

7. RANDOMIZATION AND BLINDING

7.1 Central Randomization Procedures

7.1.1 CALERIE Randomization

The CALERIE study will be using Almac Clinical Technologies for central randomization.

The Interactive Voice Response System (IVRS) can be accessed 24/7 by touch keypad phone and by the steps below you can randomize a subject at any time.

Step 1: Dial 1-877-695-4284

Step 2: Enter the 4-digit study code: **1755**

Step 3 Enter your 8-digit User ID

Step 4: Enter your 7-digit password*

* You will be asked to change your password the first time you access the system. Your password must be kept confidential and should not be shared with anyone at any time

Once you entered the about information you can gain access to the main menu options. Option 1 (Subject Randomization) will allow you to randomize a subject. When you select Option 1, you will need the following information on hand:

- 6-digit CALERIE ID Number
- Subject's Date of Birth (dd/mm/yyyy)
- Subject's Gender
- Subject's Screening BMI [two digits before and after the decimal point.]

7.1.2 What If You Need to Back Up During the Randomization Process

The IVRS always confirms your manual entry, but there is always a possibility for error. If you realize during the randomization process, you did make an error, you may hang up and retry, as long as the subject's randomization has not been provided. If you are not sure if the transaction went through you should call technical support which is available 24/7 to confirm whether the subject was randomized or not. The second option is more preferable than the first.

7.1.3 Sample Script

IVRS: Welcome to the Subject Randomization module.

IVRS: Please enter the Subject ID.

Caller: 020101

IVRS: You have entered 020101. Is this correct? For yes, press one; for no, press zero.

Caller: 1

IVRS: Please enter the subject's date of birth in dd-mm-yyyy format specifying two digits for the day, two digits for the month and four digits for the year.

Caller: 02251972

IVRS: You have entered February 25, 1972. Is this correct? For yes, press one. For no, press zero.

Caller: 1

IVRS: Please enter the subject's gender. If the subject is male, press one, if the subject is female, press zero.

Caller: 1

IVRS: You have entered one for male. Is this correct? For yes, press 1. For no, press 0.

Caller: 1

IVRS: Please enter the subject's BMI at screening. Two digits before and two digits after the decimal must be entered. Zeros can be used for whole numbers or number with even tenths. Press the star key to enter a decimal point.

Caller: 23.50

IVRS: You have entered 23.50. Is this correct? For yes, press one; For no, press zero.

Caller: 1

IVRS: Please assign this subject to Treatment Group B (the Ad Libitum control group). This subject's randomization has been recorded.

7.1.4 What If You Realize You Made a Mistake?

If you realize after review of the confirmation fax that you possibly made an entry error, which may have caused a randomization problem, please notify Almac immediately. Depending on the situation, Almac may need to discuss any misrandomization issues with the DCRI statistician for correction.

7.1.5 What You Will Receive

At the end of randomization you will receive the following:

- Verbal and fax confirmation that the subject is randomized
- Subject's Treatment Group (Treatment A is 25% CR and Treatment B is the ad lib group (control)).

Please take the time to carefully review all IVRS confirmation faxes you receive to ensure that the information was entered correctly in the IVRS. If you identify incorrect data on the confirmation fax, please do the following:

On the confirmation fax:

- Strike through the incorrect data and write the correct data next to it.
- Sign and date the change (just like you would do on a CRF page).
- Fax the corrected form back to Almac Clinical Technologies at (267) 685-4262.

All confirmation faxes should be filed in the subject's research folder, as a confirmation of the treatment assignments.

7.1.6 What If You Need Help?

Technical support is available 24/7. You can access Technical Support by dialing (877) 738-8831 and pressing "0" when prompted. You can also obtain help by using the e-mail address listed below.

IVRSSupport@almacgroup.com

When you access Technical Support, please have the following information readily available:

- Sponsor/Protocol (CALERIE)
- Study Code (1755)
- Site Number (01, 02 or 03)
- Your Phone Number

When it is outside normal business hours the Almac call center will answer your call. Non-urgent messages will be returned the next business day. Attached under Appendix A is the sample IVRS Quick Reference card that sites will get at start-up.

7.1.7 Practicing With the IVRS

Appendix B includes a sample IVRS CALERIE Worksheet that can be used to have information on hand, prior to randomizing a "real" subject.

