26. PERIODIC SAFETY REPORTS

This MOP section describes CALERIE safety reports and reporting procedures that must be followed in Phase 2 study. There are two types of reports: a) individual case reports presenting adverse findings in a participant and b) summary reports. Case reports are to be reviewed by CALERIE Safety Committee, and, except the SAE, will not be routinely provided to the DSMB. However, the DSMB may request any of these reports at any time. Summary safety reports are to be reviewed by both CALERIE Safety Committee and the DSMB as described in section 26.1.2 below.

26.1 Individual Case Reports

At monthly calls, physician-investigators are to inform CALERIE Safety Committee about all new serious adverse events and severe adverse events, all cases of elevated potassium levels, anemia, depression, newly diagnosed diseases that require treatment, all cases where the CR intervention was temporary or permanently discontinued, and other significant safety issues observed at their clinical sites. However, because of the low overall value of many of such events, only the following individual case reports need to be prepared and provided to the Safety Committee by the sites.

26.1.1 Candidate Ineligibility Report

Exclusion criterion "History or clinical manifestation of any other significant metabolic, hematologic, pulmonary, cardio-vascular, gastrointestinal, neurologic, immune, hepatic, renal, urologic disorders, or cancer that, in opinion of the investigator, would make the candidate ineligible for the study" provides a reasonable room for applying the best medical judgment by a physician-investigator when assessing eligibility of the participants.

However, this criterion also introduces some level of arbitrariness about the definition of "significant." Thus, when physician-investigator is hesitant about the candidate's eligibility either due to some disease/condition or an abnormal test result, and in order to ensure uniformity in applying this exclusion criterion across the three clinical sites, he is required to prepare candidate eligibility report for the Safety Committee.

The CALERIE Safety Committee will review medical information for such candidate provided by the site's physician-investigator and confirm candidate's ineligibility via email. Within 48 hours of receiving the candidate ineligibility report from the CC, members of the Safety Committee will provide their opinion about candidate's ineligibility to the Committee's Chair and the CC via email. After receiving emails from the Committee's members, the Chair will immediately inform the site's physician-investigator about the Committee's decision.

Candidate ineligibility report is to be written using the Candidate Ineligibility Report form (MOP section XX) and is to provide the following information:

- Participant ID
- Demographics (gender, age, height, weight, BMI)
- Relevant medical and medication history

- Relevant physical examination
- Relevant laboratory and/or other test results (e.g., K+, BDI score, etc.)
- Candidate's eligibility status (eligible, not eligible, could be eligible at a later time – e.g. reassessment in 2 months)

Roles and Responsibilities

Study Manager
Immediately after receiving Candidate Ineligibility Report from physician-investigator, email the report to the CC at:

- Galan006@notes.duke.edu and bill.blasko@duke.edu

Coordinating Center
Within 24 hours of receiving report from the site, email it to all members of the Safety Committee:

- James Rochon, Ph.D. at rocho001@notes.duke.edu
- Sergei Romashkan, M.D. at romashks@nia.nih.gov
- William E. Kraus, M.D. at william.kraus@duke.edu
- Edward Saltzman, M.D. at ESaltzman@tufts-nemc.org
- Steve Smith, M.D. at SmithSR@pbrc.edu
- John Holloszy, M.D. at JHOLLOSZ@im.wustl.edu

Safety Committee Members

- If necessary, request any additional information from the study manager who emailed the report
- Inform the Committee Chair about your request and indicate what information was requested
- Review the report
- By email, confirm candidate's ineligibility to the Committee's Chair within 48 hours of receiving the report from the CC

26.1.2 SAE Report

Standard SAE form (CRF pages 282-284) must be used to submit all initial and follow-up SAE reports. For details on completing SAE form please refer to MOP section 23.0 *Serious Adverse Events*. At monthly teleconferences (or emergency calls), CALERIE Safety Committee is to review the SAE reports and determine whether and what corrective action is necessary.

Roles and Responsibilities

Study Manager
Within 24 hours of first knowledge of the event:

- Complete all sections of the SAE form except those that will be completed by physician-investigator and provide form to the physician-investigator for further completion

- Fax initial SAE reports to:
    - DCRI at **(919) 668-7138** or **1-866-668-7138 to the attention of "CALERIE".**
- Fax the follow-up report to the Coordinating Center, when available

Coordinating Center

Within 24 hours of receiving the SAE report from a site:

- Fax initial SAE reports to:
    - Members of the Safety Committee
        - **Provide Report personally** Attn.: James Rochon, Ph.D.
        - **(301) 480-1066** Attn.: Sergei Romashkan, M.D.
        - **(919) 684-8907** Attn.: William E. Kraus, M.D.
        - **(617) 556-3344** Attn.: Edward Saltzman, M.D.
        - **(225) 763-3027** Attn.: Steve Smith, M.D.
        - **(314) 362-7657** Attn.: John Holloszy, M.D.
    - DSMB Chairman Jeff Halter at **(734) 763-2064**
- Fax the follow-up report to the CALERIE Safety Committee and the DSMB Chairman, when available

