There are certain events that the principal investigator or designee must report to the University of Louisville Institutional Review Board (IRB).

**TYPES OF EVENTS**

1) **Adverse event (AE):** An AE is 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. The PI should consider the following details of the AE to determine if it's reportable:

   - **Local or External:** A local event is an event experienced by subjects enrolled by the investigator at his or her institution, where as an external event is an event experienced by subjects enrolled by investigators at other institutions engaged in a multi-center clinical trial.

   - **Expected or Unexpected:** An unexpected event is any AE in which the nature, severity, or frequency is not consistent with either the risks of the research described in the research documentation (e.g. protocol, informed consent form, investigator’s brochures, etc.) or any other relevant sources of information such as product labeling or package inserts, OR the event is not consistent with the natural progression of any underlying condition of the subject(s) experiencing the event (modified from 21 CF 312.32(a)). An expected event is an AE not meeting the above criteria.

   - **Serious Adverse Event (SAE):** Any adverse event temporally associated with the subject’s participation in the research and meets any of the following criteria:
     - Results in death
     - Is life-threatening (places the subject at immediate risk of death)
     - Requires inpatient hospitalization or prolongs hospitalization
     - Results in a persistent or significant disability/incapacity
     - Results in a congenital anomaly/birth defect; or
     - Any other adverse event that may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed above

   - **Relationship:** The following should be used to assess AE relationship to study participation. If there is any uncertainty regarding AE causality, then the event must be assessed as possibly related to research participation and reported to the IRB as indicated.
     - **Definitely related:** The event was caused by study participation, and an alternative cause is unlikely
     - **Probably related:** There is a reasonable possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.
     - **Possibly Related:** An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.
     - **Unrelated:** The cause of the AE is known and the event is in no way related to any aspect of study participation. Often, the cause of an unrelated AE is disease progression.
2) **Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO):** Any incident, experience, or outcome that meets all of the following criteria:

   a. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures and (b) the characteristics of the subject population being studied;
   b. Related or possibly related to a subject’s participation in the research; and
   c. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

UPIRTSO events must be reported regardless of whether they occur during the study, after study completion, or after participant withdrawal or completion. If the study has been closed with the IRB, please notify the IRB via email at hspoffc@louisville.edu.

An event that is determined to be a UPIRTSO must be reported to appropriate entities under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). Additional regulatory requirements for reporting unanticipated problems involving risks to subjects and others may be found in 45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1).

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:

The diagram illustrates three key points:

1. The majority of AEs occurring in human subjects are not unanticipated problems (area A).
2. A small proportion of adverse events are unanticipated problems (area B).
3. Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).

[OHRP Guidance on Reviewing and Reporting UPIRTSOs](#)
3) Deviations, Violations, Misc. Event Reporting:

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator’s control and that has not been approved by the IRB. Any change that adversely affects the risk/benefit ratio of the study; the subject's rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data constitutes a major violation. In the PI’s judgement, if the event DOES NOT adversely affect: the risk/benefit ratio of the study; the rights safety, or welfare of the participants or others; or the integrity of the study, it is considered a minor violation.

**MAJOR VIOLATIONS** *(the list of examples is intended as a guide, is not all-inclusive, and can vary depending on specific scenarios and circumstances):*

1. Failure to obtain informed consent or research authorization, i.e., there is no documentation of informed consent/research authorization or Informed consent/research authorization obtained after initiation of study procedures
2. Inappropriate documentation of informed consent/research authorization, including missing subject signature, missing signature of person who obtained informed consent
3. deviation has harmed or posed a significant or substantive risk of harm to the research subject.
   a. subject received the wrong treatment or incorrect dose.
   b. subject met withdrawal criteria during the study but was not withdrawn.
   c. subject received an excluded concomitant medication.
4. deviation compromises the scientific integrity of the data collected for the study.
   a. subject was enrolled but does not meet the protocol’s eligibility criteria.
   b. Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes. (if it involves patient safety it meets 4)a. above)
   c. Inadvertent loss of samples or data.
5. Enrollment of a subject who did not meet all inclusion/exclusion criteria
6. Performing study procedure not approved by the IRB or changing the protocol without IRB approval
7. Failure to report an unanticipated problem or serious adverse event to the IRB and/or sponsor
8. Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity
9. Study visit conducted outside of required timeframe that, in the opinion of the PI, may affect subject safety
10. Enrollment of subjects after IRB-approval of study expired or failure to submit continuation review
11. Use of invalid consent form, i.e. consent form without IRB approval stamp or expired.
MINOR VIOLATIONS (Reportable at Continuation Review) (the list of examples is intended as a guide, is not all-inclusive, and can vary depending on specific scenarios and circumstances):

