PROMPTLY REPORTABLE EVENTS

PURPOSE AND SCOPE

To define the structure and responsibility for reporting unanticipated problems that occurs during the conduct of research.

APPLICABLE REGULATIONS

Policy II.02 *Unanticipated Problems*
45 CFR 46.103 (b)(5)
21 CFR 56.108 (b)
21 CFR 56 312.64

DEFINITIONS

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Types of Study Events

1. **Unanticipated problem involving risk to subjects or others**: Any problems which were not contemplated when the research was approved and which present risk of serious harm to subjects or to others, including the research team, the university community, or the broader community. Unanticipated problems (UPs) are always related to an approved study, either ongoing or closed.

Examples of Unanticipated Problems that present the risk of serious harm to participants and must be reported to the IRB are:

- subpoena to the PI for sensitive participant data;
- the arrest of a PI on a felony charge;
- the pregnancy of a participant in a study of an unapproved drug;
- the loss of copies of participant data carelessly left somewhere outside the study site;
- the results of data safety monitoring of the investigational agent showing an unexpected toxicity that puts other participants at risk.

2. Adverse Events: "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.

3. Protocol Deviations –

Significant Deviations Any unapproved deviation from the protocol that significantly affects the safety of the subject, the scientific quality of the study, or the safety of researchers. Protocol deviations can include deviations from eligibility criteria, from the manner of completing pretreatment procedures, in using an incorrect form for obtaining informed consent or failing to reconsent a participant when required by the IRB, in administering study treatments, complications from study procedures, or failures of safety monitoring.

Non-Significant Deviation – A non-significant deviation is highly unlikely to have any impact on the safety of the subject or the scientific integrity of the study. A Non-significant deviation will typically not impact the data collected to answer the main hypothesis of the study. A Non-Significant Deviation may become a Significant Deviation if it occurs in a significant number of subjects.

Subject Non-Compliance – Subject non-compliance occurs when, despite the best efforts of the research staff, the subject fails to follow the protocol. Note that failure of the research staff should not be classified as Subject Non-Compliance (ex. the subject did not complete a six-month telephone follow-up because a staff member forgot to call). Also note that Subject Non-Compliance may become a Significant Deviation if it occurs in a significant number of subjects. Subject Non-Compliance may also be considered a Safety Violation (ex. the subject takes medication that is contraindicated by the study drug).

4. Complaints - an expression of dissatisfaction or concern about safety, privacy or protection of a subject regarding human subject research.

- Minor complaint – a complaint that alleges an inconvenience to human participants but does not result in an unanticipated problem or serious adverse event or increase in risk. Examples are questions about the amount of participant payment; no close parking available; study personnel were rude; incorrect form was used.

- Major complaint – a complaint that alleges that human participants are being put at risk or increased risk compared with what is described in the consent form. Examples are PI not allowing enough time for the consent process; PI not following inclusion/exclusion criteria; failure to follow protocol; failure to report unanticipated problems or SAEs; participant feels like their rights have been violated; PI not complying with HRC policies or federal regulations; a series of minor complaints.

Additional terms relevant to this policy

Relatedness

- **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: 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: An event occurring in research at a site(s) other than UC, over which another (non-UC) IRB has jurisdiction.

Reporting Events to the IRB

All reports to the IRB of unanticipated problems should explain clearly why the event is

"unanticipated" and clearly explain why the event represents a "problem involving risks to human subjects or others."

The UC IRB expects reports to the IRB of unanticipated problems to include a corrective action plan to address the issue, or written justification for why none was provided.

FDA guidance documents recognize that:

1. individual adverse event reports generally require an evaluation of their relevance and significance to the study, including an evaluation of other adverse events, before they can be considered to be an unanticipated problem," and

All reports to the IRB of unanticipated problems should explain clearly whey the event described represents a 'problem' for the study and why it is 'unanticipated'."

The FDA believes that reports that lack such evaluation should not be provided to the IRB.

