

Study Management
SM – 306.00

STANDARD OPERATING PROCEDURE FOR
Adverse Event Reporting

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1. INTRODUCTION

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 pharma (the manufacturer of the investigational product) and to the IRB is mandatory. This standard operating procedure (SOP) describes the steps Georgia CORE follows to fulfill the regulatory and clinical requirements for adverse event reporting.

2. SCOPE

This standard operating procedure (SOP) describes the responsibilities of Georgia CORE for managing, 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 its resolution have been completed. This SOP also describes the mechanisms used to provide the information necessary for Georgia CORE to prepare Investigational New Drug (IND) safety reports. Finally, the procedures for Georgia CORE to process and transmit IND safety reports received from pharma 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
01 March 2014	NCI Guidelines for Auditing Clinical Trials for the NCI National Clinical Trial Network for the (NCTN) Program, Community Clinical Oncology Program (CCOP/NCI Community Oncology Research Program (NCORP) and Research Bases.
23 November 2016	Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS): NCI Guidelines for

	Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs https://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm
October 1998	FDA Information Sheets: Continuing Review After Study Approval
May 1997	International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline
January 15, 2007	Office for Human Research Protections (OHRP), Department of Health and Human Services (HHS): Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
January, 2009	FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection

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 3500A
- D. Algorithm for Review and Distribution of IND Safety and MedWatch Reports

6. RESPONSIBILITY

This SOP applies to Georgia CORE leadership and staff members involved in ensuring the appropriate management of adverse events. This includes the following:

- President and CEO
- Chief Medical Officer (CMO)
- Georgia CORE staff and consultants

7. DEFINITIONS AND GLOSSARY

The following definitions from the Code of Federal Regulations and the International Conference on Harmonization, 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) (also known as Serious Adverse Event (SAE): 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.

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

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 Pharma
- C. Reporting to the IRB

9. PROCEDURES

A. Managing adverse events

- Research Staff/Consultant When a site reports an adverse change in a subject from

	baseline or pretreatment condition, check 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 applicable to Non-NCTN trials only)
	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 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 pharma 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/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 for Research staff learning of SAE: https://ctepcore.nci.nih.gov/ctepaers/pages/task?rand=1490109392775
	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.

B. Handling IND safety reports from pharma

<ul style="list-style-type: none"> • Research Staff/Consultant 	<p>Promptly review IND safety reports received from pharma and follow the Algorithm for Review and Distribution of IND Safety and MedWatch Reports (Attachment D).</p>
	<p>File IND safety reports and MedWatch Reports and related communication in the Georgia CORE IND Safety Report electronic folder for the appropriate trial.</p>

C. Reporting to the IRB

<ul style="list-style-type: none"> • Research Staff/Consultant 	<p>Notify the central IRB of all serious or alarming events occurring at a Georgia CORE network site, which is using the central IRB, according to the central IRB guidelines.</p> <p>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.</p> <p>Ensure that all IND safety reports received from pharma 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).</p> <p>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.</p> <p>Obtain documentation from Georgia CORE network sites, using local IRBs, showing that they have completed reports to the local IRB as noted in the above 3 action items.</p> <p>File documentation in the Georgia CORE IND Safety Report electronic folder for the appropriate trial.</p>
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10. History of Changes

Version Number	Section Number	Modification	Approval Date
306.00	All	Original Version	
306.00	All	No change was necessary	09 March 2012
306.00	All	No change was necessary	01 June 2014
306.00	3, 7, 9A, C	Additional guidelines added, clarification, NCTN and NCI CIRB reporting guidelines added	21 March 2017

Attachment A

PROCEDURES for MANAGING ADVERSE EVENTS

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

REGULATIONS	PROCEDURES
<p>Definition of an adverse event (AE):</p> <ul style="list-style-type: none"> • 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 <p>Serious adverse events (SAEs) include:</p> <ul style="list-style-type: none"> • 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 	<p>Ensure that the following are appropriately investigated:</p> <ul style="list-style-type: none"> • 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 <p>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:</p> <ul style="list-style-type: none"> • Discontinue the investigational product, comparator, or placebo • Reduce dosage (as per protocol) • Interrupt drug (as per protocol) • Challenge (as per protocol) <p>Follow the subject and assess the adverse event until stabilized/resolved.</p>

2. Site SAE Reporting to Sponsor (Georgia CORE)

- 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.

SPONSOR RESPONSIBILITIES	SITE RESPONSIBILITIES
<p>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 10 calendar days after initial receipt of the information. When Georgia CORE is the sponsor, Georgia CORE is required to notify pharma within the time period specified in the protocol.</p> <p>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.</p>	<p>To meet expedited reporting requirements, inform the sponsor as soon as possible after the subject is stabilized.</p> <p>Provide as much of the following information as is available:</p> <ul style="list-style-type: none"> • 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. Site Research documentation

SOURCE DOCUMENTATION	CASE REPORT FORM COMPLETION
<p>Record in the source documentation, noting</p> <ul style="list-style-type: none"> • 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 	<p>Complete the appropriate case report form(s)</p> <ul style="list-style-type: none"> • The site-prepared data collection form for SAEs or • The sponsor-generated CRF for routine AEs

4. Pharma-generated IND safety reports

RESPONSIBILITIES TO IRB	RESPONSIBILITIES TO Pharma
<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • Acknowledge receipt of expedited safety report to Pharma with letter/facsimile. • Copy Pharma on the transmittal memo to the IRB, if required. • Inform Pharma of action required by the IRB, such as revisions to the informed consent form. • Follow up with the Pharma as required.

Attachment B
FORM FDA 3500

Attachment C
FORM FDA 3500B

To retrieve the above forms go to the appropriate web site:

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>

Download the appropriate form.

Attachment D

