ADVERSE EVENT REPORTING

PURPOSE AND SCOPE

This SOP describes the procedures study personnel will use to fulfill the regulatory and ethical responsibilities to identify and report adverse events.

APPLICABLE REGULATIONS AND UC POLICIES

21 CFR 312
Policy II.02 Reporting Unanticipated Problems
IRB Guidebook

DEFINITIONS

Adverse Event: An adverse event (“AE”) is “any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research”. The event is undesirable and has an unintended outcome, but is not necessarily unexpected. The event may have been described in the informed consent as a risk of the study. Adverse events include abnormal laboratory findings, a symptom, or disease temporally associated with the use of an investigational agent, or the progression of disease, whether or not related to the medicinal (investigational) product.

Serious Adverse Event: A serious adverse event (“SAE”) includes:

- The death of a study subject, whether related to an investigational agent or not related
- A reaction which, in the opinion of the investigator, threatens the study subject with risk of death
- A disability or incapacity which, in the opinion of the investigator, causes substantial disruption of a study subject's ability to conduct normal life functions
- Hospitalization or extension of an existing hospitalization (excluding elective hospitalization for conditions unrelated to the study)
- A birth defect in an offspring of a study participant, regardless of the time after the study the congenital defect is diagnosed
- Any intervention required to prevent one of the above outcomes

Note: drug overdose and cancer have been removed from the list of adverse events that are characterized as SERIOUS (unless the overdose or cancer meets the above criteria).
Related Adverse Event: - The adverse event could have been caused by any drug given to a subject as part of the study, a device used in the study, or a procedure that is carried out as part of the study. The term “adverse drug reaction” (ADR) is also used if the AE or SAE is related to the investigational product.

Unexpected Adverse Event: -the adverse event is not an anticipated event for the study drug, device, or procedure and is not explained in the Informed Consent Statement that the study subject signed.

Imminent Threat of an AE in Research – Any situation in which an AE in research has not yet occurred but is very likely to occur without preventative measures (VA term).

Unexpected Death: The death of a research participant in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention definitely, probably or possibly hastened the participant’s death. A participant’s death that is determined to be clearly not associated with the research is also not an “unexpected death” for purposes of the reporting requirements of these procedures.

Reportable Adverse Event – A reportable adverse event is any adverse event that meets the reporting requirements of Institutional Policy II.02 Reporting Unanticipated Problems and SOP # 3-1 Promptly Reportable Events. All other adverse events must be evaluated in accordance with the protocol’s data and safety monitoring plan.

Relatedness to the Event

Related: Associated of having a timely relationship with the study agent or procedures; a reasonable possibility exists that an outcome may have been caused or influenced by the study in question (e.g., administration of a study drug), although an alternative cause/influence may also be present. Related events may be definitely, probably, or possibly related.

Unrelated: Unassociated or without a timely relationship to the study agent or procedures; evidence exists that an outcome is definitely related to a cause other than the event in question (e.g., underlying disease, environment).

Location

Internal Event: An event occurring in research at University of Cincinnati (UC), sites affiliated with UC or at a site(s) under an UC IRB’s jurisdiction.

External Event: An event occurring in research at a site(s) other than UC, over which another (non-UC) IRB has jurisdiction.
Review of safety information - The sponsor or investigator-sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the FDA.

PERSONS RESPONSIBLE

Research personnel in contact with subjects must be aware of their responsibility to note and report to appropriate study personnel all adverse events directly observed or reported by the study subject.

**Principal Investigator.** The Principal Investigator is responsible and accountable for:

- assuring that the procedures for the clinical management of adverse events are carried out.
- making the final decision regarding (a) attribution of the adverse event to study treatment and (b) clinical management of the participant.
- assuring that the AE/SAEs are reported to the sponsor (and to the FDA if the study is investigator initiated), to the IRB, and to the Data Safety Monitoring Board, if applicable.
- assuring that the IND Safety Report information is reported to the sub-investigators on the trial.

The PI may delegate responsibilities to another qualified researcher involved in the study, but may not delegate accountability.

**Clinical Research Coordinator/Clinical Research Nurse** - The Clinical Research Coordinator/Clinical Research Nurse is responsible for:

- screening for adverse events on an ongoing basis using patient-reported history, physical examination, laboratory data, chart review and other available data for each patient enrolled in a clinical trial
- informing the Principal Investigator about the procedures mandated in the protocol for the clinical management of adverse events. He/She should also attempt to judge the possible cause or relationship of the AE to the investigational product and document this relationship.

