Study Management
SM 306.01

STANDARD OPERATING PROCEDURE
Adverse Event Reporting

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President and CEO

04 Feb 2021
(Signature and Date)

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04 Feb 2021
(Signature and Date)

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1. INTRODUCTION AND PURPOSE

Subject safety is of scientific, clinical, and ethical significance for the clinical trial, study subjects, and Investigators conducting clinical trials. Investigators are required to report all adverse events occurring during the treatment and follow-up periods of a clinical trial to the Sponsor. If the event is serious and unexpected, prompt reporting to the manufacturer of the investigational product and to the IRB is mandatory.

The purpose of this SOP is to describe the responsibilities of Georgia CORE staff, consultants, Research Network site Investigators and staff in recognizing, managing, reporting, and documenting adverse events occurring during the course of a clinical trial.
2. **SCOPE**

This SOP applies to all Georgia CORE staff and consultants involved monitoring, reporting, and documenting adverse events from the time Georgia CORE is notified that an adverse event is identified until all follow-up activities associated with it resolution have been completed.

This SOP also describes the mechanisms used to provide information necessary for Georgia CORE staff and consultants to prepare Investigational New Drug (IND) safety reports. Finally, the procedures for Georgia CORE to process and transmit IND safety reported received from the manufacturer of the drug and the sponsor to the IRB are defined.

3. **APPLICABLE REGULATIONS AND GUIDELINES**

The Code of Federal Regulations and the International Conference on Harmonization, Good Clinical Practice: Consolidated Guideline and selected program and guidance documents apply to this SOP (Appendix A).

4. **REFERENCES TO OTHER APPLICABLE SOPS**

   - GA -102 Sponsor Responsibility and Delegation of Responsibility
   - SM - 301 Communication
   - SM - 302 Interactions with the IRB
   - SM -304 Routine Monitoring Visits
   - SM - 305 Closeout Visits
   - DM - 401 Data Management

5. **ATTACHMENTS**

   - A. Procedures for Managing Adverse Events
   - B. FDA Form 3500
   - C. FDA Form 3500 A
   - D. Algorithm for Review and Distribution of IND Safety and MedWatch Reports

6. **RESPONSIBILITY**

This SOP applies to those members of Georgia involved in involved in ensuring appropriate management of adverse event reporting, including,

- President and CEO
- Chief Medical Officer
- Georgia CORE Research Network site Investigator, Subinvestigators, and staff
- Georgia CORE staff and consultants

7. **DEFINITIONS**

The following definitions apply to this SOP (Appendix B):

- Adverse event
- Associated with the use of the drug
- Disability
Life-threatening adverse drug experience
Serious adverse drug experience (ADE) (also known as a serious adverse event (SAE)
Sponsor
Unexpected adverse drug experience

8. **PROCESS OVERVIEW**

A. Managing adverse events
B. Handling IND safety reports from the drug manufacturer or Sponsor
C. Reporting to the IRB

9. **PROCEDURES**

A. **Managing Adverse Events**

- **Georgia CORE staff and consultants**
  When a Research Network site reports an adverse change in a subject from baseline or pre-treatment condition, ensure that all appropriate resources have been directed toward subject safety and well-being and that the subject is followed until the event is resolved (Attachment A: Site Procedures for Managing Adverse Events).

  At the next site visit, ensure that details of the adverse event are recorded in the source documentation and the appropriate CRFs are completed.

  At the next site visit, ensure that originals or photocopies of all relevant documentation, including facsimile confirmations have been filed in the study binder and document findings in the monitoring report.

- **PI for Study**
  If necessary for the immediate medical care of the subject only, facilitate breaking the drug blind after consultation (if possible) with the Investigator who initiated the study or the Georgia CORE Chief Medical Officer.

  Determine if the adverse event is serious and/or unexpected with the assistance of the Investigator who initiated the study and/or Chief Medical Officer, if needed, and inform the drug manufacturer as directed in the protocol.

  - Provide as much information as is available from the site using the Med Watch Form FDA 3500 or 3500A (Attachment B and Attachment C) and/or the Serious Adverse Event Report Form in the protocol, if applicable.
  - For NCI NCTN trials report online at CTEP-AERs within 24 hours.
B. Handling IND Safety Reports from Drug Manufacturer or Sponsor Pharma

Georgia CORE staff and consultants
Research Network site Investigators and staff

Promptly review IND safety reports received from drug manufacturers or Sponsors and follow the algorithm for review and Distribution of IND Safety and MedWatch site Investigators Reports (Attachment D).