It is highly suggested that randomization practice be followed by a site, prior to randomizing the first subject. If new personnel are added later, that will be randomizing subject participants, it too is recommended they practice first, before entering "real" subject data.

Almac will maintain to practice site for CALERIE for the duration of the trial. The following IVRS option will be available to you to practice with:

- Step 1: Dial (877) 695-4284
- Step 2: Enter the 4-digit study number: **1755**
- Step 3: Enter your 3-digit Test site number: **999**
- Step 4: Enter you 8-digit Test User ID: **99999999**
- Step 5: Enter your 7-digit Test password: **9999999**

Once you entered the above information you can gain access to the main menu options. Option 1 (Subject Randomization) will allow you to practice the randomization procedure. Since this is a test environment, you will not receive a confirmation fax at the end of practice.

If you need further information on how to practice in the test IVRS or require additional training on the use of the IVRS, please contact Almac Technical Support by following the dialing instructions listed above and selecting "0" when prompted. Alternatively, please e-mail your request to IVRSSupport@almacgroup.com ; listing your study code, site

number, name and telephone number and the Almac technician will contact you to arrange a suitable time and date.

Attached under Appendix C is the IVRS Practice Sheet for Quick reference.

Appendix A

Protocol: **CALERIE**

Study Coordinator
IVRS Quick Reference Card
Study Code **1755**

ALMAC Clinical Technologies
Direct Numbers

IVRS: 1-877-695-4284

Tech Support: 1-877-738-8831

Fax: 1-267-685-4262

Email: IVRSSupport@almacgroup.com

Technical Support

Technical Support is available twenty-four hours a day, seven days a week. You can access Technical Support by following the dialing instructions listed in the “**IVRS Access Information**” section.

Alternatively you can dial one of the office numbers located on the front of the card or by using the email address listed below.

IVRSSupport@almacgroup.com

When you access Technical Support, please have the following information available:

- Sponsor / Protocol
- Study Code
- Site Number
- Your Phone Number

If it is outside normal business hours the Almac call center will answer your call. Non-urgent messages will be returned the next business day.

IVRS Database Changes

Please carefully review all IVRS confirmation faxes you receive to ensure that the information was entered correctly in the IVRS. If you identify incorrect data on the confirmation fax, please use the following procedure.

On the confirmation fax:

- Strike through the incorrect data and write the correct data next to it.
- Sign and date the change (just like you would on a CRF)
- Fax the form back to Almac Clinical Technologies at 1-267-685-4262

IVRS Access Information

Please follow the steps below to access
the IVRS for **DCRI**
Protocol **CALERIE**

Step 1: Dial 1-877-695-4284

Step 2: Enter the 4-digit study Code: **1755**

Step 3: Enter your 8-digit User ID

Step 4: Enter your 7-digit password*

You will be requested to change your password for the first time you access the system. Your password must be kept confidential at all times

Once you have entered this information you will gain access to the main menu options.

If you are having difficulty accessing the IVRS, please contact Almac Clinical Technologies Technical Support by Dialing the appropriate toll free number for your country and pressing “0” when prompted.

Option 1: Randomize a Subject

What you will need:

- 6-digit Subject ID Number*
- Subject's date of birth (dd/mm/yyyy)
- Subject's Gender
- Subject's BMI

What you will receive:

- Verbal and fax confirmation that subject is randomized.
- Subject's Treatment Group (Treatment A is 25% CR and Treatment B is the ad lib group (control))



Complete and have
available for the
randomization call.

**CALERIE
Randomization
Worksheet**

Demographics	Subject Initials ___ ___ ___
<p>Date of Birth: <u> </u> / <u> </u> / <u> </u> <u> </u> <u> </u> <u> </u> <u> </u></p> <p>Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female</p> <p>Screening Weight: <u> </u> kg.</p> <p>Screening Height: <u> </u> cm.</p> <p>Screening BMI: <u> </u> kg/m²</p>	

Inclusion Criteria <i>(must answer "Yes" to the following to be eligible for randomization)</i>	
<p>Age must be between 21 and 50 years of age (inclusive) for men</p> <p>Age must be between 21 and 47 years of age (inclusive) for women</p> <p>Body mass index (BMI) must be greater than or equal to 22.0 kg/m² and less than 28.0 kg/m².</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