Physician-investigator

Within 24 hours of first knowledge of the event

- Complete the following sections of the SAE form:
    - Serious Reporting Criteria
    - Causality
    - Outcome
    - Medical History
    - Relevant Lab Tests
    - Description of a Serious Adverse Event
- Return form to the study manager

Safety Committee

Within 48 hours:

- Review the SAE reports
- If necessary, request any additional information from the study manager who sent the report
- Inform the Committee Chair about your request and indicate what information was requested
- In your correspondence to the Safety Committee Chair indicate whether you want to request an emergency teleconference of the committee to discuss an event, or the event could be discussed at a regular monthly teleconference
- At monthly teleconference (or emergency call): determine whether and what corrective action is necessary
- Inform CALERIE Steering Committee whether it is safe to continue the study and provide recommendations about the corrective action, if necessary

26.1.3 Safety Surveillance Reports

The Safety Surveillance Reports are to be prepared by the study manager and physician-investigator or psychologist (for eating or psychiatric disorder and/or depression) when any of the following events occur:

- Potassium level > 5.5 mEq/L
- Anemia (Hb, Htc, RBC below the LLN or 5% decrease in Htc from baseline)
- Excessive weight loss (BMI < 18.5 kg/m^2)
- Depression (BDI-II score > 20)
- Possible eating disorder (BAM t-score < 30 and ≥ 70 and/or MAEDS t-score ≥ 70)

There are five separate safety surveillance report forms that must be used to monitor implementation of the appropriate safety surveillance protocols:

- Elevated Potassium Episode Report (CRF pages 291-292)
- Anemia Episode Report (CRF pages 293-295)
- Excessive Weight Loss Episode Report (CRF pages 285-286)
- Depression Episode Report (CRF pages 287-288)
- Eating Disorder Episode Report (CRF page 289)

For details on safety surveillance protocols please refer to MOP section 24.

General Reporting Requirements

A study manager needs to start a report form for each confirmed event listed above that triggers any of the safety surveillance protocols. If initial abnormality is confirmed by a repeated test or appropriate medical professional, follow a safety surveillance protocol for an appropriate event and complete the report form. Completed event report **MUST BE SENT** to the CC. Initial abnormality must be confirmed by a repeated test for:

- potassium levels elevated above 5.5 mEq/L;
- decrease in Hb, Htc, RBC levels below the lower limit of normal (LLN) or 5% decrease in Htc from baseline;

For excessive weight loss (BMI < 18.5 kg/m^2), a repeated calculation of the BMI serves as a confirmatory test.

For depression and eating disorders, initial abnormality must be confirmed as follows:

- depression (BDI-II score is ≥ 20): a study psychologist or a qualified mental health professional must confirm a diagnosis
- an eating disorder must be confirmed by IDED-IV-IV semi-structured interview administered by a study psychologist or a qualified medical professional

Roles and Responsibilities

Physician-investigator or psychologist

For confirmed events:

- Complete “Description of the episode” section

NOTE: you do not need to complete this section if a discontinuation report for this event was already submitted to the CC

Study Manager

For confirmed events:

- Complete all sections of the form except "Description of the episode" section and provide form to the physician-investigator or psychologist for further completion
- Fax completed report to the CC to: **(919) 668-7138 or 1-866-668-7138 to the attention of "CALERIE"**

For events that were not confirmed by a repeated test and/or medical professional:

- Complete appropriate sections of the form
- Retain completed form in a participant binder

Coordinating Center

At least 48 hours prior to the teleconference, fax the reports to all members of the Safety Committee (please see section 26.1.2 for contact information).

26.1.4 Discontinuation from CR Intervention Reports

Discontinuation report is to be prepared by physician-investigator or psychologist (for eating or psychiatric disorder and/or depression) when events leading to temporary or permanent discontinuation of the CR intervention do not meet criteria for the SAE. These reports must be provided to the CC within 5 days of discontinuation of the CR intervention using the Discontinuation from CR Intervention Report form (CRF Pages 298-301) and must include the following information:

- Participant ID
- Type of discontinuation (temporary or permanent)
- CR intervention discontinuation date
- Reason for discontinuation
- Demographics (gender, age, height, weight, BMI)
- Relevant medical and medication history
- Relevant physical examination
- Relevant laboratory and/or other test results (e.g., K+, BDI score, etc.)
- Action taken (observation, advise to seek medical help outside of the study)

At monthly teleconferences (or emergency calls), CALERIE Safety Committee is to review the Discontinuation from the Intervention Reports and determine whether and what corrective action is necessary.

Roles and Responsibilities

Physician-investigator or Psychologist

Within 5 days of discontinuation of the CR intervention:

- Complete, sign and date Discontinuation from CR Intervention Report form
- Provide report to the study manager

Study Manager

Immediately after receiving a report from physician-investigator, fax the report to:

- DCRI at **(919) 668-7138 or 1-866-668-7138 to the attention of "**CALERIE".

Coordinating Center

Within 48 hours fax the reports to all members of the Safety Committee (please see section 26.1.2 for contact information).