**Regulatory Manager (If these positions exist, describe the responsibilities for each)**

**Data Manager**
PROCEDURES

1. The participant should be assessed at each visit, or study assessment, for AEs that may have occurred since the previous visit or assessment, insuring that the following are appropriately investigated:

   - Spontaneous reports of adverse events by subjects
   - Observations of adverse events by clinical research staff
   - Reports by family members or medical care providers
   - Events documented in medical records or progress notes that may be AEs
   - Reports of the death of a participant during the protocol-defined follow-up period, whether considered treatment-related or not

2. (Optional section for those studies where the protocol requires a toxicity grade) A toxicity grade should be assigned using the grading scale described in the protocol (if present). If a toxicity grading scale is not provided, grades 1, 2, 3, 4, are used for mild, moderate, severe and life-threatening, respectively. Grades 3 and 4 events should be reported to the Principal Investigator or sub investigator within 24 hours of site awareness. All new and unexplained grades 3 and 4 laboratory toxicities should be repeated within one week to exclude the possibility of error.

3. All appropriate resources will be directed toward insuring the participant’s safety and well-being. (Optional section for those studies where the protocol requires a toxicity grade: Clinical management of adverse events will follow the toxicity guidelines outlined in the protocol unless contraindicated).

4. If necessary for the immediate medical care of the participant, the Principal Investigator may elect to break the drug blind after consultation with the sponsor. Therapeutic intervention measures will be taken as outlined in the protocol. The subject should have clinical assessments (frequency to be determined by the primary investigator unless dictated by protocol) until the AE has stabilized or resolved.

5. If the adverse event is serious and unexpected, the sponsor should be informed as soon as possible after the occurrence of the event becomes known to study staff and when the participant has stabilized (whether the AE is considered drug-related or not) so that the sponsor can fulfill its reporting obligations to the FDA. The sponsor should be updated as information on the AE becomes available. If applicable, the form provided by the sponsor should be completed. As much of the following information as possible should be provided:

   - Protocol name and number
   - Possible test articles: investigational product, comparator, or placebo
   - Lot number and expiration date
• Study subject number/identification
• Demographic data
• Nature of the event
• Severity of the event (may be clarified in the protocol)
• Probable relationship of the AE to the investigational product
• Date (and time) of AE onset
• Date (and time) of AE resolution, if available
• Dose, frequency, and route of administration of the investigational product
• Start and stop dates of test article administration
• Concomitant medications and therapies
• Clinical assessment of the subject at this time
• Results of any laboratory and/or diagnostic procedures, treatments, autopsy findings
• Follow-up plan
• Outcome

6. If the study is investigator initiated, and no other SAE form has been identified, the Med Watch Form should be completed and forwarded to the FDA (FDA Form 3500 available at http://www.fda.gov/opacom/morechoices/fdaforms/ceder.html). If the PI has sites other than UC sites, the Med Watch Form should be complete and forwarded to the FDA for SAEs at each site.

7. If the AE results in the subject’s death an autopsy report or death certificate should be obtained, if required by the protocol.

8. Source documentation must be completed, as appropriate. The appropriate case report form must be completed for collection of adverse event information, and copies of all reports should be maintained in the participant’s file and the regulatory files.

9. All deaths or serious, unexpected and possibly study drug related events, which occur at the UC site, must be reported to the IRB using either the IRB form or the sponsor’s form, so long as the sponsor’s form contains all the information required by the IRB. The IRB Event form is available on the University of Cincinnati IRB website. The completed Event Reporting Form and a copy of the IND Safety Report (and 3 copies of the revised ICF, if applicable) should be submitted to the IRB within ten (10) days of receipt of the report from the sponsor or within 48 hours of the onset of the event or the site’s having been made aware of the event.

10. If the adverse event occurs at a site other than the UC site, the sponsor should forward an IND Safety Report to each site using the investigational agent. Receipt of expedited safety reports from the sponsor should be acknowledged by letter or fax
from the site and signed by the Principal Investigator. IND safety reports and any correspondence with the IRB should be kept in the regulatory file with the Investigator’s Brochure (if applicable). These expedited IND Safety Reports are to be submitted to the UC IRB when required by Institutional Policy II.02 and SOP # 3-1 on Promptly Reportable Events.

11. If the PI, the sponsor or the IRB determines that a change is required to the informed consent statement, the revised consent form should be submitted to the IRB as soon as reasonably possible.

12. If further action is required by the IRB, the sponsor should be informed.

13. A summary of all adverse events (both serious and non-serious) must be reported to the IRB as part of continuing review.