23. SERIOUS ADVERSE EVENTS

23.1 Definition of Serious Adverse Event

Seriousness

A serious adverse event is any adverse event that results in any of the following outcomes:

- death;
- is life-threatening;
- requires in-patient hospitalization, or prolongation of an existing hospitalization;
- results in persistent or significant disability or incapacity;
- results in a congenital anomaly / birth defect; or
- is an otherwise important medical event.

"Life-threatening" means that, in the view of the Investigator, the participant was placed at immediate risk of death from the event as it occurred.

A "disability" is a substantial disruption of a person's ability to conduct normal life functions.

An **"important medical event"** is any other event that jeopardized the health of the participant and required medical or surgical intervention to prevent one of the other outcomes listed above from occurring.

"Requires or Prolongs Hospitalization": Hospital admissions scheduled prior to the study are not considered serious adverse events unless the hospitalization is prolonged due to an adverse event. Planned admissions as part of a study, hospitalizations for scheduled treatment of a preexisting condition that has not worsened, and hospitalization for an elective procedure are not considered serious adverse events. Hospitalizations for fewer than 24 hours and emergency room/department visits do not meet the SAE category of "New or prolonged hospitalization".

Intensity

Mild
Events are usually transient, require no special treatment, and do not interfere with the participant's daily activities.

Moderate
Events usually introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe
Events interrupt a participant's usual daily activity and generally require systemic drug therapy or other treatment.

Causality

Very Likely
The adverse event was definitely related to the study intervention. The temporal relationship of the serious adverse event to the study intervention makes a causal relationship definite. There are no other explanations for the event.

Probably Related
There is a reason to believe that the serious adverse event was probably caused by the study intervention. The temporal relationship of the serious adverse event to study intervention makes a causal relationship probable, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event.

Possibly Related
There is a reasonable possibility that the serious adverse event may have been caused by the study intervention. The temporal relationship of the serious adverse event to study intervention makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event.

Doubtful
It is unlikely that the serious adverse event was caused by the study intervention. The temporal relationship of the serious adverse event to the study intervention administration makes causal relationship unlikely and other drugs, therapeutic interventions or underlying conditions provide a more likely explanation for the event.

Not related
There is not a reasonable possibility that the serious adverse event may have been caused by the study intervention. The temporal relationship of the serious adverse event to study intervention makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide sufficient explanation for the observed event.

23.2 Expedited SAE Reporting Protocol

Note: The participants will be able to notify any of the site Principal Investigators or research staff by phone or page, day or night, to report a serious adverse event. Participants will be asked by study staff to immediately inform the Principal Investigators or their staff of any problems that occur, especially a serious illness or hospitalization. It

is the sites' responsibility to query the participant for the occurrence of any adverse events when in contact with the study participant for any reason.

Initial submission

Site Manager is responsible to report all Serious Adverse Events that occur from the first baseline visit through the participant's completion or early discontinuation from the study within 24 hours of the knowledge of the event. The first report must be marked as "initial." A three pages SAE form should be faxed directly to Coordinating Center at:

DCRI Safety Surveillance
Fax number: (919) 668-7138 or 1-866-668-7138
Phone number: (919) 668-8624 or 1-866-668-7799

If requested, supporting documentation must be sent by the site in a **blinded fashion**, and the participant will only be identified by the participant's number on each page of supporting documentation. All other participant's identifiers should be deleted from the supporting documents before forwarding to the Coordinating Center.

The SAE forms and the fax confirmation sheet must be retained at the investigational site in a participant's binder. The Coordinating Center will contact you if additional data and/or data clarifications are required.

All SAEs must be reported to the site's local IRB in accordance to the site's local practices and IRB requirements in reporting of adverse and serious adverse events.
.

Follow-up submission

For all SAE not resolved at the time of Initial submission of SAE, a Follow-up SAE form will be required. A new SAE form (this time report type must be marked as "Follow-up" with appropriate number indicated) should be submitted to Coordinating Center as soon as the data becomes available.