Exclusion Criteria <i>(must answer "No" to the following to be eligible for randomization)</i>	
Medical Exclusion Criteria	
<p>1. History or clinical manifestation of cardiovascular disease or an elevated blood pressure (greater than 140/90 mm Hg.....</p> <p>2. Abnormal resting ECG demonstrating: Type II second or third degree heart block; ventricular ischemia; left bundle branch block, cardiac hypertrophy by any criteria, QRS complex > 100 ms in duration; abnormal QTc interval, supraventricular tachycardia of any type but not including APC's, or ventricular arrhythmia of any type (including VPC's more than 60 per minute)</p> <p>3. History or clinical manifestation of diabetes.....</p> <p>4. History or clinical manifestation of cholelithiasis.....</p> <p>5. History of anaphylaxis, severe allergies, or asthma.....</p> <p>6. History or clinical manifestation of any other significant metabolic, hematologic, pulmonary, cardiovascular, gastrointestinal, neurologic, immune, hepatic, renal, urologic disorders, or cancer that, in opinion of the investigator, would make the candidate ineligible for the study</p> <p>7. History of stomach or intestinal surgery (except appendectomy) or major abdominal, thoracic or non-peripheral vascular surgery within one year prior to the randomization date.....</p> <p>8. Any disease or condition that seriously affects body weight and/or body composition.....</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
Laboratory Exclusion Criteria	

9. Potassium level above the upper limit of normal at the screening visit confirmed by a test repeated within two weeks..... Yes No
10. Hemoglobin, hematocrit, RBC, or iron level below the lower limit of normal at the screening visit confirmed by a test repeated within two weeks..... Yes No
11. Evidence of active liver disease or ALT levels above 1.5 times the upper limit of normal..... Yes No

Exclusion Criteria (continued)

Psychiatric and Behavioral Exclusion Criteria

12. Individuals who practice a vegan dietary lifestyle..... Yes No
13. History or clinical manifestation of any eating disorder as determined by IDED-IV when the ratings for each of the diagnostic criteria are rated as “3” or more. Potential participants will also be excluded if they are experiencing a sub threshold eating disorder (defined as IDED-IV ratings of “3” or more on 5 of the 8 combined symptoms for bulimia nervosa and anorexia nervosa) Yes No
14. Any history of pharmacologic treatment for a psychiatric disorder within one year prior to the randomization date or a history of more than one episode of a pharmacologic treatment for a psychiatric disorder within lifetime..... Yes No
15. History of drug or alcohol abuse (up to 14 drinks a week are allowed) within the past two years Yes No
16. Individuals who present with a BDI score of ≥ 20 at screening or baseline Yes No

Medication Exclusion Criteria

17. Short-term (less than a month) treatment with steroids within six months prior to the randomization date..... Yes No
18. Treatment with steroids for more than a month within five years prior to the randomization date Yes No
19. Regular use of other medications,

Other Exclusion Criteria

21. Individuals who participated in the CALERIE Phase 1 studies..... Yes No
22. Individuals who have lost or gained ≥ 3 kg over the past six months..... Yes No
23. A volunteer must be either be a never-smoker of tobacco products or an ex-smoker who quit completely at least 12 months prior to the screening visit..... Yes No
24. Individuals who donated blood within 30 days prior to the randomization date..... Yes No
25. Concurrent participation in any other interventional study Yes No
26. Breast-feeding or pregnant women, or women not practicing an acceptable method of birth control..... Yes No
27. Individuals who were engaged in a regular program of physical fitness involving some kind of heavy physical activity (e.g., jogging, running or riding fast on a bicycle for 30 minutes or more) five or more times per week over the past year..... Yes No
28. Unwilling to be assigned at random to the CR or control intervention..... Yes No
29. Unwilling or unable to adhere to the rigors of the CR intervention over the entire two-year intervention period..... Yes No
30. Individuals who unable or unwilling to discontinue dietary supplements or adhere to the alcohol consumption restrictions during the study Yes No
23. Unwilling or unable to adhere to the rigors of the data collection and clinical evaluation schedule over the entire two-year period follow-up period Yes No

Randomization

If the subject is eligible for CALERIE randomization, please call: **1-877-695-4284** Enter 1755 as your 4-digit study code. Enter your 8-digit user ID and your 7-digit password.*

*You will be asked to change your password the first time you access the system. Your password must be kept confidential.

