24. SAFETY SURVEILLANCE PROTOCOLS

This MOP section describes procedures that the study staff need to follow to monitor for abnormal potassium levels, anemia, eating disorders, accelerated bone loss and depression, and to ensure nutritional adequacy.

24.1 Potassium Surveillance Protocol

Site physician-investigator, cardiologist, phlebotomist and study coordinator will implement this protocol.

Definitions

The following definitions of hyperkalemia will be used in CALERIE Phase 2:

Hyperkalemia is defined as a potassium level greater than 5.5 mEq/L.

Mild hyperkalemia -	potassium levels between 5.5 mEq/L and 6.0 mEq/L.
Moderate hyperkalemia -	potassium levels between 6.1 mEq/L and 7.0 mEq/L.
Severe hyperkalemia -	potassium levels above 7.0 mEq/L.

Roles and responsibilities

Phlebotomist

- Perform phlebotomy as described in section 12
- Collect blood sample for chemistry panel at screening, baseline, months 1, 3, 6, 9, 12, 18, and 24 as described in section 12
- Collect blood sample for potassium and creatine phosphokinase (CPK) as described in section 12
- Inspect a specimen for visible signs of hemolysis. If signs of hemolysis are present, do not ship a specimen to the laboratory and ask the study coordinator to reschedule the participant for phlebotomy for the next day or two
- If no visible signs of hemolysis are present, ship the specimen to Esoterix laboratory as described in section 12

Study coordinator

- Schedule participant for blood collection and ECG in accordance with test schedule presented below or reschedule the phlebotomy, if necessary
- Ensure that the participant is fasting when s/he comes to the clinic. If the participant is not fasting, reschedule the tests and ensure that test schedule is met.
- Provide physician investigator with the laboratory tests report and ECG recording and interpretation

Cardiologist

- Review the ECG report for signs of hyperkalemia
- On the ECG report, describe signs of hyperkalemia, if any, or indicate that no signs are present
- Initial and date the ECG report

All other procedures described below will be performed by the physician-investigator.

Tests to be performed

- Potassium
- Creatine phosphokinase (CPK)
- ECG

Test schedule

Both Control and CR Groups

- Screening and baseline: potassium and CPK as part of chemistry panel. For schedule please refer to sections 5.0 and 6.0.

Screening and Baseline Visits

- Review chemistry laboratory report and confirm that potassium level is within the reference range for the laboratory
- If no abnormalities observed, recommend continuing participant in the study
- If potassium level is outside of the reference range, repeat chemistry panel in two weeks
  Note: only one repeated test is allowed
- If a repeated test is outside of the reference range, disqualify the participant and request to terminate his participation in the study
- Initial and date each of the laboratory reports reviewed

On-study Visits (Months 1, 3, 6, 9, 12, 18, and 24)

The following procedures should be followed for participants enrolled in the CR and control groups. **Note:** increase in calorie intake and discontinuation of the CR intervention are not applicable to the participants enrolled in the control group.

- Review laboratory report and confirm that potassium level is within the reference range for the laboratory
- Review ECG report and confirm that there are no signs of hyperkalemia (please see below)
- Initial and date laboratory and ECG reports reviewed
- If no abnormalities observed, recommend continuing participant in the study

If potassium level is between 5.5 mEq/L and 6.0 mEq/L

- Request the study coordinator to repeat potassium, CPK and ECG in one week
- Review repeated laboratory report
- Forward ECG report to the cardiologist for review for signs of hyperkalemia
- If a repeated test shows potassium level elevated above 5.5 mEq/L, or ECG report shows signs of hyperkalemia:
    - request an interventionist to increase participant's calorie intake to the baseline level
    - advise a participant to seek medical help outside of the study
    - inform the study manager about temporary discontinuation of the CR intervention
    - request the study coordinator to repeat potassium, CPK and ECG in one month
- Review repeated laboratory report
- Forward ECG report to the cardiologist for review for signs of hyperkalemia
- If potassium level is below 5.0 mEq/L, and no ECG signs of hyperkalemia are observed, recommend a participant to restart the CR intervention
- If potassium level is above 5.0 mEq/L:
    - inform a participant that the CR intervention cannot be restarted and encourage a participant to continue in the study and undergo all study procedures
    - request an interventionist to permanently discontinue the CR intervention
    - inform the study manager about permanent discontinuation of the CR intervention