SAEs not resolved by the end of the study or that have not resolved upon discontinuation of the participant, will be followed by the CALERIE clinical site until the event resolves, stabilizes or returns to baseline or until 30 days after the last randomized subject completes the study.

Any follow-up data should be submitted in the same format and timeline as described above.

Note:

Make sure that SAE information captured on the AE page is matching the information for the same event captured on the SAE form.

CALERIE 2

Frequently Asked Questions for Expedited Reporting of Serious Adverse Events

1. Who do I call if I have questions and where do I send the serious adverse event information?

DCRI Safety Surveillance
Phone - 919-668-8624 or 1-866-668-7799
Fax - 919-668-7138 or 1-866-668-7138
E-mail address: Safetysurveillance@dcri.duke.edu
Hours: 8 AM – 5 PM Monday – Friday
(All voice mail messages answered the next business day.)

2. How soon do I need to submit information about a serious adverse event?

All serious adverse events occurring **from baseline through participant's discontinuation from the study** must be reported to DCRI Safety Surveillance (by faxing SAE form) **within 24 hours** of your first knowledge of the event.

Do NOT delay faxing the SAE form because of missing information or signatures. In most instances, because DCRI Safety Surveillance is dealing with regulatory and/or sponsor timelines, it is more important that we receive notice of the occurrence of the SAE. DCRI Safety Surveillance will work with you to amend and/or complete the forms in an appropriate time period.

3. What forms should I use to report an SAE?

- Serious adverse events must be recorded on the **SAE Form.**
- All AE s and SAEs will also be recorded on the AE page in the Case Report Form.

4. What is a serious adverse event?

A serious adverse event is any untoward event that:

- Is **fatal**
- Is **life-threatening**
- Requires inpatient **hospitalization** or causes prolongation of existing hospitalization
- Results in a **persistent or significant disability/incapacity**
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** that may not result in death, be life-threatening, or require inpatient hospitalization, but may be considered an SAE when, **based on appropriate medical judgment**, it may **jeopardize** the patient **and may require medical or surgical intervention** to prevent one of the outcomes listed above. (CFR Title 21 Part 312.32)

5. Who should determine the causality?

Site's Principal Investigator (if an M.D.) or site's physician (co investigator) should determine causality.

6. Do we need to submit any source documents with the SAEs form?

Every effort should be made to include requested information on the form rather than simply submitting source documents. Source documents may be submitted to clarify information, but should be limited to a small number

of pages unless absolutely necessary. Source documents should be used as supporting documentation rather than as a substitute for completing the form. If specific documents are needed, they will be requested.

7. How will I know if any additional information is needed to complete the reporting of serious adverse event?

Each time we receive an SAE form, we will fax you a "Request for Additional Information" or a "Request for Follow-up Information". These faxes will provide you and DCRI Safety Surveillance with a listing of all outstanding items that are required to complete each form. DCRI Safety Surveillance will not fax a notice that the form is completed.

8. What is the difference between an initial form and a follow-up form?

Follow-up forms should be used to submit additional information when:

- There is a change in the participant's status
- There is additional data available
- There are changes in data previously reported
- The outcome of the event reported is determined

For example, if you listed the outcome on an initial form as "IMPROVING", when sufficient information becomes available to update the outcome, you must submit a new SAE form marked as a Follow-up report type. For another example, if the date your PI signs the initial form is January 15 and new information concerning the SAE occurs on January 20, that new information must be submitted on a new SAE form with Follow-up checked as report type.

When you submit the Follow-up form, we only require you to list the new information concerning the event and the identifying information from the initial form (i.e., site number, participant's study number, participant's initials, SAE term, and SAE onset date). You do not need to reproduce all of the information from the previous form. Please DO NOT send us a copy of the initial SAE form with the initial block on page 1 crossed out and Follow-up checked. A Follow-up form must be a completed NEW form with only the identifying and new information provided on it.

9. What is an amended initial or an amended follow-up form?

Any time you make a change to information previously reported on an initial or follow-up form, you are making an amendment to the form. All changes or additions need to be dated and initialed for tracking purposes.

