25. DISCONTINUATION FROM THE CR INTERVENTION

This MOP section describes procedures that the study staff needs to follow when there is a need to either temporary or permanently discontinue the CR intervention in a participant. Site physician-investigator, interventionist, psychologist, study manager, and research assistant will implement the CR discontinuation protocol.

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

25.1 Temporary Discontinuation of the CR Intervention

CALERIE protocol defines temporary discontinuation of the CR intervention as cessation of the 25% CR regimen for up to 30 days. The CR intervention must be temporarily discontinued if any of the following is observed:

- Increase in potassium level > 5.5 mEq/L and <6.0 mEq/L at any point during the study confirmed by a second test repeated in one week
- Increase in potassium level of 6.1 mEq/L and above at any point during the study confirmed by a second test repeated within 48 hours if at this, second measurement, potassium level is elevated above 5.5 mEq/L)
- Treatment-resistant anemia (anemia that is not improving or is worsening after one month of treatment)
- Decrease in BMI <18.5 at any point during the study
- Moderate depression (BDI score ≥ 20)
- Any disease or condition that requires temporary discontinuation of the CR intervention, including but are not limited to severe infections, recovery from trauma or surgery.

Roles and responsibilities

Physician-investigator

- Confirm that a participant met a criterion for temporary discontinuation of the intervention (except depression)
- Provide a note for the participant's binder describing reasons for temporary discontinuation of the CR intervention
- Provide the study manager with an action plan that the study staff needs to follow to monitor resolution of an event leading to temporary discontinuation of the CR intervention. For specifics on action plan due to:
    - Increase in potassium - refer to MOP section 24.1
    - Anemia - refer to MOP section 24.2
    - Any other disease or condition - exercise best medical judgment and follow current standard of care

NOTE: if any further diagnostic tests and procedures and/or treatment are required, please advise a participant to seek medical help outside of the study

- Immediately inform the interventionist that a participant met a criterion for temporary discontinuation of the CR intervention and request interventionist to increase participant's CR intake
- Inform a participant that his/her CR intake will temporary increase and ask a participant to continue study visits if possible
- Within 5 days of temporary discontinuation of the CR intervention complete the Temporary Discontinuation from CR Intervention Report and provide it to the study manager

If event leading to the temporary discontinuation of the CR intervention has been resolved within 30 days:

- Confirm that event has been resolved and provide a progress note for the participant's binder
- Inform the study manager and interventionist that event has been resolved and request to restart the CR intervention
- Recommend a participant to resume his CR regimen and continue in the study

If event leading to the temporary discontinuation of the CR intervention has not been resolved within 30 days:

- Confirm that event has not been resolved and provide a progress note for the participant's binder
- Inform the study manager and interventionist that event has not been resolved and request interventionist to permanently discontinue the CR intervention
- Inform a participant that his/her CR regimen cannot be restarted and encourage a participant to continue in the study and undergo all study procedures
- Advise a participant to seek medical help outside of the study
- Within 5 days complete the Permanent Discontinuation from CR Intervention Report and provide it to the study manager

Psychologist

- Confirm that a participant has moderate depression (BDI score ≥ 20)
- Provide a note for the participant's binder describing reason for temporary discontinuation of the CR intervention
- Provide the study manager with an action plan that the study staff needs to follow to monitor resolution of depression. For specifics on action plan refer to MOP section 24.4.
- Immediately inform the study manager, physician-investigator and the interventionist that a participant met a criterion for moderate depression and request interventionist to increase participant's CR intake
- Inform a participant that his/her CR intake will temporary increase and ask a participant to continue study visits if possible

- Within 5 days of temporary discontinuation of the CR intervention complete the Temporary Discontinuation from CR Intervention Report and provide it to the study manager
- Follow all other procedures as described in MOP section 24.4.

If depression has been resolved within 30 days:

- Confirm that depression has been resolved and provide a progress note for the participant's binder
- Inform the study manager and interventionist that depression has been resolved and request to restart the CR intervention
- Recommend a participant to resume his CR regimen and continue in the study

If depression has not been resolved within 30 days:

- Confirm that depression has not been resolved and provide a progress note for the participant's binder
- Inform the study manager, physician-investigator and interventionist that episode of depression has not been resolved and request interventionist to permanently discontinue the CR intervention
- Inform a participant that his/her CR regimen cannot be restarted and encourage a participant to continue in the study and undergo all study procedures
- Advise a participant to seek medical help outside of the study
- Within 5 days complete the Permanent Discontinuation from CR Intervention Report and provide it to the study manager

Interventionist

- Please follow procedures described in the Intervention Manual section XX.