If potassium level is 6.1 mEq/L and above

- Request the study coordinator to repeat potassium, CPK and ECG within 48 hours
- Follow all other steps as described above for potassium levels between 5.5 mEq/L and 6.0 mEq/L

Increase in potassium level of 5.5 mEq/L and above after the CR was restarted

- Inform a participant that the CR intervention needs to be permanently discontinued and encourage a participant to continue in the study and undergo all study procedures
- Request an interventionist to permanently discontinue the CR intervention
- Inform the study manager about permanent discontinuation of the CR intervention

Early ECG signs of hyperkalemia:

- Peaked T waves
- Shortened QT interval
- ST segment depression

24.2 Anemia Surveillance Protocol

Site physician-investigator, phlebotomist and study coordinator will implement this protocol.

Definitions

For the purpose of this study anemia is defined **as hemoglobin (Hgb) and / or hematocrit (Hct) level below the lower limit of normal (LLN) for the laboratory.**

Roles and responsibilities

Phlebotomist

- Perform phlebotomy as described in MOP section 12
- Collect blood samples for hematology panel at screening, baseline, months 1, 3, 6,
- 9, 12, 18, and 24 as described in section 12
- Collect blood samples for iron, if necessary

Study coordinator

- Schedule participant for blood collection in accordance with test schedule presented below or reschedule the phlebotomy, if necessary
- Ensure that the participant is fasting when s/he comes to the clinic. If the participant is not fasting, reschedule the tests and ensure that test schedule is met
- Provide physician investigator with the laboratory tests report

All other procedures described below will be performed by the physician-investigator.

Tests to be performed

- Hgb
- Hct
- RBC
- Iron (part of the chemistry panel)

Test schedule

This schedule applies to participants enrolled in any group.

- Screening and baseline: Hgb, Hct, and RBC; for schedule please refer to sections
- 5.0 and 6.0
- On-study: Hgb, Hct, and RBC at months 1, 3, 6, 9, 12, 18, and 24

- Repeated tests: Hgb, Hct, RBC, and iron (iron is not repeated at screening and baseline)

Screening and Baseline Visits

- Review hematology laboratory report and confirm that Hgb, Hct, and RBC levels are within the reference ranges for the laboratory
- If no abnormalities observed, recommend continuing participant in the study
- If Hgb, Hct, or RBC level is outside of the reference range, repeat hematology
- panel and iron in two weeks
  Note: only one repeated test is allowed
- If a repeated test is outside of the reference range, disqualify the participant and
- request to terminate his participation in the study
- Initial and date each of the laboratory reports reviewed

On-study Visits (months 1, 3, 6, 9, 12, 18, and 24)

The following procedures should be followed for participants enrolled in the CR. For participants enrolled in the control group, after anemia was confirmed by a repeated test, participant should be advised to seek medical help outside of the study. **Note**: increase in calorie intake and discontinuation of the CR intervention are not applicable to the participants enrolled in the control group. These participants continue all study procedures as per protocol.

- Review hematology laboratory report and confirm that Hgb, Hct, and RBC levels
- are within the reference ranges for the laboratory
- Initial and date laboratory reports reviewed
- If no abnormalities observed, recommend continuing participant in the study

If Hgb, Hct, or RBC level is below the LLN or there is a decrease of 5 percentage points in Hct level from the baseline

- Request the study coordinator to repeat Hgb, Hct, RBC and iron in two weeks
- Review repeated laboratory report
- If a repeated test confirms anemia:
  - advise a participant to seek medical help outside of the study
  - provide a participant with a brief note to his/her physician indicating that iron, folic acid and/or vitamin could be administered
  - request the study coordinator to repeat Hgb, Hct, RBC and iron one month after the treatment was initiated
- Review repeated laboratory report
- If no signs of anemia are present, recommend a participant to continue in the
- study
- If anemia is not improving or worsens:

- request an interventionist to increase participant's calorie intake to the baseline level
- inform the study manager about temporary discontinuation of the CR intervention
- request the study coordinator to repeat Hgb, Hct, RBC and iron one month after the treatment was initiated