Note:
Please make sure that the information provided on the SAE form is matching information provided on the AE page for the same event.

CALERIE 2

Frequently Asked Questions for Expedited Reporting of Serious Adverse Events

10. How do I complete these sections on the SAE form?

SAE term	Only one SAE term should be checked per form. If participant had more then one event, please submit a separate SAE form for each event. Remember that **"Death"** is an outcome and it should not be used as a SAE term. The cause of death should be listed as a SAE term.
SAE onset date	The date that the event became serious rather than the date of first signs/symptoms should be provided.
Outcome	The date the specific event itself resolved should be entered here. If participant died , please enter date of participant's death as a "date of outcome"
Narrative	A narrative description of the event from onset through the initial report date or resolution of the event must be provided. Relevant laboratory/diagnostic tests and any treatments provided must be included. Information should be provided in a concise, easy to follow format commenting on the participant's enrollment in the study, the occurrence of the event, and the resolution of the event. Dates and times relevant to the description of the event must be included. The narrative may be continued on a separate page if necessary.
Information Source	Be sure to complete this section. Do not delay faxing the forms because of missing signature. After Principal Investigator signs the forms, you will re-fax them to us.

.

Date received at DCRI Safety Surveillance

SERIOUS ADVERSE EVENT FORM

Report Type: ❒ **Initial** ❒ **Follow-up #** ____

Participant's Number: __ __ -- __ __ __ __ **Participant's initials:** __ __ __

SAE Details:	**Participant's Details:**
SAE Term (*Medical Diagnosis*)**:**	**Date of birth:** __ __ / __ __ __ / __ __ __ __ (day month year)
SAE Onset Date: __ __ / __ __ __ /__ __ __ __ (day month year)	**Gender:** ❒ **Male** ❒ **Female**
SAE Stop Date: __ __ / __ __ __ /__ __ __ __ (day month year)	

Serious Reporting Criteria: (check all that apply)	**Causality & Intensity:** (check only one)	**Outcome:** (at time of report) (check only one)
❒ Death ❒ Life-threatening ❒ Persistent or significant disability or incapacity ❒ Prolonged or required hospitalization ❒ Congenital anomaly or birth defect ❒ Other significant event requiring medical and/or surgical intervention	**Causality:** ❒ None ❒ Doubtful ❒ Possibly ❒ Probably ❒ Very Likely **Intensity:** ❒ Mild ❒ Moderate ❒ Severe	❒ Still present and unchanged ❒ Improving ❒ Resolved ❒ Resolved with sequelae ❒ Death If Death, date of death __ __/__ __ __/ __ __ __ __ (day month year)

Action Taken with Study Intervention:

❒ None

❒ Intervention interrupted

❒ Medical therapy required

❒ Intervention discontinued **Complete and fax the Permanent Discontinuation from CR Intervention Form**

*****Notify DCRI Safety Surveillance of the SAE within 24 hours after your knowledge**
*****Fax SAE form to DCRI Safety Surveillance at 919-668-7138 or 1-866-668-7138**

Date received at DCRI Safety Surveillance

SERIOUS ADVERSE EVENT FORM

Report Type: ❒ **Initial** ❒ **Follow-up #** ____

Participant's Number: __ __ -- __ __ __ __ **Participant's initials:** __ __ __

❒ Other _____

*****Notify DCRI Safety Surveillance of the SAE within 24 hours after your knowledge**
*****Fax SAE form to DCRI Safety Surveillance at 919-668-7138 or 1-866-668-7138**

calerie

Date received at DCRI Safety Surveillance

SERIOUS ADVERSE EVENT FORM

Report Type: ❒Initial ❒ Follow-up # ____

Participant's Number: __ __ -- __ __ __ __ Participant's initials __ __ __

Medical History (*relevant to event):*

Concomitant Medication *(do not list medication administered to treat this event)*:

