

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>			
<b>Revision #9</b>	<b>TITLE: Unanticipated/Anticipated Problem/Adverse Event Reporting (UK)</b>		<b>Page 1 of 8</b>
Approved By: ORI Director	Signature	Date	Date First Effective: 05-30-05
Approved By: Nonmedical IRB Chair	Signature	Date	
Approved By: Medical IRB Chair	Signature	Date	Revision Date: 03/02/2016

## **OBJECTIVE**

To describe the policies and procedures for prompt investigator reporting of unanticipated problems or adverse events, investigator reporting of problems/adverse events that do not meet the prompt reporting requirements, and the procedures for Institutional Review Board (IRB) review of investigator reports for University of Kentucky (UK) studies

## **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 risks to human subjects or others. In response to the regulatory obligation, the UK 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) risks to subjects or others; 2) the risk/benefit ratio; 3) the approved informed consent document; and the 4) need for re-consent.

The UK reporting categories are as follows:

1. Prompt Reporting to the IRB/IBC of an unanticipated problem involving risks to subjects or others or research-related deaths to the IRB and IBC;
2. Non-Prompt Reporting to the IRB/IBC of anticipated problems/anticipated serious adverse events or unrelated deaths (required by sponsor but not by UK);
3. Continuation Review Reporting to the IRB/IBC includes a written summary of both unanticipated problems and available information regarding adverse events since the last IRB review. The summary must include the PI's assessment of whether the problems/adverse events warrant changes to the protocol, consent process, or risk/benefit ratio. For multisite

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>		
<b>Revision #9</b>	<b>TITLE: Unanticipated/Anticipated Problem/Adverse Event Reporting (UK)</b>	<b>Page 2 of 8</b>

studies, the written summary should describe external events determined to be unanticipated problems involving risks to subjects.

The policy on prompt reporting, non-prompt reporting, and continuation review reporting of problems/events is the basis for the SOP. 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.

### *Definitions*

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

See [UK IRB Policy on Unanticipated Problem and Safety Reporting](#) for additional definitions.

### **RESPONSIBILITY**

Execution of SOP: IRB Chair, IRB, Office of Research Integrity (ORI) Staff, Principal Investigator (PI)/Study Personnel, Institutional Biosafety Committee

### **PROCEDURES**

#### *UK Reporting Requirements for Prompt Reporting of Problems/Adverse Events*

1. The PI reports unanticipated problems involving risks to subjects or others and research-related deaths using the UK Internal *or* External Prompt Reporting Form. Unanticipated problems involving risks to subjects or others are problems/adverse events which are unexpected AND related to the study procedures AND 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. For multi-site studies, the PI reports external events determined to be unanticipated problems involving risks to subjects or others AND research-related deaths using the UK External Prompt Reporting Form.
2. The PI reports unanticipated life-threatening events and unanticipated adverse device effects (UADE) within 7 calendar days of his/her receipt of the information and all other

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>		
<b>Revision #9</b>	<b>TITLE: Unanticipated/Anticipated Problem/Adverse Event Reporting (UK)</b>	<b>Page 3 of 8</b>

unanticipated problems involving risks to subjects or others within 14 calendar days of his/her receipt of the information. Institutional policy requires the investigator to provide follow-up reports on life-threatening events within 14 calendar days of his/her receipt of the information.

3. The PI reports all deaths related to study procedures occurring during a study using the appropriate UK 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).
4. 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*

1. The PI makes the preliminary determination if the event meets the criteria for an IRB reportable internal problem/event in accordance with the UK Policy on Unanticipated Problem and Safety Reporting.
2. The PI completes the UK Internal Prompt Reporting Form and submits the form to the ORI in the time period outlined in the IRB Policy on Unanticipated Problem and Safety Reporting.
3. If the PI recognizes the problem/event involves risks 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 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.
4. ORI staff screen the report to determine whether it is complete, enter the report into the ORI database, and place the report on an IRB agenda.
5. Staff then forward the report(s) and related material(s) to the IRB Chair or designee who serves as the primary reviewer.
6. The individual serving as primary reviewer receives, at a minimum, the completed UK 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.

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>		
<b>Revision #9</b>	<b>TITLE: Unanticipated/Anticipated Problem/Adverse Event Reporting (UK)</b>	<b>Page 4 of 8</b>

7. After reviewing the materials, the primary reviewer makes comments and returns the report to the ORI.
8. ORI staff send copies of each internal reporting form with the IRB reviewer comments in the agenda packet to each IRB member.
9. The IRB reviews internal events and problems at a convened IRB meeting using initial full review procedures.
10. 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 SOP.)
11. ORI staff separate new internal reports submitted at CR from the CR materials and process them according to the provisions of this SOP.

*Review Outcome(s)*

1. For all problems/events submitted under the IRB's prompt reporting policy, the IRB determines whether the problem/event meets the UK definition of unanticipated problem involving risks to subjects or others. If the unanticipated problem/event involves risks to subjects or others, the IRB follows the established reporting policy. (See Mandated Reporting to External Agencies SOP.) 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 continuation review;
  - Further inquiry into other protocols utilizing the particular drug, device, or procedure in question;
  - Suspension or termination of the study; or
  - Request for quality improvement review or other actions deemed appropriate by the IRB.