Safety Committee Members

Within 48 hours:

- Review Discontinuation from CR Intervention Reports
- If necessary, request any additional information from the study manager who sent the report
- Inform the Committee Chair about your request and indicate what information was requested
- In your correspondence to the Safety Committee Chair please indicate whether you want to request an emergency teleconference of the committee to discuss an event or event could be discussed at a regular bi-weekly teleconference
- At monthly teleconference (or emergency call): determine whether and what corrective action is necessary
- Inform CALERIE Steering Committee whether it is safe to continue the study and provide recommendations about the corrective action, if necessary.

26.2 Summary Reports

Using information provided by the clinical sites, laboratories and reading centers, the CC is to prepare summary safety reports including all discontinued participants, adverse events, laboratory and other safety test abnormalities. These reports are to be reviewed by the Safety Committee and by the DSMB as indicated below. The Safety Committee and the DSMB are to determine whether there are concerns about participants' safety and whether and what study-wide corrective action is necessary.

Reports Review Schedule

Safety Committee:

The following reports to be reviewed semi-annually prior to the DSMB meetings:

- Serious and Severe AE Report
- Discontinuation Report
- AE Report
- Elevated Potassium Reported
- Anemia Report
- Depression Report
- Excessive Weight Loss Report
- Eating Disorders Report

DSMB

The following reports to be reviewed semi-annually, unless otherwise requested by the Board:

- Serious and Severe AE Report
- AE Report
- Depression Report
- Excessive Weight Loss Report
- Eating Disorders Report

Roles and Responsibilities

Coordinating Center

- Prepare summary reports
- At least two weeks prior to review date, provide semi-annual reports to the Safety Committee (please see MOP section 26.1.2. for contact information)
- At least two weeks prior to the DSMB meeting, provide semi-annual reports to the DSMB

Safety Committee and DSMB

- Review the reports and determine whether there are concerns about the participants' safety, and whether and what corrective action is necessary
- Inform CALERIE Steering Committee whether it is safe to continue the study and provide recommendations about the corrective action, if necessary.

26.2.1 Serious and Severe AE Report

The SAE report (CRF pages 282-284) is to provide the following information to the Safety Committee and the DSMB:

- Participant ID
- Demographics (gender, age, height, weight, BMI)
- Seriousness
- Intensity
- MedDRA preferred term
- Verbatim report
- Days since intervention start
- Duration (days)
- Causality
- Action taken
- Outcome
- Criteria for SAE

26.2.2 Discontinuation Report

There are two types of the discontinuation reports: a) Temporary Discontinuation from CR Intervention report and b) Permanent Discontinuation from CR Intervention report. Temporary discontinuation report is to present information about all participants who had the CR intervention temporarily discontinued during the reporting period. Permanent discontinuation report is to present cumulative information about all participants who had their CR intervention discontinued. Both reports are to be reviewed by the Safety

Committee and by the DSMB, if the Board requests these reports. For report templates please refer to CRF Pages 298-299 and 300-301).

26.2.3 AE Report

AE reports (Section 22.0) must present all AEs that occurred on or after the randomization date. There are two types of AE reports including: a) all AEs, and b) only AEs that, in the opinion of the investigator, were related to the CR intervention. All cases of depression, eating and/or psychiatric disorders, excessive weight or bone loss, menstrual irregularities are to be reported as adverse events and monitored using the AE reports. For report templates please refer to CRF page 280.

26.2.4 Elevated Potassium Report

Elevated potassium report is to be reviewed semi-annually by the Safety Committee and by the DSMB, if the Board requests these reports. Elevated potassium report is to list every participant who had elevated potassium level above 5.5 mEq/L at any point during the study. The report also needs to show all potassium levels for these participants for all time points. For report template please refer to CRF pages 291-292.

26.2.5 Anemia Report

Anemia report is to be reviewed semi-annually by the Safety Committee and by the DSMB, if the Board requests these reports. Because of the high expected number of marginal, clinically insignificant abnormalities in Hb, Htc, or RBC levels during the study, listing each participant who had such an abnormality and all observed Hb, Htc and RBC values for this participant is not feasible or necessary. For all severe cases of anemia leading to discontinuation of the CR intervention information about Hb, Htc, and RBC levels will be available for review through the Individual Case Reports. Thus, participants' safety will not be compromised. For anemia summary report template please refer to CRF pages 293-295.

26.2.6 Depression Report

Depression report is to be reviewed semi-annually by the Safety Committee and by the DSMB. Depression report is to list every participant who had BDI-II score ≥ 20 at any point during the study. The report also needs to show all BDI-II scores for these participants for all time points. For report template please refer to CRF pages 287-288.

26.2.7 Excessive Weight Loss Report

Excessive weight loss report is to be reviewed semi-annually by the Safety Committee and by the DSMB. Excessive weight loss report is to list every participant who had BMI $\leq$ 18.5 kg/m2 at any point during the study. For report template please refer to CRF pages 285-286.

26.2.8 Eating Disorders Report

Eating disorders report is to be reviewed semi-annually by the Safety Committee and by the DSMB. Eating disorders report is to list every participant who had an eating disorder at any point during the study. For report template please refer to CRF page 289.