Medication	Dose & Unit	Frequency	Route	Start Date day/month/year	Continued	Stop Date day/month/year
					❒Yes ❒ No	
					❒Yes ❒ No	
					❒Yes ❒ No	
					❒Yes ❒No	
					❒Yes ❒No	
					❒Yes ❒ No	
					❒Yes ❒No	

Relevant Lab Tests:

Tests	Date day/month/year	Value/Results	Normal Range

*****Notify DCRI Safety Surveillance of the SAE within 24 hours after your knowledge**
*****Fax SAE form to DCRI Safety Surveillance at 919-668-7138 or 1-866-668-7138**

Date received at DCRI Safety Surveillance

SERIOUS ADVERSE EVENT FORM

Report Type: ❒Initial ❒ Follow-up # ____

Participant's Number __ __ -- __ __ __ __ **Participant's initials** __ __ __

Please Provide a Brief Summary of the Event
_____
Please Describe the Sequence of Events Including Action Taken, Treatment Given, Hospital Dates, etc.

Information Source	
Date Investigator Notified of event: __ __/__ __ __/__ __ __ __ (day month year)	Date of this report: __ __/__ __ __/__ __ __ __ (day month year)
Person completing form: _____	Phone #: _____
PI name: _____	Fax # : _____
PI signature**:** _____	Date of signature: __ __/__ __ /__ __ __ __ (day month year)

*****Notify DCRI Safety Surveillance of the SAE within 24 hours after your knowledge**
*****Fax SAE form to DCRI Safety Surveillance at 919-668-7138 or 1-866-668-7138**

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

CALERIE phase 2

SAE REPORTING

All serious adverse events that occur **from the baseline through participant's discontinuation from the study** must be reported within 24 hours of your first knowledge of the event to the
DCRI Safety Surveillance.

Please call if you have any questions about SAE reporting or forms completion.

DCRI Safety Surveillance

☎ Phone - 919-668-8624 or 1-866-668-7799

⁎ Fax - 919-668-7138 or 1-866-668-7138

E-mail – safetysurveillance@dcri.duke.edu
Hours: 8 AM – 5 PM Monday – Friday
(All voice mail messages answered the next business day)

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

calerie

From: _____

Fax Number: _____

Phone Number: _____

Date: _____

Page 1 of ____

SAFETY
SURVEILLANCE
Phone: 919-668-8624
Phone: 1-866-668-7799

Fax: 919-668-7138
Fax: 1-866-668-7138

Trial: CALERIE (phase 2)

SERIOUS ADVERSE EVENT REPORT

Participant's Number: __ __ - __ __ __ __

The following are included in this transmission:

- ❑ Initial SAE Form
- ❑ Follow-up SAE Form
- ❑ Answer to Query
- ❑ Source Documents (*specify):*

_____

_____

ALL SERIOUS ADVERSE EVENTS THAT MEET EXPEDITED PROTOCOL REPORTING CRITERIA
MUST BE REPORTED WITHIN 24 HOURS of your knowledge of the event

Please fax this form to DCRI Safety Surveillance at 919-668-7138 or 1-866-668-7138.
Please contact DCRI Safety Surveillance at 919-668-8624 if you have any questions.

SAE form instruction

All serious adverse events that occur from beginning of study intervention through the follow-up period will be reported to DCRI Safety Surveillance within 24 hours

Fax all completed SAE forms to:

Duke Clinical Research Institute Safety Surveillance • Fax number: (919) 668-7138 or 1-866-668-7138; Phone: (919) 668-8624 or 1-866-668-7799

General Instructions for form completion:

- **Print legibly.**
- **Avoid using abbreviations.**
- **Complete all information on the form as you know it at the time of the report. Minimum information required for a valid initial submission is the participant number, the event, the study name and a reporter.**
- **Date format DD/MMM/YYYY (i.e., 01/Oct/2006)**
- **When data items are unknown, such as a date, enter UNK.**
- **Changes to the initial SAE forms may be made by drawing one line through the initial information; initial and date the change, and write the changed information in the field.**
- **A Follow-up SAE form is required when new follow-up information is submitted. Complete participant's ID number, initials, report type, SAE term SAE onset date and the information source.**
- **Ensure that the SAE data and the AE case report form (CRF) data are consistent.**
- **Enter relevant information from source documents on the SAE form, e.g., summarize the discharge summary in the narrative field on page 3, and write the relevant lab results on the SAE form in the lab field on page 2. Do not leave a field blank by writing "see attached" in reference to hospital records.**