File IND safety reports and MedWatch Reports and related communications in the Georgia CORE: IND Safety Report electronic folder for the appropriate clinical trial.

All serious or adverse events occurring at a Georgia CORE Research Network site, which is using the Central IRB, should be reported using the Central IRB guidance.

For NCTN trials approved by the local IRB or NCI CIRB, notify the local IRB of all serious or alarming events. If no local IRB of record, report SAEs and any updates to Georgia CORE by including them on the CTEP-AERS report.

Ensure that all IND safety reports received from the drug manufacturer or Sponsor are submitted to the Central IRB according to the Central IRB guidelines and the Algorithm for Review and Distribution of IND Safety and MedWatch Reports (Attachment D).

Ensure that all routine adverse events are reported to the Central IRB as part of the periodic or annual reporting requirements as outlined in the Central IRB guidelines.

Obtain documentation from Georgia CORE Research Network sites using local IRBs, showing that they have completed reports to the local IRB as noted in the above 3 action items.

File documentation in the Georgia CORE IND Safety Report electronic folder for the appropriate trial.

10. HISTORY
ATTACHMENT A:
Procedures for Managing Adverse Events

1. Identification, assessment and management of an adverse event by the Georgia CORE Network Sites

<table>
<thead>
<tr>
<th>REGULATIONS</th>
<th>PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>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 therapeutic intervention/support measures</td>
<td>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)</td>
</tr>
</tbody>
</table>
surgical intervention to prevent any of the above

- Interrupt drug (as per protocol)
- Challenge (as per protocol)

Follow the subject and assess the adverse event until stabilized/resolved

## 2. Georgia CORE Research Network Site SAE Reporting

- Report **serious and unexpected** adverse experiences, whether considered drug-related or not, to the Sponsor as directed in the protocol.
- 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.

<table>
<thead>
<tr>
<th>SPONSOR RESPONSIBILITIES</th>
<th>SITE RESPONSIBILITIES</th>
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</thead>
<tbody>
<tr>
<td>Sponsors are required to notify the FDA by IND safety reports of <strong>any serious adverse experience associated with use of the drug</strong> in the clinical studies conducted under an IND as soon as possible but no later than <strong>10 calendar days</strong> after initial receipt of the information.</td>
<td>To meet expedited reporting requirements, inform the sponsor as soon as possible after the subject is stabilized.</td>
</tr>
<tr>
<td>Georgia CORE is required to notify the drug manufacturer as specified in the protocol.</td>
<td>Provide as much of the following information as is available:</td>
</tr>
<tr>
<td></td>
<td>• Protocol name and number</td>
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<tr>
<td></td>
<td>• The possible test articles: investigational product, comparator, or placebo</td>
</tr>
<tr>
<td></td>
<td>• Lot number and expiration date</td>
</tr>
<tr>
<td></td>
<td>• Subject identifiers</td>
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<tr>
<td></td>
<td>• Demographic data</td>
</tr>
<tr>
<td></td>
<td>• The nature of the event</td>
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<td></td>
<td>• The severity of the event</td>
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<tr>
<td></td>
<td>• The probable relationship of the AE to the investigational product</td>
</tr>
<tr>
<td></td>
<td>• The date (and time) of AE onset</td>
</tr>
<tr>
<td></td>
<td>• The date (and time) of AE resolution, if available</td>
</tr>
<tr>
<td></td>
<td>• The dose, frequency, and route of administration</td>
</tr>
<tr>
<td></td>
<td>• The start and stop dates of test article administration</td>
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<tr>
<td></td>
<td>• Concomitant medications and therapies</td>
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<tr>
<td></td>
<td>• Clinical assessment of the subject at this time</td>
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<td>• The results of any laboratory and/or diagnostic procedures, treatment, autopsy findings</td>
</tr>
</tbody>
</table>

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.
• The follow-up plan
• The outcome
### 3. Site Research documentation

