Investigator Standard Operating Procedures

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<th>SOP No.: 605</th>
<th>Adverse Event Recognition and Reporting</th>
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This SOP pertains to: All personnel involved in conducting human subject research within the Memorial Healthcare System and who are responsible for identifying, recording and reporting Adverse Events and Serious Adverse Events to the applicable authorities.

Responsibility for executing this SOP: Investigator and Designated Research Personnel

Approved By (Sign & Date):

Senior Vice President & Chief Medical Officer, MHS

Approved By (Sign & Date):

Chief Medical Research Officer, OHR

1 PURPOSE

This procedure describes the regulatory requirements for identifying, investigating, and reporting adverse events that occur in subjects who are participating in any clinical study at Memorial Healthcare System.

2 GENERAL INSTRUCTIONS AND RESPONSIBILITIES

a) The Sponsor is responsible for ensuring that all participating Investigators understand the requirements to report all serious adverse events or experiences (SAE) and adverse events (AE) according to applicable regulations and guidelines.

b) The Investigator is responsible for recognizing and reporting SAE, which may require immediate reporting to the Sponsor, FDA, IRB, and other regulatory authorities.

c) The Investigator is responsible for recognizing and reporting all other expected, unexpected, non-serious and/or routine AE as required by the clinical protocol.

d) The Investigator is responsible for the appropriate medical management and follow-up of subjects who have experienced an AE while on study, irrespective of relationship to study treatment or investigational product.

e) The Investigator is responsible for communicating details of AE and any follow-up data to the IRB and any other relevant internal research review group.

f) The Investigator is responsible for documenting AE on the appropriate case report form (CRF) and other regulatory reporting forms (e.g. See Attachment E, FDA MedWatch Form 3500A).

g) The Sponsor is required to prepare IND Safety Reports or other appropriate notification to all Investigators as a result of an SAE, including death, that are reported to the Sponsor.
h) The Investigator or their designees are responsible for forwarding IND Safety Reports or other appropriate device-related notification to the IRB of record and in accordance with the IRB requirements (See Attachment C).

3 SPECIFIC PROCEDURES

3.1 Identifying Adverse Events at the Clinical Site

3.1.1 Subject Assessment

The Investigator should assess each subject for the following throughout each subject's study participation and during the follow-up period specified in the protocol:

a) Any adverse change from baseline (pretreatment) condition
b) Any intercurrent illness that occurs during the course of a clinical study after treatment with the investigational product/treatment has started, whether considered related to the investigational product/treatment or not

c) Any effect that is unintended and unfavorable, such as a sign, a symptom, a laboratory abnormality, or a disease

3.1.2 Events for Investigation and Reporting

The Investigator should ensure that the following are appropriately investigated and reported:

a) Spontaneous reports by subjects
b) Observations by key study personnel
c) Reports to study staff by the subject's family or medical care providers
d) Possible AE documented in medical records, progress notes, etc.
e) Reports of a subject death within thirty (30) days after stopping treatment or during the protocol-defined follow-up period, whichever is longer, whether considered treatment-related or not.
f) Hospital admissions

3.1.3 Adverse Event Monitoring

The Investigator should consistently and routinely monitor for AE by taking proactive measures such as the following:

a) Interview subjects
b) Review lab reports
c) Review subjects' medical records for additional information
d) Review (if applicable) subjects' diaries
e) Communicate with subjects' medical providers
3.1.4 Determination of Adverse Event Type

The Investigator should determine whether the AE is an SAE or not. The FDA definition for an SAE is:

Any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of outcomes noted above. Any event not qualifying as an SAE is considered an AE.

An unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

3.2 Clinical Management and Documentation of Adverse Events

3.2.1 Therapeutic Intervention

The Investigator or his designee and should ensure that all appropriate resources are directed toward subject safety and well-being. He/she shall implement therapeutic intervention/support measures for subjects experiencing an AE. If applicable:

a) Discontinue therapy with the investigational product, comparator, or placebo
b) Reduce dosage as per protocol
c) Interrupt drug treatment as per protocol
d) Challenge as per protocol and if performed, under medical supervision

3.2.2 Adverse Event Follow-up

The Investigator should follow up and assess the AE until stabilized/resolved by:

a) Directed or complete physical examination and clinical assessment
b) Appropriate laboratory tests, diagnostic procedures and/or studies
c) Medical/surgical consultants as needed
3.2.4 Adverse Event Documentation