- If no signs of anemia are present, recommend a participant to restart the CR intervention
- If anemia is not improving or worsens:
  - inform a participant that the CR intervention cannot be restarted and encourage a participant to continue in the study and undergo all study procedures
  - request an interventionist to permanently discontinue the CR intervention
  - Inform the study manager about permanent discontinuation of the CR intervention

Decrease in Hb, Hct, or RBC level below the LLN or decrease of 5 percentage points in Hct level from the baseline after the CR was restarted

- Follow the protocol described in "If Hgb, Hct, or RBC level is below the LLN or there is a decrease of 5 percentage points in Hct level from the baseline" above

24.3 Monitoring Nutritional Adequacy and Eating Disorders

This MOP section describes procedures that the study staff members need to follow to monitor for nutritional adequacy and eating disorders.

24.3.1 Monitoring for Nutritional Adequacy

The major role of the intervention staff will be to screen and recommend dietary changes to promote nutrition adequacy. Frequent review of dietary records will identify those participants who will benefit from dietary changes. Individual sessions with intervention staff will provide a venue for discussions on improving dietary habits.

In addition, supplementation with a multivitamin including minerals and calcium will be provided. Intervention staff will check with participants to verify they are taking their supplements by verbal confirmation and estimation of supplement replacement. Participants not requesting new bottles at the appropriate intervals will be questioned as to their supplement use. The Study Coordinator will distribute bottles of supplements and will also monitor participant's requests for replacement bottles.

24.3.2 Monitoring for Eating Disorders

The site measurement leader and measurement technicians will implement this protocol.

Definitions

- A possible eating disorder is defined as:
  - A t-score above 70 on any subscale of the MAEDS
  - A t-score of ≤ 40 and > 30, and a t-score of ≥ 70 on the BAM is indicative of a body image disturbance.
  - A t-score of 30 or below on the BAM is indicative of a severe body image disturbance.
- An eating disorder (anorexia nervosa, bulimia nervosa, or binge eating disorder) is defined by the criteria outlined in the DSM-IV (please refer to Appendix 24.I) as determined by the IDED-IV interview assessment:
  - A participant meets the diagnostic criteria for anorexia nervosa, bulimia nervosa, or binge eating disorder if the IDED-IV ratings for each of the diagnostic criteria are "3" or more
  - A participant meets the diagnostic criteria for a sub threshold eating disorder if the IDED-IV ratings are "3" or more on 5 of the 8 combined symptoms for bulimia nervosa and anorexia nervosa

Roles and Responsibilities

Measurement Technician

- Administer and score MAEDS and BAM as described in MOP Section 9.10.3
- If MAEDS and/or BAM are indicative of an eating disorder, immediately inform the site measurement leader
- Direct the participant back to the study coordinator or appropriate personnel for completion of any remaining visit procedures

All other procedures described below will be performed by site measurement leader or clinical psychologist (if a site measurement leader is not a clinical psychologist).

Tests to be Performed

- Body Acceptability Morph (BAM)
- The Multiaxial Assessment of Eating Disorder Symptoms (MAEDS)
- Interview for the Diagnosis of Eating Disorders (IDED-IV) - administered when MAEDS and/or BAM indicates possible eating disorder

Test Schedule
Eating disorder assessments are performed at screening, Months 3, 6, 12, 18 and 24.

Screening Visit

- Review all MAEDS and BAM results for all candidates and confirm that they are not indicative of an eating disorder
- If no abnormalities observed, recommend continuing participant in the study
- If MAEDS and/or BAM are indicative of an eating disorder, administer IDED-IV
- If IDED-IV confirms a presence of an eating disorder, disqualify the candidate and request to terminate any further screening procedures
- Advise a participant to seek medical help outside of the study
- Initial and date each MAEDS and BAM results reviewed

On-study Visits (months 3, 6, 12, 18, and 24)

The following procedures should be followed for participants enrolled in the CR and control groups. **Note:** discontinuation of the CR intervention is not applicable to the participants enrolled in the control group.