The Subject is assigned to: _____

Randomization date and time: / / : / hour

Signature: _____ Date: / /

Appendix C



DCRI Protocol: CALERIE IVRS Practice Sheet

Practicing with the IVRS

This is a test IVRS only. Do not use the information listed below to enter “real” patient data.

ICTI will maintain this practice site for the duration of the trial. The following IVRS options will be available for you to practice with:

- *Subject Randomization*

To practice using the IVRS, please follow the steps listed below:

Step 1: Dial 1-877-695-4284

Step 2: Enter the 4-digit study code: **1755**

Step 3: Enter your 3-digit TEST site number **999**

Step 4: Enter your 8-digit TEST UserID **99999999**

Step 5: Enter your 7-digit TEST password **9999999**

If you need further information on how to practice in the test IVRS or require additional training on the use of the IVRS, please contact Technical Support by following the dialing instructions listed above and selecting ‘0’ when prompted. Alternatively, please email your request to ivrssupport@almacgroup.com listing your study code, site number, name and telephone number and we will contact you to arrange a suitable time and date.

Please note: You will not receive confirmation faxes from the test environment.

7.2 Masking

Masking of study assignment will be accomplished through a series of requests, physical separation, and masking of forms. First, the study ID will be coded so that treatment assignment can not be determined by staff. Masking is most important for staff involved in assessing QOL and cognitive measures, thus masking of the measurement technicians will be of the highest importance. Additional staff who should be masked are those involved in the DEXA, RMR, VO2 max and strength testing measurements.

Study Manager

- Randomization assignment will be known to the Study Manager and coordinator at each site however attempts will be made to mask all other personnel involved in assessment activities. Any documents that contain the randomization assignment should not be shared with other personnel, especially personnel that will be performing measurements in the study.
- Study participants will be told not share their study assignment with clinic staff or other study participants. Thus, a do not ask; do not tell policy will be in effect.
- Study coordinator or intervention staff will be a back-up to the Study Manager

Measurement Technicians

Assessment of QOL and cognitive measures, thus masking of the measurement technicians will be of the highest importance.

Research technicians and measurement personnel

- Other staff that should be masked are those involved in the DEXA, RMR, VO2 max and strength testing measurements.
- If possible, staff involved in obtaining weight and BP should be masked. This can be accomplished by providing only the CRF for the immediate visit and preventing access to forms from previous visits.

Evaluation Nutrition Staff

Dieticians evaluating food records for DLW procedures should remain masked as much as possible.

Physicians and nurses

Physicians and nurses involved in biopsies should also be blinded unless they are also the staff that collects other measurements such as the safety blood work and EKGs.

Intervention Staff

Another form of masking is physical separation of participants from measurement staff. Intervention and Control participants will be scheduled to attend clinic visits on different days as frequently as possible to reduce commingling between treatment arms. In addition, Intervention staff will become quite familiar with Intervention participants therefore some precautions should be taken. Intervention staff should not openly greet Intervention participants in the clinic areas. Explain this to Intervention participants ahead of time so they will not think you are being rude.

- Intervention sessions and individual appointments should be held in space away from the main clinic areas whenever possible.

- Meals will be consumed away from assessment staff.
- Meals packaged to be consumed off site will be distributed away from assessment staff.
- Study materials such as study notebooks, home scales, diaries, and PDAs will not be openly displayed nor training conducted in the clinic areas. Distribution of all materials to participants such as study scales should be done away from evaluation areas.

Wherever possible outside laboratories and reading centers will perform tests and report their results to the Coordinating Center by CALERIE ID. The calculated CR prescription will be forwarded from the DLW lab to the designated DLW expert at the sites. If these calculations appear acceptable by the site's DLW expert, these will be provided to the Study Manager. The Study Manager is responsible for sharing the CR prescription the Site Intervention Leader and the feeding nutritionist. The feeding nutritionist will confer with the kitchen staff for meal preparation. The Site Intervention Leader will be responsible for entry of CR prescription into the CTS System.