SM-404 STANDARD OPERATING PROCEDURE FOR ADVERSE EVENT REPORTING

I. INTRODUCTION AND PURPOSE

Subject safety is of the greatest importance for both the individual subject and the goals of the clinical study. Investigators are required to report to the sponsor all adverse events occurring during a study. If the event is serious and unexpected, prompt reporting to the sponsor and to the IRB is mandatory. This standard operating procedure (SOP) describes the steps this clinical research team follows to fulfill the regulatory and clinical requirements for adverse event reporting.

2. SCOPE

This standard operating procedure (SOP) describes the responsibilities of the research team for managing, reporting and documenting adverse events from the time an adverse event is identified until all follow-up activities associated with its resolution have been completed. This SOP also describes the mechanisms used to provide the information necessary for sponsors to prepare Investigational New Drug (IND) safety reports. Finally, the procedures for processing and transmitting IND safety reports received from the sponsor to the IRB are defined.

3. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 312.32	IND safety reports
21 CFR 312.33	Annual reports
21 CFR 312.44	Termination
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

4. REFERENCES TO OTHER APPLICABLE SOP'S

GA-102	Responsibilities of the Research Team
PM-301	Site-Sponsor/CRO Communications
PM-302	Interactions with the Institutional Review Board
SM-403	Subject Management While on Study
DM-501	Data Management

5. ATTACHMENTS

A. Procedures for Managing Adverse Events

6. RESPONSIBILITY

This SOP applies to those members of the clinical research team involved in ensuring the appropriate management of adverse events. This includes the following:

- Principal investigator
- Sub-investigator
- Research Director/Manager
- Research coordinator
- Support staff

7. DEFINITIONS

The following definitions from the Code of Federal Regulations and the International Conference on Harmonisation, Good Clinical Practice: Consolidated Guideline apply to this SOP.

Adverse event: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An 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.

Associated with the use of the drug: There is a reasonable possibility that the experience may have been caused by the drug.

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.

Serious adverse drug experience (ADE): Any experience that results in death, in a life-threatening ADE, inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability or incapacity, or congenital anomaly.

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.

8. PROCESS OVERVIEW

A. Managing adverse events
B. Handling IND safety reports from sponsors
C. Reporting to the IRB

9. PROCEDURES

A. MANAGING ADVERSE EVENTS

RESPONSIBILITY	DESCRIPTION OF PROCEDURE
PI Sub-investigator Research coordinator	Follow up appropriately when a research subject experiences any adverse change from baseline or pretreatment condition, ensuring that all appropriate resources are directed toward subject safety and well-being. Follow the subject until the event is resolved or per protocol specifications.
PI Sub-investigator Research coordinator	If necessary for the immediate medical care of the subject only, break the drug blind after consultation (if possible) with the sponsor.
PI Research coordinator	If the adverse event is serious and/or unexpected, inform the sponsor as soon as possible after the subject is stabilized and within 24 hrs of being notified of an event. Provide as much information as is available.
PI Research coordinator	Record the details of the adverse event in the source documentation and complete the appropriate CRFs.
Research coordinator Support staff	Request Medical Records from treatment facility. Keep originals or photocopies of all relevant documentation, including facsimile confirmations, and file in the study binder with appropriate documents.

B. HANDLING IND SAFETY REPORTS FROM SPONSOR

RESPONSIBILITY	DESCRIPTION OF PROCEDURE
PI Sub-investigator Research coordinator	Promptly review IND safety reports received from sponsors. PI should initial and date upon reviewing
Research coordinator Support staff	File IND safety reports in the study regulatory file.

C. REPORTING TO THE IRB

RESPONSIBILITY	DESCRIPTION OF PROCEDURE
PI Research coordinator Support staff	Ensure that the IRB is notified of all serious or alarming events occurring at this site during the approval period for the ongoing study. Ensure that all IND safety reports received from sponsors are promptly submitted to the IRB if not done so by the sponsor. Ensure that the clinical site reports to the IRB all routine adverse events as part of the periodic or annual reporting requirements.

