

KCMC Clinical Trials Unit	STANDARD OPERATING PROCEDURE	Effective Date	SOP-Number CTU 007-02
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Title: TOXICITY MANAGEMENT AND ADVERSE AND SERIOUS ADVERSE EVENT REPORTING			
SOP References:		Supersedes: N/A	
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PURPOSE: The safety of research participants is of utmost importance. Rapid identification, grading, management and communication of toxicities, adverse events (AE) and serious adverse events (SAE) is crucial in order to take action against additional harm from occurring both in the individual subject and other study participants.

POLICY: The management of toxicities, AE and SAE will occur in a timely manner that protects patient safety, maintains the chain of responsibility, and meets protocol and regulatory authorities' reporting guidelines.

RESPONSIBILITY: The Principal Investigator, Clinical Research Coordinator, Research Nurse and Research Laboratory are responsible for continued surveillance and grading of toxicities, AE, and SAE. The Clinical Research Coordinator, Research Nurse and Research Laboratory will report any such toxicities promptly to the Principal Investigator so that action may be taken to remove additional harm the study participants. The Principal Investigator assures that protocol specifics for toxicity management and reporting are followed and reported to the regulatory authorities.

A. DEFINITIONS:

ADVERSE EVENT (AE): In clinical research, an AE is any unfavorable or unintended sign, symptom, or disease occurring during the course of participation in a research study. An AE may also be a worsening of a pre-existing illness or laboratory abnormality, regardless of whether or not associated with study medication or procedures. Some research protocols, such as longitudinal trials may not require reporting of AE to the study sponsor or Institution, though referral for health management must still occur in

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order to safeguard patients. Some research protocols may only require reporting and action to be taken when the AE reaches a certain level or grade.

SERIOUS ADVERSE EVENT (SAE): Any untoward medical occurrence that is immediately life-threatening, requires or prolongs hospitalization, results in permanent or significant disability or congenital anomaly (birth defect) or results in death whether associated or not with study medication or procedures. An initial report of the SAE must be transmitted via facsimile or web-based electronic mail to the Sponsor and Institutional Ethics Committee within 24 hours of the site becoming aware of the SAE. As additional information is known or as the SAE evolves follow-up reports will be submitted, through to resolution or final death report.

TOXICITY GRADING: Clinical trials use a grading system for documenting the severity of abnormal events, whether symptoms or laboratory abnormalities. All NIH Division of AIDS (DAIDS) trials share a common toxicity grading system. This same scale is often used for other trials, including academic and pharmaceutical trials. Toxicity grades go from one to four. One refers to an event with minor impact on the participant's life, whereas four is considered serious and often life threatening. (See DAIDS Toxicity Table included at the end of this SOP.)

UNEXPECTED ADVERSE DRUG REACTION: An adverse reaction, related to study product that has not previously been described or is more severe than previously described in the product's package insert or investigational drug brochure. Unexpected adverse drug reactions require expedited reporting similar to SAE reporting.

B. PROCEDURES:

1. AE Reporting:

a. Assessment: The study coordinator (or designee) will continuously screen for AE events on an ongoing basis using patient-reported histories, physical assessment/exam, laboratory reports, chart review, and any other available data and communicate this with the Principal Investigator. An AE may be a symptom (e.g., pruritis), a sign (e.g., rash), a lab result (e.g., ANC of 450) or a diagnosis (e.g., PCP). Each protocol or Sponsor will specify requirements for recording AE and the toxicity scale to use in recording.

b. Documentation:

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i. When an AE is identified, the clinical coordinator (or designee) will document the AE and the appropriate toxicity grade from the study assigned toxicity grading scale specified in the protocol or by the sponsor. Documentation of the AE may be done on the study visit flow sheet or an AE log specific to that study participant. If the clinical research coordinator (or designee) chooses to use an AE log, the source clinic note or flow sheet should note that a new AE was noted and the AE log was updated. If the particular toxicity is not included in the toxicity table, grades 1,2,3,4 for mild, moderate, severe, and life threatening should be used.

ii. The Principal Investigator will review all AE, assess causality, and required course of action in accordance with the protocol and clinical trial's regulations.

iii. All AE should be followed to resolution.

iv. All grade 3 or 4 AE should be reported to the Principal Investigator (or sub-Investigator if unavailable) within 24 hours of awareness. A plan for follow-up of clinically significant AE should be documented in the patient's source documents.