The Investigator and/or designees should record AE(s) in appropriate source documents, noting the following (See Attachment B)

a) Nature of the event
b) Severity of the event
c) Probable relationship (causality) of AE to investigational product
d) Date and time of AE onset
e) Date and time of AE resolution, if available
f) Possible test articles involved (investigational product comparator, or placebo) with administration start/stop dates
g) Dose, frequency, and route of administration, if applicable
h) Concomitant medications and therapies: the Investigator and/or the designee should separately list the concomitant medications that the subject was taking for the treatment of his/her underlying medical conditions and also the concomitant medications used for the treatment of the AE
i) Clinical assessment of the subject conducted at time of SAE/AE
j) Results of any laboratory tests and/or diagnostic procedures
k) Follow-up plan
l) Record date/time of SAE/AE resolution and outcome, when available

Documentation should be entered into the subject's medical record (EPIC) by the Investigator or their designee that captures the criteria used to grade the AE, how severity and causality was determined, and the relationship to the investigational agent.

3.3 Participating Investigator SAE(s) Reports to the Sponsor

a) The participating Investigator is expected to report any serious and unexpected adverse experiences, whether or not they are considered related to the investigational product, to the Sponsor in the time frame as specified in the protocol, usually within 24 hours (Attachment A may be used when an SAE form has not been provided by the sponsor).

b) The Investigator is expected to provide as much of the following information as is available to the Sponsor:
   - Protocol name and number
   - Possible test articles involved (investigational product, comparator, or placebo) with administration start/stop date
   - Subject identifiers
   - Demographic data
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• Nature of the event
• Severity of the event
• Probable relationship (causality) of AE to investigational product
• Date and time of AE onset
• Date and time of AE resolution, if available
• Dose, frequency, and route of administration, if applicable
• Concomitant medications that the subject was taking for an underlying medical condition or disease and the therapeutic agents used for the treatment of the adverse event
• Clinical assessment of subject conducted at time of SAE/AE
• Results of any laboratory and/or diagnostic procedures, and treatment
• Follow-up plan
• Outcome
• Autopsy findings (if appropriate)

c) The Investigator will provide details in a follow-up report about the AE to the Sponsor as they become available. If additional information cannot be obtained for whatever reason, this will be documented.

d) The Investigator should communicate to the Sponsor in a final report when no other information is expected.

e) The Investigator should provide the Sponsor with a logical, complete, and accurate narrative description of the SAE based upon the above information.

f) The Investigator should promptly determine an assessment of causality.

g) The Investigator should communicate to the Sponsor if the IRB requires revisions to the protocol and informed consent form or other measures to include new risk assessment or side effects that subjects should be aware of.

h) The Sponsor will evaluate the AE(s) and determine, based on the severity of the adverse events or a change in incidence, whether the results require an evaluation by the Data Safety Monitoring Board, if one has been constituted. The Data Safety Monitoring Board can institute measures such as stopping enrollment in the study, stopping one of the treatment arms, or modifying the dose of the study medications.

i) The participating Investigator or designee should keep originals or photocopies of all relevant documentation, including facsimile confirmations, and file them in the subject's study file.

3.4 Reporting SAE(s) to the FDA by Sponsor

a) The Sponsor is required to notify the FDA by IND Safety Reports of any serious adverse experiences that are both unexpected and associated with the use of the
drug/biologic in the clinical studies conducted under an IND as soon as possible but no later than 15 calendar days after the initial receipt of the information from any source.

b) If the SAE is fatal or life-threatening and associated with use of the drug/biologic, in clinical studies conducted under an IND, the Sponsor is required to notify the appropriate FDA review division by telephone or fax within 7 calendar days of initial receipt of the information.

c) If the Sponsor identifies an SAE, or is notified of an SAE by another participating (See Attachment C) investigator, the Sponsor is required to prepare either an FDA MedWatch Form 3500A or a narrative describing the details of the SAE. The assessment of the SAE by the Sponsor should include a review of similar SAE that were previously reported in the study to determine trends or clinical significance.

d) The Sponsor should amend the Investigator Brochure according to the SAE findings, and distribute the revised Investigator Brochure as required.