Research Assistant (or Clinic Staff):

- Repeat the BMI calculations to confirm that a participant has BMI <18.5
- Immediately inform the site measurement leader, study manager and physician-investigator about participant's BMI decreasing below 18.5

Study Manager:

- Assign responsibilities to appropriate staff members for implementing an action plan developed by physician-investigator or psychologist
- Ensure that all staff members are following an action plan
- Ensure that CR intake for a participant has been increased by reviewing an appropriate note by interventionist
- Immediately after receiving the Temporary Discontinuation from CR Intervention Report from physician-investigator, fax the report to **DCRI Safety Desk at 919-668-7138**

Coordinating Center
Within 48 hours of receiving the Temporary Discontinuation from CR Intervention Report from a site:

- Fax the Discontinuation from the Intervention Report to members of the Safety Committee (please see section 26.1.2 for contact information).

25.2 Permanent Discontinuation of the CR Intervention

The CR intervention needs to be permanently discontinued and a participant must be advised to seek medical help outside of the study if any of the following is observed:

- Increase in potassium level > 5.5 mEq/L resistant to one month of treatment
- Re-challenge hyperkalemia (increase in potassium level of 5.5 mEq/L and above after the CR was temporary discontinued and then restarted)
- Persistent anemia (anemia that is not improving or worsening after temporary discontinuation of the CR intervention)
- Cancer
- Cardiovascular MACE (Major Averse Clinical Event including myocardial infarction, stroke, transient ischemic attack) confirmed by appropriate medical professional
- Eating or psychiatric disorder including severe depression
- Further decrease in BMI after temporary discontinuation of the CR intervention, or repeated decrease in BMI <18.5 after the CR intervention was restarted
- Re-challenge moderate depression (reoccurrence of moderate depression after the CR intervention was restarted), or moderate depression that is not improving or is worsening after temporary discontinuation of the CR intervention
- Trauma requiring prolonged hospitalization or bed rest for more than one month
- Pregnancy
- Menstrual irregularities or acyclicity for more than one year
- BMD loss at any one site (total hip or spine L1-L4) of ≥ 10% from the baseline at any time during the study confirmed by a second scan repeated within one month from the initial scan.
- BMD t-score at any one site (total hip or spine L1-L4) of less than 2.5 at any time during the study.

Roles and responsibilities

Physician-investigator

- Confirm that a participant met a criterion for permanent discontinuation of the intervention (except eating or psychiatric disorder and/or severe depression)
- Provide a note for the participant's binder describing reasons for permanent discontinuation of the CR intervention
- Immediately inform the study manager and the interventionist that a participant met a criterion for permanent discontinuation of the CR intervention and request interventionist to increase participant's CR intake to baseline level

- Inform a participant that his/her CR intervention should be discontinued due to safety concerns and encourage a participant to continue in the study and undergo all study procedures
- Advise a participant to seek medical help outside of the study
- Within 5 days of permanent discontinuation of the CR intervention complete the Permanent Discontinuation from the Intervention Report and provide it to the study manager

Psychologist

- Confirm that a participant has eating or psychiatric disorder, repeated episode of moderate or severe depression
- Provide a note for the participant's binder describing reason for permanent discontinuation of the CR intervention
- Immediately inform the study manager, physician-investigator and the interventionist that a participant has eating or psychiatric disorder, including severe depression, and request interventionist to discontinue the CR intervention
- Inform a participant that his/her CR intervention should be discontinued due to safety concerns and encourage a participant to continue in the study and undergo all study procedures
- Advise a participant to seek medical help outside of the study
- Within 5 days of permanent discontinuation of the CR intervention complete the Permanent Discontinuation from CR Intervention Report and provide it to the study manager

Interventionist

- Please follow procedures described in the Intervention Manual section XX.

Research Assistant (or Clinic Staff):

- Repeat the BMI measurement to confirm that a participant has BMI <18.5
- Immediately inform the study manager and physician-investigator about participant's BMI decreasing below 18.5

Study Manager:

- Ensure that CR intervention was discontinued by reviewing an appropriate note by interventionist
- Immediately after receiving the Permanent Discontinuation from CR Intervention Report from physician-investigator, fax the report to **DCRI Safety Desk at 919-668-7138**

Coordinating Center

Within 48 hours of receiving the Permanent Discontinuation from CR Intervention Report from a site:

- Fax the Discontinuation from the Intervention Report to members of the Safety Committee (please see section 26.1.2 for contact information).