<table>
<thead>
<tr>
<th><strong>SOURCE DOCUMENTATION</strong></th>
<th><strong>CASE REPORT FORM COMPLETION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Record in the source documentation, noting</td>
<td>Complete the appropriate case report form(s)</td>
</tr>
<tr>
<td>• The nature of the event</td>
<td>• The site-prepared data collection form for SAEs or</td>
</tr>
<tr>
<td>• The severity of the event</td>
<td>• The sponsor-generated CRF for routine AEs</td>
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<tr>
<td>• The probable relationship of the AE to the investigational product</td>
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<tr>
<td>• The date (and time) of AE onset</td>
<td></td>
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<tr>
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<td>• The outcome</td>
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</table>

### 4. Pharma-generated IND safety reports

<table>
<thead>
<tr>
<th><strong>RESPONSIBILITIES TO IRB</strong></th>
<th><strong>RESPONSIBILITIES TO Pharma</strong></th>
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<tbody>
<tr>
<td>• Submit IND safety reports to the IRB if applicable, see Algorithm for Review and Distribution of IND Safety and MedWatch Reports (Attachment D) and retain a copy of the transmittal memo in the study regulatory binder.</td>
<td>• Acknowledge receipt of expedited safety report to Pharma with letter/facsimile.</td>
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<td>• Copy Pharma on the transmittal memo to the IRB, if required.</td>
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<td></td>
<td>• Inform Pharma of action required by the IRB, such as revisions to the informed consent form.</td>
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<td></td>
<td>• Follow up with the Pharma as required.</td>
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</table>
FORM FDA 3500

For VOLUNTARY reporting of adverse events, product problems and product use/medication errors

A. PATIENT INFORMATION

1. Patient Identifier
   - Name(s)
   - Date of Birth
   - Sex
   - Race
   - Ethnicity
   - Other Relevant History, Including Preexisting Medical Conditions

2. Other Relevant History
   - Drugs, alcohol, smoking, or other substances
   - Other Relevant History

B. ADVERSE EVENT, PRODUCT PROBLEM

3. Date of Event
   - Reporting Date
   - Date of Event
   - Date of Report

4. Product Name
   - Brand Name
   - Model
   - Lot

C. PRODUCT AVAILABILITY

5. Product Available for Evaluation?
   - Yes
   - No
   - Unknown

D. SUSPECT PRODUCTS

6. Name, Strength, Manufacturer/Compounder
   - Name
   - Strength
   - Manufacturer/Compounder

7. Other (Concomitant) Medical Products
   - Name
   - Strength

8. SUSPECT MEDICAL DEVICE

9. Event:
   - Was the device removed?
   - Did the device cause serious harm or mortality?

10. F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

11. REPORTER (See confidentiality section on back)

12. Source:
    - https://www.fda.gov/media/76299/download
SM-306.01 SOP for Adverse Event Reporting
Effective date of Version: 01 September 2020
Replaces previous Version: 01 June 2017

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For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

1. Type of Report
   - Initial
   - Follow-up

2. Key Event Data
   - Description
   - Date
   - Location
   - Cause

3. Event Summary
   - Description
   - Date
   - Location
   - Cause

4. Medical Device
   - Description
   - Date
   - Location
   - Cause

5. Other
   - Description
   - Date
   - Location
   - Cause


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ATTACHMENT D:
Algorithm for Review and Distribution of IND Safety and Med Watch Reports

IND Safety and/or MedWatch Reports sent to Georgia CORE and the Principal Investigator (i.e. the Investigator who initiated the study) by pharma

<\= 48 hours of receipt

Georgia CORE determines if action plan (e.g., recommended change to protocol and/or informed consent) is present

YES

PI modifies protocol and/or informed consent

<\= 10 days (7 da7s is threatening or fatal

Send revised protocol and/or informed consent to PI’s IRB with IND safety report

NO

Georgia CORE sends IRB approved revised protocol and/or informed consent to the central IRB for community investigators

NO

Georgia CORE sends documents to community investigators with note that states that upon review by the PI there is no need to change the protocol and/or informed consent

PI reviews documents to determine if adverse events place subjects or others at greater risk of physical or psychological harm than was previously known or recognized as it applies to the Georgia CORE PI initiated study

NO

Community investigators review the documents and determine if they need to discuss a potential need for a change with the PI

YES

Community investigators send documents to local IRB, if required by their local IRB guidelines

NO