DATA ITEM on SAE form	INFORMATION REQUIRED for the DATA ITEM
Date and time received at DCRI (pages 1, 2 & 3)	Leave blank. This field will be completed by DCRI Safety Surveillance.
1. Report Type (pages 1, 2 & 3)	Check the appropriate box, 'Initial' for the initial reporting of an event, including changes. Check 'Follow-up' when a new follow-up SAE form is required for reporting additional or follow-up information. For Follow-up reports enter the number of the report (i.e., Follow-up #1, #2, etc.).
2. Subject # (pages 1, 2 & 3)	Enter the 2-digit number assigned to the site, and the 4-digit number assigned to the subject.
3.Subject's initials (pages 1, 2 & 3)	Enter the subject's initials as recorded in the CRF.
4.SAE term (Medical Diagnosis) (page 1)	State the diagnosis, whenever possible. If diagnosis is unknown, state the primary symptom. Only <u>one</u> event should be reported per form. Do not list procedures as the SAE term; rather list the medical reason

SAE form instruction

	for the procedure. ****Note: Remember that "Death" is an outcome and it should not be used as a SAE term. The cause of death should be listed as the SAE term.*
5.SAE onset date (page 1)	Enter the date the event first met serious criteria.
6.SAE Stop Date (page 1)	Enter the date the event resolved or resolved with sequelae. (See the outcome field.) Leave blank if outcome is still present and unchanged or improving.
7.Date of birth (page 1)	Enter the subject's date of birth as recorded in the CRF.
8.Gender (page 1)	Check the appropriate box for either Male or Female.
9.Serious Reporting Criteria (page 1)	Check all relevant serious criteria that apply as assessed by the Principal Investigator.
10.Causality and Intensity (page 1)	• Enter the appropriate relationship of the event to study as assessed by the Principal Investigator. • Enter the appropriate intensity of the event as assessed by the Principal Investigator.
11.Outcome (page 1)	• Check the current outcome of the event at the time of the report (may not be final outcome for event). Check only one box. If the event is resolved or resolved with sequelae, complete the stop date on page 1. • If the outcome was death, enter the date of death.
12.Action taken with study (page 1)	Check the action taken with study intervention as a direct result of the event.
13.Medical History (page 2)	Enter any past or current conditions that are relevant to the event, including allergies and prior occurrences of similar events. If there is no relevant history, enter "none".
14.Concomitant medications (page 2)	Enter any medications that the subject was taking <u>at the time of</u> <u>the onset of the event</u>. Include dose/unit, frequency and the start date. Check "No" for continuing and enter the stop date if the medication was discontinued. Check "Yes" for continuing if the medication was continued. Do not include treatment medications for the event in this field. If there are no concomitant medications, enter "none".
15.Relevant Lab Tests (page 2)	Enter any lab tests relevant to this event, including date performed, value/results, units, and normal range. If there are no relevant lab tests, enter "none".
16.Brief Summary of the Event (page 3)	Enter a 1 sentence summary of the event on the line provided.
17.Description of Serious Adverse Event (page 3)	Enter a summary of the event (including action taken, treatment, hospitalization dates, etc.).

SAE form instruction

18.Information Source (page 3)	Date Investigator notified of event: • Enter the date the Investigator became aware of this event. Date of this report: • Enter the date this form was completed. Person completing form: • Enter the name of the person completing this form. Fax and telephone numbers: • Enter the fax and telephone number of the person to be contacted for information regarding this event. PI name: • Enter the name of the Principal Investigator. PI signature and Date of signature: • Principal Investigator must sign and date this form when completed. Please provide PI's signature with every submission of the SAE form.