the completed HU Prompt Reporting Form. Related material(s) the primary reviewer may receive include, but are not limited to: the complete or relevant portions of the IRB protocol file; documents revised as a result of the problem/event; or documents which provide additional assessments or summary information.
- After reviewing the materials, the primary reviewer makes comments and returns the report to the ORRC.
- ORRC staff uploads copies of each internal reporting form with the IRB reviewer comments in the agenda folder for each IRB member.
- The IRB reviews internal events and problems at a convened IRB meeting using initial full review procedures.
- If the study is federally funded (e.g., by the Department of Health and Human Services), or is regulated by the Food and Drug Administration, additional IRB reporting requirements may be in effect (See the Mandated Reporting to External Agencies SOPP).
- ORRC staff separates new internal reports submitted at CR from the CR materials and process them according to the provisions of this SOPP.

15.5.1 Review Outcome(s)

- For all problems/events submitted under the IRB's prompt reporting policy, the IRB determines whether the problem/event meets the HU definition of unanticipated problem involving risks to subjects or others. If the

unanticipated problem/event involves risk to subjects or others, the IRB follows the established reporting policy (See Mandated Reporting to External Agencies SOPP). The IRB actions may include, but are not limited to:

- Acknowledgement/acceptance without further recommendation;
 - A request for further clarification from the investigator;
 - Changes in the protocol (e.g., additional test or visits to detect similar events in a timely fashion);
 - Changes in the consent/assent form(s);
 - A requirement to inform subjects already enrolled or to re-consent (e.g., when the information may relate to the subject's willingness to continue to take part in the research);
 - A change in frequency of CR;
 - Further inquiry into other protocols utilizing the particular drug, device, or procedure in question;
 - Suspension or termination of the study; or
- If the IRB acknowledges/accepts without recommendation the internal problem/event, ORRC staff generates and sends a notification letter to the PI indicating the review outcome.
 - If the committee requests clarification(s) or additional information or revisions, ORRC staff notifies the PI in writing of the need for additional information and/or changes.
 - The PI responds to IRB requests for information or revisions in writing and sends the response to the ORRC. ORRC 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.
 - 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. ORRC staff sends correspondence to the PI on the IRB's final determination.

15.5.2 Submissions/Screening and Review of External Problems/Events: Prompt Report

- 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 HU Policy on Prompt Reporting.
- The PI completes the HU Reporting Form and submits it to the ORRC in the time period outlined in the Policy on Prompt Reporting.

- ORRC staff screens the External Prompt Reporting Form for completeness.
- ORRC staff forwards 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.
- The expedited reviewer determines that the unanticipated event is an unanticipated problem involving risks to subjects or others, he/she completes the External Prompt Reporting Form and returns the materials to the ORRC. ORRC staff schedule review of the unanticipated event(s) by the convened IRB. ORRC staff sends copies of each External Prompt Reporting Form with the expedited reviewer's comments in the agenda packet to each IRB member.
- If the expedited reviewer determines the event 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. ORRC staff place the original report in the protocol file.
- ORRC staff list the external problem/event on the IRB agenda for a convened meeting. Any IRB member may request to review the entire IRB file and the expedited reviewer's recommendations.
- ORRC staff separates new external problem/event reports submitted at CR from the CR materials and process them as outlined in this SOPP.

15.5.3 Review Outcomes

- The IRB actions may include, but are not limited to:
 - Acknowledgement/acceptance without further recommendation;
 - A request for further clarification from the investigator;
 - Changes in the protocol (e.g., additional tests or visits to detect similar events in a timely fashion);
 - Changes in the consent/assent form(s);
 - A requirement to inform subjects already enrolled or to re-consent (e.g., when the information may relate to the subject's willingness to continue to take part in the research);
 - A change in frequency of CR;
 - Further inquiry into other protocols utilizing the particular drug, device, or procedure in question;
 - Recommendation for full review; or
 - Suspension of the study or termination of IRB approval.

- If the IRB acknowledges/accepts without recommendation the external unanticipated problem/event, ORRC staff generates and send a notification letter to the PI indicating the review outcome.
- If the reviewer requests clarification(s) or additional information or revisions, ORRC staff notifies the PI in writing of the need for additional information and/or changes.
- The PI responds to those requests for information or revisions in writing and sends the response to the ORRC. ORRC staff forwards 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.
- 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 ORRC staff notify the PI in writing in a timely manner.
- 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. ORRC staff sends correspondence to the PI notifying him/her of the final IRB determination.

15.5.4 Reporting of Problems/Events that do not Meet Prompt Reporting Requirements (Non-Prompt Reporting) to the IRB (Required by Sponsors, Not Required by the HU IRB)

- 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 may refer the sponsor to the IRB's letter describing the HU IRB Policy on Problems/Adverse Events That Require Prompt Reporting to the IRB (available on the ORRC website). Investigators may submit this letter to sponsors in response to a sponsor request for event submissions that do not meet the prompt reporting requirements.
- If the sponsor requires additional IRB documentation for submission of reports to the IRB of events which do not meet the HU IRB's prompt reporting requirements, the PI may submit these events to the IRB using the cover form for Problems/Adverse Events Non-Prompt Reporting (hereafter referred to as Non-Prompt Report). PIs submit two copies of the Non-Prompt Report and attachments to the ORRC, as described in the cover form.

- Upon receipt of Non-Prompt Report materials, ORRC staff enters the applicable code in the ORRC database to indicate receipt of a Non-Prompt Report. ORRC staff then forward the Non-Prompt Report and its attachments to the IRB Chair or designee.
- If the IRB Chair or designee determines that the PI should report the problem(s)/event(s) per the prompt reporting requirements, he/she documents this on the Non-Prompt Report materials and returns the materials to the ORRC. ORRC staff notifies the PI of the requirement to submit the Internal/External Prompt Reporting Form.
- 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 Non-Prompt Report to acknowledge receipt and returns the notated Non-Prompt Report and materials to the ORRC.
- ORRC staff enters the applicable code in the ORRC database to indicate IRB acknowledgement of the Non-Prompt Report materials. ORRC staff generates a notification letter from the IRB acknowledging the materials received although the problem(s)/event(s) does not meet the HU IRB's prompt reporting requirements.
- The ORRC retains a copy of the Non-Prompt Report materials and IRB acknowledgement letter in the IRB protocol file.

15.5.5 Continuation Review Reporting of Problems and/or Adverse Events

- If any problems or adverse events occurred within 12 months prior to the CR 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 (For policies and procedures for conducting CR, see the Continuation Review SOPP).

15.5.6 Gene Transfer/Gene Therapy Protocols

- For gene transfer/therapy clinical trials, the PI also reports to the National Institutes of Health (NIH) internal/external problem(s)/event(s) which fall under the HU IRB/IBC prompt reporting requirements.
- The PI may use the HU Internal Prompt Reporting Form, which contains all the components NIH requests in its reporting requirements.

15.6 REFERENCES

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