- Review all MAEDS and BAM results for all participants and confirm that they are not indicative of an eating disorder
- Initial and date each test results reviewed
- If no abnormalities observed, recommend continuing participant in the study

If MAEDS and/or BMA are indicative of a possible eating disorder

- Administer IDED-IV as soon as you became aware of MAEDS and/or BAM scores suggestive of an eating disorder
- If the IDED-IV does not confirm the presence of an eating disorder, then the participant should continue in the trial with no follow-up assessment other than the regular assessment batteries included in the CALERIE measurement protocols.
- If IDED-IV confirms a presence of an eating disorder:
    - inform a participant that s/he may developed an eating disorder and it is not safe for him/her to continue the CR regimen
    - refer a participant to a clinical specialist with experience in eating disorders for an interview (could be performed by a study psychologist, or any other staff member who has appropriate expertise. Otherwise, the sites must ensure that such interview has been conducted by a specialist outside of the study)
    - advise a participant to seek medical help outside of the study

- encourage a participant to continue in the study and undergo all study procedures
- request an interventionist to permanently discontinue the CR intervention
- inform the study manager about permanent discontinuation of the CR intervention

24.4 Depression and Mental/Behavioral Health Surveillance Protocol

The site measurement leader and measurement technicians will implement depression monitoring protocol. However, other adverse mental/behavioral health conditions may also develop in the study. The study psychologist and/or the study physician must advise any participant who develops any mental health condition other than depression to seek medical help outside of the study.

Definitions

CALERIE protocol defines depression as a BDI-II score of more or equal to 20

Roles and Responsibilities

Measurement Technician

- Administer and score BDI-II as described in MOP Section 9.10.4
- If a participant has a scores of 20 or above, immediately inform the site measurement leader
- Direct the participant back to the study coordinator or appropriate personnel for completion of any remaining visit procedures

All other procedures described below will be performed by site measurement leader or clinical psychologist (if a site measurement leader is not a clinical psychologist).

Tests to be Performed

- BDI-II

Test Schedule

BDI-II is administered at screening, baseline, Months 1, 3, 6, 9, 12, 18 and 24.

Screening and Baseline Visits

- Review all BDI-II scores for all participants and confirm that the scores are below 20

- If no abnormalities observed, recommend continuing participant in the study
- If BDI-II score is ≥ 20, disqualify the participant and request to terminate his participation in the study
- Advise a participant to seek medical help outside of the study
- Initial and date each BDI-II results reviewed

On-study Visits (months 1, 3, 6, 9, 12, 18, and 24)

The following procedures should be followed for participants enrolled in the CR and control groups. **Note:** discontinuation of the CR intervention is not applicable to the participants enrolled in the control group.

- Review all BDI-II results for all participants and confirm that the scores are below 20
- Initial and date each BDI-II results reviewed
- If no abnormalities observed, recommend continuing participant in the study

If BDI-II score is ≥ 20

- Request the study coordinator to schedule BDI-II administration in one week
- Review repeated test results
- If a repeated test score is < 20, no further action is necessary
- If a repeated test score is still ≥ 20:
    - request an interventionist to increase participant's calorie intake to the baseline level
    - advise a participant to seek medical help outside of the study
    - inform the study manager about temporary discontinuation of the CR intervention
    - request the study coordinator to schedule BDI-II administration in one month
- Review repeated test results obtained after one month of temporary CR intervention discontinuation
- If the BDI-II score is < 20:
    - inform a participant that his/her CR intervention will be restarted
    - request an interventionist to restart the CR intervention
    - inform the study manager that it is safe to restart the CR intervention
- If the BDI-II score is still ≥ 20:
  NOTE: Intervention can be restarted when the BDI-II score is ≥ 20 if a qualified mental health professional treating participant's depression indicates in writing that it is safe to restart the CR intervention. Be sure to place such a note in the participant binder prior to restarting the

intervention. If there is no such a note or it indicates that it is unsafe to restart the intervention, follow the steps described below.

- inform a participant that the CR intervention cannot be restarted and encourage a participant to continue in the study and undergo all study procedures
- request an interventionist to permanently discontinue the CR intervention
- inform the study manager about permanent discontinuation of the CR intervention

Increase in BDI-II score ≥ 20 after the CR was restarted

- Inform a participant that the CR intervention needs to be permanently discontinued and encourage a participant to continue in the study and undergo all study procedures
- Request an interventionist to permanently discontinue the CR intervention
- Inform the study manager about permanent discontinuation of the CR intervention

24.5 Monitoring Bone Mineral Density and Bone Mineral Content

Site physician-investigator, dual energy x-ray (DXA) technician, study coordinator will implement this protocol.

