SOP 109-ADM  Adverse Event and Serious Adverse Event Reporting

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Purpose:
Subject safety is of the greatest importance for the study participant as well as the objectives of the clinical study. Investigators are required to report to the sponsor all adverse events occurring during a clinical study. If the event is serious and unexpected, prompt reporting to the sponsor, IRB and regulatory agencies is mandatory. This standard operating procedure describes the responsibilities of the clinical research team for managing, reporting and documenting adverse events and serious adverse events from the time they are identified until all follow-up activities associated with their resolution have been completed.

References:
- 21 CFR 312.32 IND safety reports
- 21 CFR 312.33 Annual reports
- 21 CFR 312.44 Termination
- 21 CRF 314.80 Post marketing reporting of adverse drug experiences
- 21 CFR 50.25 Elements of informed consent
- 21 CFR 56.108 IRB functions and operations
- 21 CFR 56.109 IRB review of research
- 21 CFR 56.115 IRB records
- 45 CFR 46.103 Assuring compliance with this policy-research conducted or supported by any Federal Department or Agency
- 45 CFR 46.109 IRB review of research
- 45 CFR 46.115 IRB records
- 45 CFR 46.116 General requirements for informed consent
- FDA information sheets, October 1998
- International Conference on Harmonization (ICH); Good Clinical Practice (GCP): Consolidated Guideline, November 2003.
- Introduction to Clinical Data Management. Barnett International/Clinical Training Group. Module 10
- Data and Safety Monitoring Plan, Arizona Cancer Center, approved May 27, 2008, National Cancer Institute
- All SOPs are applicable to this SOP.
SOP 109-ADM  Adverse Event and Serious Adverse Event Reporting

Authors:
Revised by SOPRC.

Target Audience or Responsibilities:
This SOP applies to those members of the clinical research team involved in ensuring the appropriate management and reporting of adverse events and serious adverse events. This includes the following:

- Principal Investigator (PI)
- Co-Principal Investigator (Co-PI)
- Sub-Investigator
- Clinical Trials Office (CTO)
- Research Nurse Coordinator
- Clinical Research Coordinator
- IRB (Institutional Review Board)
- IBC (Institutional Biosafety Committee)
- Support Staff

Tools:
- Investigational Therapy Adverse Events Record Form, CC-1322 (Rev. 11/06), Attachment 1.

Definition of Terms:
- **Adverse Event (AE):** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any adverse change from baseline (pretreatment) intercurrent illness which occurs during the course of a clinical study after consent has been signed, whether considered related to treatment or not.
- **Anticipated adverse event (Expected adverse drug experience):** There is a reasonable possibility that the experience may have been caused by the investigational product(s). Adverse events outlined in the protocol, Investigator’s Brochure and Informed Consent Form as known side effects that are expected.
- **Common Toxicity Criteria (CTC)**
- **Disability:** A substantial disruption of a person’s ability to conduct normal life functions.
- **Life-threatening adverse drug experience:** Any adverse drug experience that places the patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

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- **Medical Dictionary for Regulatory Activities (MedDRA):** A dictionary of clinically validated international medical terminology designed to support the classifications, retrieval, presentation, and communication of medical information throughout the medical product regulatory cycle.

- **MedWatch Form 3500A:** FDA form for mandatory reporting of adverse events as set forth in 21 CFR sections 310.305, 312.32 and 314.80

- **OnCore:** Database used to store protocol and patient data at the Arizona Cancer Center.

- **Protocol number:** A number assigned by the IRB to identify individual research projects (may be previously known as HSC or BIO number).

- **Serious Adverse Event (SAE):** Any event or experience that is a significant hazard, contraindication, side effect, or precaution experienced by a study subject once they have signed an informed consent form.
  - An SAE is any untoward medical occurrence at any dose of drug (investigational or not) and is considered a serious adverse event when it:
    - results in death or is life-threatening (immediate risk of death);
    - results in patient hospitalization or prolongation of existing hospitalization;
    - results in persistent or significant disability/incapacity;
    - is a congenital anomaly/birth defect;
    - important medical events that may not result in death, be immediately life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the outcomes listed in this definition.