1. Missing original signed and dated consent form/research authorization (only a photocopy available)
2. Missing pages of executed consent form/research authorization
3. Copy not given to the person signing the form/research authorization
4. Someone other than the subject dated the consent form/research authorization
5. Failure to follow the approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity
6. Failure to perform a required lab test
7. Missing lab results
8. Study visit conducted outside of required time frame
9. Failure of subject to return study medication
10. Over-enrollment.
### Reporting Events to the IRB

<table>
<thead>
<tr>
<th>Local Adverse Events</th>
<th>When to Report</th>
<th>iRIS Form</th>
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</thead>
<tbody>
<tr>
<td>Local Adverse Event PI determines to be:</td>
<td>Report within 5 working days of UofL site awareness</td>
<td>Complete the Serious Adverse Event (SAE) Reporting Form within the iRIS system</td>
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<tr>
<td>• Definitely, Probably, or Possibly related to the research intervention,</td>
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<td>• Serious, and</td>
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<td>• Unexpected</td>
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<tr>
<th>Unanticipated Problems (UPIRTSOs)</th>
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<tr>
<td>Local Event PI determines to be:</td>
<td>Report within 5 working days of UofL site awareness</td>
<td>Complete the UPIRTSO Reporting Form within the iRIS system</td>
</tr>
<tr>
<td>• unexpected (in terms of nature, severity, or frequency), and</td>
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<th>Deviations/Violations/Misc.</th>
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<tr>
<td>Major Deviations/Violations/Misc.</td>
<td>Report within 5 working days of UofL site awareness</td>
<td>Complete the Deviation/Violation/Misc. form in iRIS. Attach notification of deviation to the study sponsor (if applicable) in iRIS</td>
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<tr>
<td>• The PI and/or study sponsor is responsible for determining if a deviation is major or minor</td>
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<tr>
<td>• Note: Intentional deviation from the inclusion/exclusion criteria should be submitted prospectively and include a copy of the sponsor’s approval.</td>
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<tr>
<td>• The PI and/or study sponsor is responsible for determining if a deviation is major or minor</td>
<td>Report with the next continuation review application</td>
<td>Attach documentation with the continuation review application:</td>
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<td>These can be combined on one document (e.g. an excel file)</td>
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<th>External Safety Reports</th>
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<tr>
<td>The majority of IND Safety Reports, MedWatch Reports do not need to be reported to the UofL IRB. The only reports that must be reported are those that reveal an unanticipated problem involving risks to participants and others.</td>
<td>Not Required</td>
<td>Other-Amendment</td>
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</table>

We understand that some sponsors require submission of all reports to the board regardless of the nature of the event reported. If you are submitting to fulfill such a requirement, please indicate this in your submission.
ADDITIONAL EXAMPLES OF EVENTS THAT REQUIRE REPORTING TO THE IRB:

a) Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm.
b) Any accidental or unintentional change to the IRB approved research protocol or plan that involved risks or has the potential to recur.
c) Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research.
d) Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff.
e) Any non-compliance or continuing non-compliance.
f) Any other event appropriate to the local context.

VIOLATIONS OF THIS POLICY

Any principal investigator who conducts research under the auspices of the University of Louisville IRBs must adhere to this policy. The University’s IRBs must follow this policy. Failure of investigators to report problems as required by this policy could result in a range of penalties. These penalties are outlined in the University’s Administrative Sanctions for Violations of University of Louisville Research Policies found at: [http://louisville.edu/research/integrity/administrative-sanctions-for-violations-of-university-of-louisville-research-policies-pdf].

IRB REPORT OF FINDINGS

HSPPO staff will follow the University of Louisville IRB Report of Findings policy for reporting unanticipated problems involving risks to subjects or others to the Executive Vice President for Research and Innovation. This policy is located on the HSPPO website at [http://louisville.edu/research/humansubjects/policies/policies/report-of-findings].