v. All new or unexplained clinically significant grade 3 and 4 lab results should be repeated as dictated by the protocol, the site investigator or within 72 hours to rule out laboratory error.

vi. Clinical management of AE should follow the toxicity guidelines outlined in the protocol unless contraindicated. If the study participant has a grade 3-4 laboratory abnormality and is non-symptomatic, the laboratory result(s) should be repeated prior to additional action being taken. For symptomatic laboratory abnormalities of grade 3-4, immediate action is warranted. It is the responsibility of the study coordinator to access the protocol toxicity management and to communicate this information to the Principal Investigator. The research coordinator should attempt to access the relationship of the AE to study treatment and include this in the communication. However, it is the responsibility of the Principal Investigator to make the final decision regarding causality of AE to study treatment or procedures, and patient management of this event.

vii. The patient's primary caregiver should be kept informed of any adverse events requiring treatment interruption or changes, as well as any results that may confuse the clinical picture or complicate care.

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2. SAE Reporting:

a. Assessment: The study coordinator (or designee) will continuously screen for SAE events on an ongoing basis using patient or family-reported events, home-base care reports, in-patient census, obituaries, or any other available data. The study coordinator (or designee) will immediately communicate SAE reports with the Principal Investigator. As soon as the site receives information of a SAE, an initial report must be made to the Sponsor and Institutional Ethics Committee within 24 hours of notification.

b. Documentation:

- i.** When an SAE is identified, the clinical coordinator (or designee) will document the SAE event, what makes this an SAE, study medication(s) and if ongoing, interrupted, or permanently discontinued, concomitant medication(s), and results of any procedures obtained. If the SAE is due to an unplanned hospitalization, the toxicity grading scale will be applied to any AE that may have prompted the unplanned hospitalization.
- ii.** The Principal Investigator will review all SAE, assess causality, and required course of action in accordance with the protocol and clinical trial's regulations.
- iii.** All SAE should be followed to resolution and interim SAE reports sent to the Sponsor and Institutional Ethics Committee as events unfold.
- iv.** The patient's primary caregiver should be kept informed of any SAE, causality, action, resolution or death.

3. Unexpected Adverse Drug Event (UADE):

a. Assessment: The study coordinator (or designee) will continuously screen for UADE adverse drug events on an ongoing basis using patient-reported histories, physical assessment/exam, laboratory reports, chart review, and any other available data compared to the package insert or investigational brochure. The study coordinator (or designee) will communicate this with the Principal Investigator.

b. Documentation:

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<p>i. When an UADE is suspected, the clinical coordinator (or designee) will work together with the research pharmacist in verifying that the event caused by the study product is unexpected or of greater severity than previously reported. The clinical research coordinator (or designee) will document the UADE and the appropriate toxicity grade from the study assigned toxicity grading scale specified in the protocol or by the sponsor. Documentation of the UADE may be done on the study visit flow sheet or an AE log specific to that study participant along as causality to the study product is clearly noted. However, if the clinical research coordinator (or designee) chooses to use the AE log to document this event, a clinic note of this event should be added for reporting to the Sponsor and Institutional Ethics Committee. If the particular toxicity is not included in the toxicity table, grades 1,2,3,4 for mild, moderate, severe, and life threatening should be used.</p> <p>ii. The Principal Investigator will review all UADE, confirm causality and unexpectedness of this event by the study product, and course of action in accordance with the protocol and clinical trial's regulations.</p> <p>iii. All UADE must be reported to the study Sponsor and Institutional Ethics Committee and be followed to resolution.</p> <p>iv. Clinical management of UADE should follow the toxicity guidelines outlined in the protocol unless contraindicated. If the UADE is a grade 3-4 laboratory abnormality in which the subject remains non-symptomatic, the laboratory result(s) should be repeated prior to additional action being taken. If the laboratory toxicity is verified, and the subject remains asymptomatic, the Sponsor should be notified before further action is taken. For symptomatic laboratory abnormalities of grade 3-4, immediate action is warranted. It is the responsibility of the study coordinator to access the protocol toxicity management and to communicate this information to the Principal Investigator.</p> <p>vii. The patient's primary caregiver should be kept informed of any UADE requiring treatment interruption or changes, as well as any results that may confuse the clinical picture or complicate care.</p>			
This SOP has been read and understood by:			
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