CALERIE Phase 2: Adherence Algorithm and Calculation of RQ and Adherence

1 Adherence Overview

1.1 %CR

For each participant, adherence is assessed via the % Caloric Restriction (%CR) achieved during specified interval(s) under the CR intervention. %CR is the % reduction in daily Energy Intake during the interval (EI_{int}) (see section 1.3) compared with the Ad Libitum daily Energy Intake (EI_{AL}) (see section 1.2).

$$\%CR = 100 \times (EI_{AL} - EI_{int}) / EI_{AL}$$

Intervals of interest include Baseline to Month 6, Baseline to Month 12, Baseline to Month 24, Month 12 to Month 24, etc.

1.2 Ad Libitum Energy Intake (EI_{AL})

EI_{AL} (kcal/day), Ad Libitum daily Energy Intake, is assumed to be equal to the Total Daily Energy Expenditure (TDEE) during the Ad Libitum Baseline period, estimated by the average of two TDEE values obtained through two consecutive 2 week DLW assessments during the baseline period. (see section 2.1 for details on TDEE)

EI_{AL} (kcal/day) = Baseline TDEE (kcal/day) = Average of Baseline 1 and Baseline 2 TDEE

1.3 Energy Intake during CR (EI_{int})

EI_{int} (kcal/day), the average daily energy intake during a specific interval during Caloric Restriction, is estimated using the Energy Balance method, as the sum of the average TDEE during the interval ($TDEE_{int}$) (see section 1.4) and the average daily change in body energy stores during the interval (ΔES) (see section 1.5).

EI_{int} (kcal/day) = $TDEE_{int}$ (kcal/day) + daily ΔES (kcal/day)

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1.4 TDEE during CR ($TDEE_{int}$)

$TDEE_{int}$ (kcal/day), the average TDEE during the interval is a weighted average of the TDEE at the start and end of the interval, including any TDEE measures taking between the start and end. (See section 2 for details on TDEE).

Baseline to Month 6 (CR arm only): $TDEE_{BL\text{-}M6}$ = (Baseline TDEE + (5 x M6 TDEE)) / 6

Baseline to Month 12 for CR arm :

$$TDEE_{BL\text{-}M12} = \frac{\left(\frac{\text{BL TDEE} + 5 \times \text{M6 TDEE}}{6}\right) \times (\text{days from BL to M6}) + \left(\frac{\text{M6 TDEE} + \text{M12 TDEE}}{2}\right) \times (\text{days from M6 to M12})}{\text{days from BL to M12}}$$

$$= \frac{(\text{weighted average of BL and M6 TDEE}) \times (\text{number of days from BL to M6}) + (\text{average of M6 and M12 TDEE}) \times (\text{number of days from M6 to M12})}{\text{number of days from BL to M12}}$$

If assessments are done exactly at 6 and 12 months, this reduces to : (0.083 x BL TDEE) + (0.667 x M6 TDEE) + (0.25 x M12 TDEE)

BL to M12 for AL arm: $TDEE_{BL\text{-}M12} = \frac{\text{Baseline TDEE} + (11 \times \text{M12 TDEE})}{12}$

Month 12 to Month 24 for CR arm:

$$TDEE_{M12\text{-}M24} = \frac{\left(\frac{\text{M12 TDEE} + \text{M18 TDEE}}{2}\right) \times (\text{number of days from M12 to M18}) + \left(\frac{\text{M18 TDEE} + \text{M24 TDEE}}{2}\right) \times (\text{number of days from M18 to M24})}{\text{number of days from M12 to M24}}$$

if the visits are made exactly at 12, 18 and 24 months, this reduces to: = (0.25 x M12 TDEE) + (0.5 x M18 TDEE) + (0.25 x M24 TDEE)

Month 12 to Month 24 for AL arm: $TDEE_{M12\text{-}M24} = \frac{\text{M12 TDEE} + \text{M24 TDEE}}{2}$ ie, the unweighted average of the M12 and M24 TEEs.