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>		
<b>Revision #9</b>	<b>TITLE: Unanticipated/Anticipated Problem/Adverse Event Reporting (UK)</b>	<b>Page 5 of 8</b>

2. If the IRB acknowledges/accepts without recommendation the internal problem/event, ORI staff generate and send a letter to the PI indicating the review outcome.
3. If the committee requests clarification(s) or additional information or revisions, ORI staff notify the PI in writing 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 ORI. ORI 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. ORI staff send correspondence to the PI on the IRB's final determination.

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

1. The PI makes a preliminary determination whether the external event meets the criteria for an unanticipated problem involving risks to subjects or others in accord with the [UK Policy on Unanticipated Problem and Safety Reporting](#).
2. The PI completes the UK External Prompt Reporting Form and submits it to the ORI in the time period outlined in the [UK Policy on Unanticipated Problem and Safety Reporting](#).
3. ORI staff screen the External Prompt Reporting Form for completeness.
4. ORI 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 completes the External Prompt Reporting Form and returns the materials to the ORI. ORI staff schedule review of the unanticipated event(s) by the convened IRB. ORI staff send copies of each External Prompt Reporting Form with the expedited reviewer's comments in the agenda packet to each IRB member.

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>		
<b>Revision #9</b>	<b>TITLE: Unanticipated/Anticipated Problem/Adverse Event Reporting (UK)</b>	<b>Page 6 of 8</b>

6. If the expedited reviewer determines the event is not an unanticipated problem involving risks to subjects or others, he/she documents his/her review by signing the original report and lists any concerns/recommendations. ORI staff place the original report in the protocol file.
7. ORI 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.
8. ORI staff separate new external problem/event reports submitted at CR from the CR materials and process them as outlined in this SOP.

#### *Review Outcomes*

1. 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 continuation review;
  - Further inquiry into other protocols utilizing the particular drug, device, or procedure in question;
  - Recommendation for full review;
  - Request for quality improvement program review or other actions deemed appropriate by the IRB; or
  - Suspension of the study or termination of IRB approval.
2. If the IRB acknowledges/accepts without recommendation the external unanticipated problem/event, ORI 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, ORI 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 ORI. ORI staff forward those responses to the IRB Chair or designee for

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>		
<b>Revision #9</b>	<b>TITLE: Unanticipated/Anticipated Problem/Adverse Event Reporting (UK)</b>	<b>Page 7 of 8</b>

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 ORI 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. ORI staff send correspondence to the PI notifying him/her of the final IRB determination.

*Reporting of Problems/Events that do not Meet Prompt Reporting Requirements (Non-Prompt Reporting) to the IRB (required by Sponsors, not required by the UK IRB)*

1. If the sponsor requires IRB documentation for submission of reports to the IRB of events which do not meet the UK IRB's prompt reporting requirements, the PI may submit these events to the IRB using the *IRB Cover Form for Non-Prompt Reporting of Problems/Adverse Events*. The PI submits two copies of the Non-Prompt Cover Form and attachments to the ORI, as described in the cover form.
2. Upon receipt of Non-Prompt Report materials, ORI staff enter the applicable code in the ORI database to indicate receipt of a Non-Prompt Report. ORI staff then forward the Non-Prompt Report and its attachments to the IRB Chair or designee.
3. 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 ORI. ORI staff notify the PI of the requirement to submit the Internal/External Prompt Reporting Form.
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 Non-Prompt Report to acknowledge receipt and returns the notated Non-Prompt Report and materials to the ORI.
5. ORI staff enter the applicable code in the ORI database to indicate IRB acknowledgement of the Non-Prompt Report materials. ORI staff generate a letter from the IRB acknowledging the materials received although the problem(s)/event(s) does not meet the UK IRB's prompt reporting requirements.

<b>University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures</b>		
<b>Revision #9</b>	<b>TITLE: Unanticipated/Anticipated Problem/Adverse Event Reporting (UK)</b>	<b>Page 8 of 8</b>

6. The ORI retains a copy of the Non-Prompt Report materials and IRB acknowledgement letter in the IRB protocol file.

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

1. At Continuation Review, the PI submits a written summary of both unanticipated problems and available information regarding adverse events since the last initial or continuing IRB review. For multisite studies, the written summary should describe external events determined to be unanticipated problems involving risks to subjects. The summary must include the PI's assessment whether the problems/adverse events warrant changes for the protocol, consent process, or risk/benefit ratio. (For policies and procedures for conducting continuation review, see the Continuation Review SOP.)

*Gene Transfer/Gene Therapy Protocols*

1. 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 UK IRB/IBC prompt reporting requirements.
2. The PI may use the UK Internal Prompt Reporting Form, which contains all the components NIH requests in its reporting requirements.

**REFERENCES**

- [21 CFR 56.108\(b\)](#)  
[45 CFR 46.103\(b\)\(5\)](#)