Definitions

CALERIE protocol provides that any participant who has BMD t-score at any site (hip or spine) equal to or less than -2.5 at the baseline visit 2 (first DXA measurement in the study) will not be eligible for the study, and his or her participation in CALERIE will be terminated at that point. Any participant who experienced a decrease in BMD at the hip or spine of 10% or greater from the baseline at any time during the study, will have the scan repeated within one month. If the second scan confirms original findings of a decrease in BMD at the total hip or spine of 10% or greater, the will have the intervention permanently discontinued. In addition, the BMD *t*-score will also be monitored and any participant who has BMD *t*-score at any site (hip or spine) of less than –2.5 at any time during the study will have the intervention permanently discontinued. A participant will be advised to seek medical help outside of the study and will follow all other study procedures to the study end.

BMD is expressed as a relationship to the expected BMD for "young normal" adults of the same sex (T-score). The difference between the patient's score and the norm is expressed in standard deviations (SD) above or below the mean. The least significant change, or LSC, is the least amount of BMD change that is considered statistically

significant. The calculations are done by multiplying the precision error (~1-1.5%) by 2.77. Therefore, more than 5% change in BMD should be considered more than LSC.

Notifications by DXA QA Center (for details on reporting requirements and scans submission to DXA QA Center please refer to DXA Quality Assurance Manual of Procedures for DXA Operators)

- Baseline visit: the DXA QA Center notifies clinical sites, CC and NIA within 24 hours (one working day) of receiving a scan if bone loss exceeds the allowable limit in this study. No repeated scan is performed and participant is discontinued from the study
- Six (6) month visit: the DXA QA Center notifies clinical sites within 24 hours (one working day) of receiving a scan if bone loss exceeds the allowable limit in this study and requests to repeat a scan
- Month 12, 18, and 24 visits: the DXA QA Center notifies clinical sites within seven (7) calendar days of receiving a scan if bone loss exceeds the allowable limit in this study and requests to repeat a scan

Roles and responsibilities

DXA technician

- Perform the DXA scans (total body, spine and hip) at baseline, Months 6, 12, 18, and 24 as required by CALERIE protocol
- For bone loss during the study that exceeds the allowable limit in this study (i.e. 10% or greater from the baseline at any time in the study), repeat the DXA scan as soon as possible after receiving notification from DXA QA Center to exclude errors related to technique (e.g. positioning)
- Immediately inform the study physician if bone loss exceeds the allowable limit in this study

Study coordinator

- Schedule participant for DXA in accordance with test schedule
- Provide physician investigator with any history related to osteoporosis or fractures
- Regularly review symptom checklist targeted to the musculoskeletal system with each participant, and triage any new or relevant symptom to the study physician
- Follow up DXA results from the DXA QA Center and refer them immediately to the study physician for review

Study physician

- Review the medical history and perform regular physical exams as per protocol
- Review results of DXA as provided by the DXA QA Center. Based on the results:
    - Exclude participants from the study

        - if the baseline DEXA shows a BMD T-score equal to or less than -2.5) as determined from the manufacturer's database at either the proximal femur or lumbar spine (L1-L4).
        - if the participant has a history of osteoporotic fracture regardless of baseline BMD
    - Request the CR intervention to be permanently discontinued if:
        - the participant has a bone loss at the total hip, or spine (L1-L4) of 10% or more from baseline at any time during the study, confirmed by a second scan performed within one month of the initial scan
        - the participant experiences any suspected osteoporosis-related clinical fractures during the study
    - Advise a participant to seek medical help outside of the study

24.6 Monitoring for Excessive Weight Loss

BMI is calculated at screening, and at Months 1, 3, 6, 9, 12, 18, and 24 as well as the off-schedule evaluations during Months 17 and 23. Any volunteer with a BMI < 22.0 kg/m^2 at screening will not be eligible for the study. Individuals who have lost or gained ≥3 kg over the six months prior to screening will be excluded. Additionally, a weight change of greater than 5% during the interval spanning the two baseline DLW measurement periods will be a basis for exclusion.