- **Study participant timeline with respect to SAE reporting:**

<table>
<thead>
<tr>
<th>Consent</th>
<th>1st dose of study drug</th>
<th>Last dose of study drug</th>
<th>30 days after last dose of study drug or as specified in the protocol if the follow-up period is longer</th>
</tr>
</thead>
</table>

  Unless otherwise specified, any SAE occurring during this time must be reported to the local IRB (within 10 working days), to the study sponsor (according to study protocol and is usually within 24 hours), and to the FDA if AZCC is the study sponsor (7-days from SAE notification).

- **Unanticipated adverse event (Unexpected adverse drug experience):** Any adverse experience the specificity or severity of which is not consistent with the current Investigator Brochure, or if an Investigator Brochure is not required, that is not consistent with the specificity or severity in the risk information described in the general investigational plan or elsewhere in the current application, as amended.
Safety Issues:
The availability of SOPs in a standard format enhances the safe delivery of clinical research practice and ensures compliance with the clinical trials protocols as well as with appropriate FDA regulations and GCP and ICH guidelines. Reporting SAEs helps recognize possible cause-effect relationships of the particular clinical trial involved, therefore allowing subjects to have full awareness of these relationships.

Process Steps:
1) Determine if this event meets the criteria of an adverse event (AE) or a serious adverse event (SAE).
2) If the event meets the criteria of an AE:
   • record the details of the AE in the source documentation and complete the appropriate case report form;
   • follow the subject until the event is resolved.
3) The clinical research team should assist in managing the adverse event to ensure that all appropriate resources are directed toward subject safety and well-being. Institute therapeutic intervention and support measures such as discontinuation of the investigational product, comparator or placebo; reduce dosage (as per protocol), interrupt drug (as per protocol); follow the subject and assess adverse event until the subject has stabilized or the event has resolved.
4) Use MedDRA or CTC criteria, either 2.0 or 3.0 depending on the protocol requirements to grade AEs as well as SAEs. Make sure to use the correct version. Use MedDRA or CTC descriptions only, i.e., Hgb instead of anemia. Outcome on the adverse event record relates to the grade of the adverse event and not the adverse event itself. Unanticipated adverse event causalities are to be reviewed with the PI. Once reviewed, the PI will sign and date the adverse event source document form under investigator review section and the PI will also initial this section for changes and/or additions periodically. As applicable, adverse events are also input electronically in the research database by the Clinical Research Coordinator or other identified research personnel.
5) If the event meets the criteria of an SAE:
   • Create/complete the SAE report; attach all applicable additional documentation/correspondence (i.e. labs, hospital admission or discharge summaries, radiology or other reports, AE information). The additional documents/correspondence must include a copy of the fax confirmation page to verify the reporting time frame to the sponsor.
   • The Clinical Research Coordinator will convert the above information to an electronic format (i.e., PDF) attach the electronic document(s) to an e-mail and notify all individuals directly involved with the particular clinical trial and care of patient, (to include at least the PI, RN, DSMB Coordinator, CRC Manager, IRB Coordinator and CTO Manager). The IRB coordinator will complete the paperwork for submission to the IRB (within 10 working days of first knowledge of SAE), and then send said SAE report to the IRB via courier. The SAE will then be entered
into OnCore and copies of the documents will be attached in the OnCore data base and in the regulatory binder.

6) The identified research personnel must report the serious adverse event to the PI and study sponsor “immediately” after initial receipt or knowledge of the information or event, typically within 24 hours of knowledge of the SAE. Refer to the study specific protocol section on SAE reporting if in doubt of timeframe.

Note: For investigator-initiated trials, the DSMB Coordinator must also be notified of the SAE “immediately” after initial receipt or knowledge of the information or event, typically within 24 hours of knowledge of the SAE.