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Baseline to Month 24 :

$$TDEE_{BL\text{-}M24} = \frac{(TDEE_{BL-M12} \text{ x days from BL to M12}) + (TDEE_{M12-M24} \text{ x days from M12 to M24})}{\text{Number of days from BL to M24}}$$

1.5 Delta Energy Stores (ΔES)
ΔES (kcal/day), the average daily change in body energy stores is based on the changes in Fat mass (FM) and Fat free mass (FFM) from the start to the end of the interval, as assessed by DXA, multiplied by their energy equivalents. (See section 4 for details on DXA)

Total ΔES (kcal) = (ΔFM (kg) x 9,300 kcal/kg) + (ΔFFM (kg) x 1,100 kcal/kg)

Daily ΔES (kcal/day) = Total ΔES (kcal) / duration of interval in days

2 TDEE

TDEE (Total Daily Energy Expenditure in kcal/day) is measured by the DLW method. There are two consecutive 14 day DLW periods at baseline, and one 14 day DLW period at each of Months 12 and 24. Participants randomized to CR also have 14 day DLW assessments at Months 6 and 18. Each DLW assessment yields the Carbon dioxide production rate (rCO_2) during the DLW period, which together with the Respiratory Quotient (RQ) (see section 3), is used to calculate the TDEE.

TDEE = 22.4 x rCO_2 x (1.2321 + 3.815 / RQ)

A provisional RQ of 0.86 was used to determine TDEE at the baseline assessments, which in turn was used to determine the energy intake prescription for CR participants. Since the prescribed energy intake was based on RQ=0.86 instead of the calculated participant specific RQ, we measured %CR two ways: 1) using participant specific RQ at baseline to determine Ad Libitum Energy intake (EI_{AL}) which produces %CR relative to the 'real' EI at baseline, and 2) using RQ=0.86 to determine EI_{AL}, which produces %CR relative to the provisional EI used for the energy intake prescription.

3 Respiratory Quotient (RQ)
The Respiratory Quotient (RQ) is calculated separately for each participant at each DLW period, using the average daily intake in grams per day of fat, carbohydrates, protein and alcohol, and the average daily change in body stores of fat and protein during the DLW period.

$$RQ = \frac{[(F - \Delta \text{ body fat}) \times 1.427] + (C \times 0.829) + [(P - \Delta \text{ body protein}) \times 0.774] + (A \times 0.972)}{[(F - \Delta \text{ body fat}) \times 2.019] + (C \times 0.829) + [(P - \Delta \text{ body protein}) \times 0.966] + (A \times 1.459)}$$

where

F = average daily Fat intake during the DLW period (g/day)
C = average daily Carbohydrate intake during the DLW period (g/day)
P = average daily Protein intake during the DLW period (g/day)
A = average daily Alcohol intake during the DLW period (gday) (see section 3.1)

Δ body fat = average daily change in body fat during the DLW period (g/day)
Δ body protein = average daily change in body protein during the DLW period (g/day) (see section 3.2)

3.1 Dietary intake
Study participants recorded dietary intake in food diaries for 6 days during each DLW period. All food diary records were used at each visit, regardless of the dates of the food diaries. Food records were analyzed at the central nutrition reading center. The raw food diary data includes the grams of fat, carbohydrate, protein and alcohol intake for each day data was collected. This is reduced to one record for each visit (BL1, BL2, M6, M12, M18, M24) by taking the average of each macronutrient intake, and total daily caloric intake over all records for that visit.
The absolute total reported dietary intakes were considered unreliable; however, the relative caloric proportions of fat, carbohydrates, protein and alcohol were more likely to be accurate. Therefore, we adjusted intakes of fat, carbohydrates, protein and alcohol grams, by multiplying the intake of each (in grams) by the ratio of estimated

EI to reported EI, where EI was estimated using a prediction equation using age, sex, FM and FFM as predictors. Details follow in sections 3.1.1 – 3.1.4.

3.1.1 Estimated Energy Intake for adjusting food diary macronutrient intakes

A Provisional Energy intake at each follow-up visit will be estimated using a prediction equation involving sex, age, fat mass and fat free mass at that visit. The prediction equation will be developed using linear regression of TEE on sex, age, FM, FFM using baseline data

3.1.2 Adjusted food diary macronutrient intakes

For each macronutrient, the number of grams are adjusted by multiplying by the ratio of estimated EI to reported EI. For example,

$$\text{F = average daily Fat intake (g/day) = average daily reported fat (g)} \times \frac{\text{Estimated EI}}{\text{Average daily EI reported in food diary}}$$

3.2 Changes in Body Fat and Protein

The average daily change in body fat and protein during the DLW period is obtained through regressions of daily body weights, and weekly clinic weights during the DLW period. Study participants record their weight daily at home during each 2 week DLW period. Clinic weights are measured on DLW days 0, 7 and 14. Because of a few timing irregularities, we will include all weights that were taken within a 7 day window before or after the DLW period.

For each individual at each DLW period, separate linear regressions are performed on the clinic and daily weights to determine the daily rate of weight change during the DLW period, which is the slope of the regression line. In order to diminish the impact of any outlier weights, we use the average of the two slopes to estimate the daily rate of weight change.