Definitions

CALERIE protocol defines excessive weight loss in the CR group as a BMI <18.5 kg/m^2 at any point during the study

Roles and Responsibilities

Measurement Technician

- Take the participant's weight as described in MOP Section 9.3.1. Using the participant's height at screening, derive his/her BMI as described in Section 9.3.3
- If a participant's BMI <18.5 kg/m^2, immediately inform the site measurement leader
- Direct the participant back to the study coordinator or appropriate personnel for completion of any remaining visit procedures

Study coordinator

- Schedule participant for weight measurement in accordance with test schedule presented below
- Ensure that the participant is fasting when s/he comes to the clinic. If the participant is not fasting, reschedule the measurement and ensure that test schedule is met

All other procedures described below will be performed by the site intervention leader!

Tests to be Performed

- Weight

Test Schedule

Weight is derived Months 1, 3, 6, 9, 12, 18, and 24 as well as the off-schedule evaluations during Months 17 and 23.

Screening and Baseline Visits

- Derive the BMI at the initial screening visit and verify that the participant's BMI is $\geq$ 22.0 kg/m^2 and < 28.0 kg/m^2.
- Verify that the volunteer has not lost or gained $\geq$3 kg over the six months prior to screening visit.
- Verify that a weight change greater than 5% has not occurred during the interval spanning the two baseline DLW measurement periods.

On-study Visits (months 1, 3, 6, 9, 12, 17, 18, 23 and 24)

The following procedures should be followed for participants enrolled in the CR and control groups. **Note:** discontinuation of the CR intervention is not applicable to the participants enrolled in the control group.

- Using the participant's height at screening and weight at the clinic visit, derive the participant's BMI
- Initial and date the corresponding section of the CRF
- If a participant's BMI $\geq$18.5 kg/m^2, recommend continuing participant in the study

If BMI <18.5 kg/m^2:

- Request an interventionist to increase participant's calorie intake to the baseline level
- Inform the study manager about temporary discontinuation of the CR intervention
- Request the study coordinator to schedule another weight measurement in one month
- Review repeated test results obtained after one month of temporary CR intervention discontinuation
- If the BMI is $\geq$ 18.5 kg/m^2:
    - inform a participant that his/her CR intervention will be restarted
    - request an interventionist to restart the CR intervention

- inform the study manager that it is safe to restart the CR intervention

- If the BMI is still <18.5 kg/m^2:
  - inform a participant that the CR intervention cannot be restarted and encourage a participant to continue in the study and undergo all study procedures
  - request an interventionist to permanently discontinue the CR intervention
  - inform the study manager about permanent discontinuation of the CR intervention

<u>Any decrease in BMI to < 18.5 kg/m^2 after the CR was restarted</u>

- Inform a participant that the CR intervention needs to be permanently discontinued and encourage a participant to continue in the study and undergo all study procedures
- Request an interventionist to permanently discontinue the CR intervention
- Inform the study manager about permanent discontinuation of the CR intervention

24.7 Pregnancy

Even though pregnancy does not meet any of the SAE definitions provided in section 27.1, it is considered an SAE. The following procedures need to be followed if a participant reports pregnancy or the urine pregnancy test result is positive.

24.7.1 Pregnancy Reported by a Participant

Study coordinator:

- Inform a participant that her CR intervention needs to be permanently discontinued and request interventionist to permanently discontinue the CR intervention.
- Request a participant to provide a note from her health care provider confirming pregnancy and put a note in the participant's binder
- Inform physician-investigator and study manager about the event
- Do not ask a participant to continue in the study and undergo all study procedures because pregnancy is a contraindication for many study measurements (e.g., DXA, blood collection)
- Complete an initial SAE report and fax it to the DCRI Safety Desk at 919-668-7138
- Follow with a participant via phone monthly till a child is born or till a pregnancy is terminated (elective abortion or miscarriage). Please note that miscarriage is not an additional SAE but an outcome of the SAE "Pregnancy"

- Complete the follow-up SAE report and fax it to the DCRI Safety Desk at 919-668-7138 when the outcome of pregnancy is known. Please note that the follow-up report needs to be specific about any congenital abnormalities

24.7.2 Positive Pregnancy Test

If the urine pregnancy test result is positive, the study coordinator must immediately refer a participant to her health care provider and request interventionist to temporary discontinue the CR intervention. If pregnancy is confirmed by the participant's health care provider, the study coordinator must follow all steps described in section 24.7.1. In the unlikely event when pregnancy is not confirmed by the participant's health care provider, the CR intervention needs to be restarted if the discontinuation period does not exceed 30 days.