Attachment A

Procedures For Managing Adverse Events

1) Identification, assessment and management of an adverse event

REGULATIONS	PROCEDURES
Definition of an adverse event (AE): ● Any adverse change from baseline (pretreatment) intercurrent illness which occurs during the course of a clinical study after treatment has started, whether considered related to treatment or not ● Any effect that is unintended and unfavorable, such as a sign, a symptom, a laboratory abnormality or a disease or condition Serious adverse events (SAEs) include: ● Death ● Life-threatening experience ● Inpatient hospitalization or prolongation ● Persistent or significant disability/incapacity ● Congenital anomaly/birth defect ● Events that would require medical or surgical intervention to prevent any of the above	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 within four weeks after stopping treatment or during the protocol-defined follow-up period, whichever is longer, whether considered treatment-related or not Manage the adverse event to ensure that all appropriate resources are directed toward subject safety and well-being. Institute therapeutic intervention/support measures. If applicable: ● Discontinue the investigational product, comparator, or placebo ● Reduce dosage (as per protocol) ● Interrupt drug (as per protocol) ● Challenge (as per protocol) Follow the subject and assess the adverse event until stabilized/resolved.

2) Reporting SAEs to the sponsor

Report **serious and unexpected** adverse experiences, whether considered drug-related or not, to the sponsor as soon as possible.

Provide details to the sponsor as they become available. If additional information cannot be obtained for whatever reason, document this.

Inform the sponsor when no other information is expected.

SPONSOR RESPONSIBILITIES	**SITE RESPONSIBILITIES**
Sponsors are required to notify the FDA by IND safety reports of any serious adverse experience associated with use of the drug in the clinical studies conducted under an IND as soon as possible but no later than 15 calendar days after initial receipt of the information. If the event is fatal or life-threatening and associated with use of the drug, sponsors are required to notify the FDA by telephone or fax within 7 calendar days of initial receipt of the information.	To meet expedited reporting requirements, inform the sponsor as soon as possible after the subject is stabilized. Provide as much of the following information as is available: ● Protocol name and number ● The possible test articles: investigational product, comparator, or placebo ● Lot number and expiration date ● Subject identifiers ● Demographic data ● The nature of the event ● The severity of the event ● The probable relationship of the AE to the investigational product ● The date (and time) of AE onset ● The date (and time) of AE resolution, if available ● The dose, frequency, and route of administration ● The start and stop dates of test article administration ● Concomitant medications and therapies ● Clinical assessment of the subject at this time ● The results of any laboratory and/or diagnostic procedures, treatment, autopsy findings ● The follow-up plan ● The outcome

3) Research documentation

SOURCE DOCUMENTATION	CASE REPORT FORM COMPLETION
Record in the source documentation, noting ● The nature of the event ● The severity of the event ● The probable relationship of the AE to the investigational product ● The date (and time) of AE onset ● The date (and time) of AE resolution, if available ● The possible test articles: investigational product, comparator, or placebo, the dose, frequency, and route of administration ● The start and stop dates of test article administration ● Concomitant medications and therapies ● Clinical assessment of the subject at this time ● The results of any laboratory tests and/or diagnostic procedures ● The follow-up plan ● The outcome	Complete the appropriate case report form(s) ● The site-prepared data collection form for SAEs or ● The sponsor-generated CRF for routine AEs

4) Sponsor-generated IND safety reports

RESPONSIBILITIES TO IRB	RESPONSIBILITIES TO SPONSOR
Submit all IND **safety reports** to the IRB and retain a copy of the transmittal memo in the study regulatory binder.	Acknowledge receipt of expedited safety report to sponsor with letter/facsimile. Copy sponsor on the transmittal memo to the IRB, if required. Inform sponsor of action required by the IRB, such as revisions to the informed consent form. Follow up with the sponsor as required.