e) The Sponsor is required to send a written report or notification of the IND Safety Report and Suspected Unexpected Serious Adverse Reaction (SUSAR) report to all participating investigators.

f) The Principal Investigator at each site should acknowledge receipt of any IND Safety Reports and SUSAR by initialing and dating printed reports and/or via electronic means, or by another method specified by the Sponsor (Reference SOP 606, Maintenance of IND Safety letters in e-format).

g) The Principal Investigator must establish a process by which sub-investigators and study staff will be informed of important SAE findings.

h) The Investigator or designee should file a copy of all expedited safety reports in the site’s Regulatory Master File.

i) Regarding investigational medical devices, the Sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect that is reported to him/her from any source.

j) If the unanticipated adverse device effect is determined by the Sponsor to present an unreasonable risk to subjects, termination of the study will occur not later than five (5) working days after the Sponsor makes the determination and not later than fifteen (15) days after the Sponsor first received notice of the effect.

k) For any investigational medical device study, the Sponsor must notify the appropriate FDA review division of any serious or unanticipated adverse device effect within 10 days of notification by a participating Investigator.

l) For any investigational medical device study, the Sponsor must also notify all reviewing IRBs and participating Investigators of any serious or unanticipated adverse device effect within 10 days of notification by a participating investigator.

3.5 Reporting SAE(s) and AE(s) to the IRB

a) The Investigator should notify the IRB of record within the required time frame, of all possible SAE(s) occurring at the site, during the study period and the protocol pre-defined time interval after the investigational product has been discontinued.
b) Investigators should ensure that all routine AE(s) are reported as part of the periodic or annual reporting requirements to the IRB of record in accordance with their policies.

c) The Sponsor will determine if any corrective actions should be initiated as a result of any known specific or collective SAE/AE(s) and inform all participating Investigators of the corrective action (e.g. revision of informed consent form, protocol, IB, CRF).

d) The Investigators should file copies of all correspondence with the IRB in the appropriate section of the Regulatory Master File.

e) The Sponsor is responsible for providing to the Investigators, the IRB, and to the FDA, information on any SAE(s) that are reported in the medical literature.

f) As the IRB of record specifies, the Sponsor will prepare periodic summaries of all AE as requested to keep the office appraised of these findings.

4 REFERENCES TO OTHER APPLICABLE SOPS

- 202 Reporting Requirements for the FDA
- 301 Clinical Protocol Development, Implementation and Compliance
- 303 Developing Documents for Informing Investigators
- 501 Communications
- 502 Investigational Product Inventory Management
- 503 Documentation and Records Retention
- 505 Study Closeout Procedure
- 601 Informed Consent
- 606 Maintenance of IND Safety Letters in e-Format
- 701 Case Report Forms

5 ATTACHMENTS

A. Serious Adverse Event Reporting Form
B. Adverse Event Log
C. Concomitant Medication Log
D. Reporting IND Safety Reports to the IRB
E. SAE Reporting Requirements Summary (Drug and Device)
F. FDA MedWatch Form 3500A

6 APPLICABLE REGULATIONS AND GUIDELINES

- Informed Consent of Human Subjects (21 CFR 50)
- Institutional Review Boards (21 CFR 56)
- General Principles of the IND Submission (21 CFR 312.22)
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- IND Safety Reports (21 CFR 312.32)
- Annual Reports (21 CFR 312.33)
- Termination (21 CFR 312.44)
- General Responsibility of Sponsors (21 CFR 312.50)
- Review of Ongoing Investigations (21 CFR 312.56)
- Investigator Reports (21 CFR 312.64)
- Scope (21 CFR 812.1)
- Report of Prior Investigations (21 CFR 812.27)
- Monitoring Investigations (21 CFR 812.46)
- Reports (21 CFR 812.150)
- The Principles of ICH GCP (ICH E6, Section 2.7)
- Medical Care of Trial Subjects (ICH E6, Section 4.3)
- Randomization Procedures and Unblinding (ICH E6, Section 4.7)
- Safety Reporting (ICH E6, Section 4.11)
- Medical Expertise (ICH E6, Section 5.3)
- Trial Management, Data Handling, and Record Keeping (ICH E6, Section 5.5)
- Safety Information (ICH E6, Section 5.16)
- Adverse Drug Reaction Reporting (ICH E6, Section 5.17)
- Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A, March 1995)