7) The identified research personnel completes an initial SAE form that can be in the format of a memo, sponsor provided form, the site electronic database (i.e., OnCore) form or a Form FDA 3500A. The identified research personnel will also obtain input from the attending physician, Principal Investigator, hospital personnel or medical records to ensure that the following are appropriately investigated; spontaneous reports by subjects, observations by clinical research staff, reports to research staff by family or medical care providers, possible AEs documented in medical records, progress notes, etc., reports of a subject death while on study, within four weeks after stopping treatment or during the protocol-defined follow-up period whichever is longer, whether considered treatment related or not.

8) To ensure proper reporting and documentation of the SAE, provide as much information as is available such as: protocol name and number, possible test article-investigational product, comparator or placebo; lot number and expiration date of drug, subject identifiers, demographic data, nature of the event, severity of the event, probable relationship of the event to the investigational product, date and time of event onset, date and time of resolution, if available; the dose, frequency and route of administration, the start and stop dates of the drug, concomitant medications and therapies, clinical assessment of the subject at the time of the report; results of any laboratory and/or diagnostic procedures, treatment or autopsy findings, and event outcome if applicable.

9) The PI signature, as applicable, is obtained on the SAE form and it is faxed, along with any de-identified supporting documentation to the appropriate person delegated in the study protocol.

10) The original SAE form and supporting de-identified documentation is copied and distributed by the clinical research coordinator to the research nurse coordinator (if one is assigned to the particular study), treating physician, DSMB program coordinator and PI. The original report is submitted to the Clinical Trials Office (CTO) to be filed in the regulatory binder for that clinical trial.

- The study sponsor is required to submit an IND safety report to the FDA as soon as possible, but no later than 15 calendar days after the initial receipt of the information. If the SAE is fatal or life-threatening and associated with the use of the investigational agent, the study sponsor is required to notify the FDA by phone or fax within 7 calendar days of the initial receipt of the information.
11) The identified research personnel will maintain contact with the patient and or patients' health care providers and documents the progress of the serious adverse event per specific protocol guidelines.

12) All SAEs must be followed until resolution or stabilization of the condition, until the event is otherwise explained, or until the subject dies or is lost to follow-up.

13) After one of the described above outcomes occurs, a follow-up SAE form must be submitted to the study sponsor by the research nurse coordinator as indicated in the study protocol. Provide details to the sponsor as they become available. If additional information cannot be obtained for whatever reason, document this in a "note to file" in the patient record. Inform the sponsor when no additional information is expected.

14) PI to promptly review IND safety reports received from the study sponsors and notifies support staff of significant changes or findings.

15) CTO staff will file IND safety reports in the study regulatory files.

16) The investigator submits all IND safety reports to the IRB in a timely manner and reports all routine adverse events as part of the IRB periodic/annual review requirements.
Attachment 1

(Investigational Therapy Adverse Events Record Form, CC-1322)
### Investigational Therapy
### Adverse Events Record

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Date of Onset</th>
<th>Date Ended</th>
<th>Grade</th>
<th>Frequency</th>
<th>Relationship to Study Drug</th>
<th>Causality other than Study Drug</th>
<th>Outcome</th>
<th>Action Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

#### GRADE
Based on current CTC grading scale unless otherwise stated:
- 1. Sqi Episode
- 2. Intermittent
- 3. Continuous

#### FREQUENCY
- 1. Not Related
- 2. Unlikely
- 3. Possible
- 4. Probable
- 5. Definitely

#### RELATIONSHIP TO STUDY DRUG
- 1. Disease Related
- 3. Intercurrent Illness
- 4. Other

#### CAUSALITY OTHER THAN STUDY DRUG
- 1. Resolved
- 2. Ongoing
- 3. Death

#### OUTCOME
- 0. None
- 1. Held
- 2. Dose Reduced
- 3. Discontinued
- 4. Medication given

**Investigator Reviews (Signature, Date, Military Time):**

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