Daily weight change (g/d) = average of slopes from regressions of clinic weights and daily weights, by day.

We use coefficients calculated from CALERIE Phase 1 data to calculate fat and protein change.

Δ body Fat (g/day) = Daily weight change (g/d) x 0.74

Δ body Protein (g/day) = Daily weight change (g/d) x 0.26 x 0.21

4 DXA measures

Body composition, including %Body Fat, Fat mass (FM) and Fat free mass (FFM) were measured by DXA on visits where DLW was measured. DXA was done twice at Baseline, once at the start of the first DLW period, and again at the end of the second DLW period. CR participants had two DXA measurements at Month 6, at the start and end of the DLW period. One DXA was done at each of the Month 12 and 24 visits, and CR participants had an additional DXA at Month 18.

The absolute mass, FM and FFM from DXA were considered to be unreliable, although the % Body fat was expected to be accurate. Therefore, we recalculated FM and FFM by multiplying the % Body fat from DXA by the clinic scale weight taken on the date of each DXA assessment. In rare cases where no clinic weight was available on the DXA date, we used the closest clinic weight within 7 days of the DXA date. If there is no clinic weight within 7 days of the DXA date, we will use the FM and FFM from the DXA.

Since DXA was performed twice at both Baseline and Month 6, at those visits we used the average (recalculated) FM and FFM from the two assessments.

Changes in FM and FFM since baseline are used to calculate delta Energy Stores as shown in section 1.5.

Δ FM (kg) = FM at end of interval – FM at start of interval

Δ FFM (kg) = FFM at end of interval – FFM at start of interval

Duration of the interval in days is the days from the midpoint of the DLW at the starting visit to the midpoint of the DLW period at the ending visit. For intervals starting at baseline, the starting date is Day 0, the day before intervention started.

5 Baseline Calculations

Separate calculations will be done for Baseline Visit 1 and Baseline Visit 2 for FM, FFM, daily intake of fat, carbohydrates, protein and alcohol, daily rate of weight change, RQ and TEE. The average TEE at baseline will be calculated from the BL1 and BL2 TEE values.

6 Missing Data

For each visit, a subject must have at least 3 food diary days and at least 3 home weights in order to calculate the RQ. If there are not enough home weights, clinic weights can be used instead. If these conditions are not met, a substitute RQ will be used from the closest visit(s). If RQ is missing at one of the two baseline visits, we will use the non-missing RQ value for both baseline visits. If RQ is missing at Month 12, we will use the average of Month 6 and Month 18 RQs if it is a CR subject, or the average of the baseline and Month 24 RQs if it is an AL subject. If RQ is missing at Month 24, the Month 18 RQ will be used if it is a CR subject, or the Month 12 RQ if it is an AL subject.

7 Short term Adherence Calculations

Short term adherence refers to the %CR during a 2 week DLW period at a single follow-up visit. We use the TEE measured by DLW at that visit, and the ΔES during the DLW period is obtained from daily weight change during the DLW period from the regression of daily and clinic weights described in section 3.2.

$\Delta ES_{Short\text{-}term}$ (kcal/day)= Daily weight change (kg/day) x EC_{wt} kcal/kg.

Where EC_{wt} is the median, treatment arm and visit specific calculated Energy Content of Weight Change

$$\text{Individual } EC_{WT} \text{ (kcal/kg)} = \frac{\text{Delta FM (kg) x 9,300 (kcal/kg) + Delta FFM (kg) x 1,100 (kcal/kg)}}{\text{Delta Weight (kg)}}$$

For the CR arm, for each follow-up visit, we will use the median EC_{wt} from the preceding 6 month interval, and for the AL arm, at the Month 12 and 24 visits, we will use the median EC_{wt} from the preceding 12 month interval. For Baseline EC_{wt},for all subjects, we will use the median EC_{wt} from the AL arm from BL – M12.

We will NOT delete any extreme values of EC_{wt} before taking the medians.

$EI_{Short\text{-}term}$ (kcal/day) = $TDEE_{visit}$ (kcal/day) + daily $\Delta ES_{Short\text{-}term}$ (kcal/day)

$\%CR_{Short\text{-}term} = 100 \times (EI_{AL} - EI_{Short\text{-}term}) / EI_{AL}$

8 Additional Data handling rules

1) Truncate any values of RQ < 0.65 or > 1.05 at 0.65 and 1.05 respectively. (there have been no values meeting these truncation criteria as of 1/18/2012).
2) Hardcode 5 baseline TDEE values at Site X because the values were considered implausible and the steering committee agreed that calculated values could replace the measured values.