24.8 Cholesterol Surveillance Protocol

Site physician-investigator, phlebotomist and study coordinator will implement this protocol.

Definitions

For the purpose of this study hypercholesterolemia is defined as LDL-cholesterol level equal to or greater than 160 mg/dl at any point during the study.

Roles and responsibilities

Phlebotomist

- Perform phlebotomy as described in MOP section 14
- Collect blood samples for chemistry panel (Esoterix/LabCorp laboratory) at screening
- Collect blood samples for outcome measurements (University of Vermont laboratory) at baseline, months 12 and 24 as described in MOP section 14

Study coordinator

- Schedule participant for blood collection in accordance with test schedule presented below or reschedule the phlebotomy, if necessary
- Ensure that the participant is fasting when s/he comes to the clinic. If the participant is not fasting, reschedule the tests and ensure that test schedule is met
- At screening, provide physician investigator with the laboratory tests report received from Esoterix/LabCorp laboratory
- During the study, provide physician investigator with the elevated LDL-cholesterol level alert received from the CC

All other procedures described below will be performed by the physician-investigator.

Tests to be performed

- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol (calculated)
- Triglycerides

Test schedule

This schedule applies to participants enrolled in both groups.

Screening (Esoterix/LabCorp laboratory), baseline, months 12 and 24 (University of Vermont laboratory)

Screening Visit

- Review laboratory report and confirm that LDL-cholesterol is less than 160 mg/dl. Recommend continuing participant in the study
- If LDL-cholesterol is equal to or greater than 160 mg/dl, repeat chemistry panel in two weeks
  Note: only one repeated test is allowed
- If a repeated test shows LDL-cholesterol between ≥160 mg/dl and <190 mg/dl
  - inform a study coordinator about elevated LDL-cholesterol level
  - make a note in participant's binder and wait till randomization
  - when randomization assignment is known
    - randomized to the CR group: no further action is necessary
    - randomized to the Control group: advise participant to follow the American Heart Association's (AHA) low-cholesterol diet
- If a repeated test shows LDL-cholesterol level equal to or greater than 190 mg/dl, disqualify the participant and request to terminate his participation in the study
- Initial and date each of the laboratory reports reviewed

On-study Visits (months 12 and 24)

If LDL-cholesterol level is equal to or greater than 160 and less than 190 mg/dl

- *CR group*: the site will not be informed about any such levels thus no action is required
- *Control group*: after receiving notification from the CC, advise participant to follow the AHA low-cholesterol diet

If LDL-cholesterol level is equal to or greater than 190 mg/dl

Both groups: after receiving notification from the CC, advise participant to seek medical help outside of the study. Encourage a participant to continue in the study and undergo all study procedures.

APPENDIX 24.I

Table 1: Summary of DSM-IV description of Binge Eating Disorder (BED)

Summary of DSM-IV Criteria for Binge Eating Disorder
A. Recurrent episodes of binge eating. A binge episode is characterized by the following: 1. eating an amount of food that is larger than others would eat in a similar time period and under similar circumstances. 2. experiencing a sense of lack of control over the eating during the episode
B. The binge eating episodes are associated with at lease three of the following: 1. eating a rapid pace compared to normal eating 2. eating until feel uncomfortably full 3. eating alone due to embarrassment of the amount of food one is eating 4. feeling disgusted, depressed, or guilty with oneself after the eating episode
C. The presence of distress regarding binge eating.
D. Binge eating occurs at least 2 days a week for 6 months, on average
E. The binge eating may not be associated with the regular use of inappropriate compensatory behaviors, and it may not occur only during the course of Anorexia Nervosa or Bulimia Nervosa.

Table 2: Summary of DSM-IV Diagnostic Criteria for Anorexia Nervosa (AN)

Summary of DSM-IV Criteria for Anorexia Nervosa
A. Refusal to maintain body weight at or above a minimally normal weight for age and height. B. Despite being underweight, the person has an intense fear of gaining weight or becoming fat. C. Body image disturbance. Denial of seriousness of low weight status. D. The absence of at least three consecutive menstrual cycles (in females who have past puberty). ***Types :*** Restricting type: The person has not regularly engaged in binge-eating or compensatory (i.e. purging behavior). Binge-Eating/Purging type: The person has regularly engaged in binge-eating or compensatory behavior.