Events Requiring Prompt Reporting

The following events may represent unanticipated problems involving risks to participants and others and should be promptly reported:

- Internal adverse events that are serious, unexpected and related;
- Adverse device effects that are unanticipated
- Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures) involving safety or integrity risks or with the potential to reoccur;
- Events requiring prompt reporting according to the protocol sponsor;
- Complaints made by research participants indicating an unanticipated event, or complaints that cannot be resolved by the research staff.
- Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant;
- Data and Safey Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports/recommendations altering the risks/benefit profile;
- New information indicating an unexpected change in risks or potential benefits (e.g., literature/scientific reports or other published findings);
- Investigator's Brochure (IB or IDB) updates or revisions to safety information; and
- Other problem or finding (e.g., breach of confidentiality, loss of study data or forms, etc.) that an Investigator or research staff member believes could influence the safe conduct of the research.

Timeframe for reporting

The events described as requiring prompt reporting above should be reported to the IRB using the Event Reporting Form **within 10 days** of the research staff member's learning of the event.

Events resulting in temporary or permanent interruption of the study activities by the Investigator or sponsor to avoid potential harm to participants should be reported immediately (**within 48 hours**).

All internal and external events that may represent unanticipated problems involving risks to subjects or others should be promptly reported (as above), regardless of whether they occur during or after the study, or to a subject who has withdrawn from or completed study participation. If changes to the research or consent process are proposed as a result of the event, or if additional information will be provided to current and/or past participants, a modification request must be submitted for IRB review.

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. When an Unanticipated Problem occurs, the principal investigator should determine if that the problem involves risk to subject or others and if related to participation in the study.

2. The investigator should complete and submit the Unanticipated Problems Report indicating if the event is related to the study.

3. Although the PI makes the initial determination of the event, this determination is subject to review **by the Sponsor** and the IRB. It will be processed by the IRB in accordance with Institutional Research Policy II.02.

4. When an Unanticipated Problem occurs, the principal investigator (PI) must do the following:

    a. Report in writing within ten (10) working days of the date the researcher becomes aware of the problem. If the unanticipated problem poses an immediate threat to the participant or others, report to the IRB within (1) business day by telephone or email with a follow-up in writing.

    b. Complete and submit the Unanticipated Problems Report Form Events or a written report and any corroborating reports to the IRB.

    d. Inform, in writing the appropriate research team members, pharmacist, support staff, administrative officials, funding or sponsoring agencies if applicable of the unanticipated problem.

REPORTABLE INFORMATION (other than UPs)

Protocol Deviations

1. **The principal investigator shall notify the sponsor, and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.**

2. **Such notice shall be given as soon as possible, but in no event later than 10 working days after the emergency occurred. The IRB deviation form may be completed for this reporting.**

3. **Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety or welfare of human subject, approval from FDA and the IRB must also be obtained.**

Complaint

1. **Any complaint that is unresolved by the research team, or that indicates increased or unexpected risks will be reported to the Sponsor and the IRB.**

Incarceration

1. **The IRB and the Sponsor must be notified when a participant is incarcerated. .**

PRINCIPAL INVESTIGATOR (OR FACULTY ADVISOR):
UC IRB PROTOCOL NUMBER:

EVENT REPORTING FORM FOR UNANTICIPATED PROBLEMS INVOLVING RISKS TO PARTICIPANTS OR OTHERS, ADVERSE EVENTS AND OTHER PROBLEMS

University of Cincinnati Institutional Review Boards
Phone: (513) 558-7324 Fax: (513) 558-4111

Events described as requiring prompt reporting should be reported to the IRB using this form within 10 days of the research staff member's learning of the event.

Events resulting in temporary or permanent interruption of study activities by the investigator or sponsor to avoid potential harm to participants should be reported **within 48 hours**.

SPONSOR:	SPONSOR PROTOCOL NUMBER:

DATE OF THIS REPORT:

DATE OF THIS EVENT:	DATE OF SITE AWARENESS:

Participant ID:

1. TYPE OF REPORT	☐ INITIAL REPORT	EVENT #	☐ FOLLOW-UP REPORT #
	☐ URGENT REPORT		☐ ROUTINE REPORT

Check all that apply

- ☐ Adverse event or injury that was serious, and unexpected, and definitely, probably, or possibly related to the study
- ☐ Adverse device effect that was unanticipated
- ☐ Serious protocol deviation (or unintentional change to protocol or procedures) involving risks or with the potential to recur
- ☐ Event requiring prompt reporting according to the protocol, sponsor, or funding agency
- ☐ Complaint made by a research participant indicating an unanticipated risk or that cannot be resolved by the research staff
- ☐ Unapproved change made to eliminate apparent immediate hazard to a research participant
- ☐ Data and Safety Monitoring Board (DSMB) report, interim analysis, or other oversight committee/monitoring report assessing safety
- ☐ New information indicating unexpected change in risks or potential benefits (e.g., literature/scientific report or other published finding)
- ☐ Other problem or finding not described above – Specify (e.g., breach of confidentiality, loss of study data or forms, etc.):

For more information and definitions of terms see http://researchcompliance.uc.edu/irb/

2. SOURCE OF THE REPORT

- ☐ Internal (research conducted at UC or at a site under an UC's IRB's jurisdiction)
- ☐ External (research conducted at a site other than UC over which another IRB has jurisdiction)

If External, please provide the following information:

☐ Yes ☐ No If the adverse event is reported in a study not conducted at UC, does the local protocol/informed consent form require modification?

☐ Yes ☐ No Is the adverse event Serious and Unexpected?

☐ Yes ☐ No Is the adverse event related to the study drug/device/procedures? (based upon the independent assessment of the UC investigator)

UC POLICY: If "Yes" is checked in all of the above boxes, please continue filling out this form and submit U.C. l IRB Office and provide the location where the research was performed and/or the event occurred. If "No" is checked for any of the questions stated above, do not submit this form to the U.C. IRB Office. For those adverse events in which you marked "No" in the boxes above, please attach this signed checklist to the sponsor provided safety reports and file with your research documents as required by the protocol.

Signature of Principal Investigator _____
Date of Review_____

3. RESEARCH INTERVENTIONS OR INTERACTIONS

The event involves (check all that apply):

☐ Drug(s)

☐ Device(s)

☐ Research-related procedure(s) or activity

☐ None of the above

Provide the names or description of any drugs, devices, or study procedures/activities involved.

4. DESCRIPTION

Describe in detail the event or problem being reported. For medical events, include relevant dose, treatment, laboratory information and whether or not participant was hospitalized. Include date of death if applicable. Please provide pertinent dosing information including; When was medication stopped, was dose reduced, was drug reintroduced, did event change after stopping drug or reintroducing drug?
(*If multiple drugs are associated with this protocol, see attachment A*)

Use complete sentences. Attach additional documents as necessary. Do not include participants' personally identifiable information.

5. Unanticipated Events – Skip if not applicable

a. Describe the 'unanticipated' component of the event. (ie. severity, not previously reported, biologic feasibility, frequency, etc.)

b. Describe the risk to human subjects

c. N/A

6. RESEARCH STATUS

a. The research participant(s) involved is/are:

☐ Still on study

☐ No longer on study

☐ N/A or unknown

b. Research recruitment (at UC or at a site under UC IRB's jurisdiction) is:

☐ Ongoing

☐ Completed (or stopped)

c. Research interventions/interactions involving other participants are:

☐ Ongoing

☐ Completed (or stopped) for all participants

7. OTHER REPORTING

The adverse event or problem will also be reported to (check all that apply):

☐ Sponsor

☐ Collaborating investigators

☐ No other reporting or unknown

☐ Other – Specify:

8. ACTIONS TO BE TAKEN

a. As a result of the event (check all that apply):

- ☐ The protocol or study procedures will be modified
- ☐ The consent form or process will be modified
- ☐ Additional information and/or follow-up will be provided to current and/or past participants
- ☐ Current participants will be asked to re-consent to participation
- ☐ The research will be voluntarily placed on hold, pending more information or resolution of problem – *requires immediate reporting*
- ☐ The (UC) research is being stopped – *requires immediate reporting*
- ☐ No action is planned
- ☐ Other

b. Provide additional explanation if no or "other" action is planned:

Provide amendment request through the UC Researchers Gateway and associated document(s) for all proposed changes and communications.

_____
Printed Name of Principal Investigator (or Faculty Advisor)

_____ _____
Signature of Principal Investigator (or Faculty Advisor) Date

_____ _____ _____
Phone number Fax Number E-mail