18. ADHERENCE CALCULATIONS

18.1 Overview

Both short term and long term adherence will be calculated over various periods of interest. Per section 14 of the CALERIE Protocol, The degree of adherence will be characterized as the percentage of CR achieved relative to Ad libitum energy intake, expressed as:

$\%CR_p = 100\ [1 - (EI_p / EI_{AL})]$, where

- **p** is the period of interest
- **EI_{AL}** (kcal/day) (Ad libitum EI) is the long-term average daily energy intake before the start of the intervention, estimated by the average of two consecutive measures of total daily energy expenditure (TDEE) by the doubly labeled water (DLW) method during the baseline period (details in section 22.2). No corrections will be made for changes in body energy stores or body weight.
- **EI_p** (kcal/day) is the average daily energy intake over the period of interest, estimated by using the intake/balance method, as:

  $EI_p = TDEE_p + \Delta ES_p$, where

  - **$TDEE_p$** (kcal/day) is the average daily energy expenditure during the period of interest (details in section 22.2)

  - **ΔES_p** (kcal/day) is the average daily change in body energy stores during the period of interest (details in section 22.4 and 22.5)

Long term adherence refers to average %CR occurring over intervals spanning DLW assessments (e.g. from baseline to month 6, month 6 to month 12), while short term adherence focuses on %CR within each 2-week DLW period.

18.2 Schedule *of Adherence analyses*

Adherence analyses will be based on data from DLW and either DEXA assessments or daily body weight assessments. There will be two consecutive 2-week DLW periods during baseline, and one 2-week DLW period at each of months 6, 12, 18 and 24. There will be 2 DXA's at baseline, one on day 1 of the first period, and one on day 14 of the second period. There will be two DXA's at month 6, one on day 1 and one on day 14 of the DLW period. Only one DXA assessment will be done at months 12, 18 and 24, each on day 1 of the DLW period.

Short term adherence will be assessed for the 2-week DLW period at months 6, 12, 18 and 24.

Long term adherence can be calculated for intervals between two consecutive DLW periods, and intervals spanning more than two DLW periods. The former will be referred to as component intervals and the latter as composite intervals. For this analysis, 'Consecutive DLW periods' refers to visits where DLW assessments were actually performed, but not to protocol specified DLW assessments that were missed.

Long term intervals of interest

- Component Intervals
  - Baseline – M6
  - M6 – M12
  - M12 – M18
  - M18 – M24

- Composite Intervals
  - Baseline – M12
  - Baseline – M18
  - Baseline – M24
  - M6 – M24
  - M12 – M24

18.3 Calculation of TDEE

Per section 12.1.1 of the CALERIE Protocol, average TDEE will be measured during two 2-week periods at baseline (two consecutive periods), months 6, 12, 18 and 24 by the DLW method. The following equation will be used to derive the TDEE for each 2-week DLW period:

$$\mathbf{TDEE = rCO_2\ (1.231 + 3.815 / RQ),}$$

Where rCO_2 (L/d) is the rate of carbon dioxide production and RQ is the respiratory quotient that is provisionally estimated as 0.86.

Baseline TDEE will be estimated by the average of the two consecutive baseline TDEEs.

18.3.1 Short term TDEE

The TDEE from the 2-week DLW period at month 6, calculated using the formula in 22.3, will be used in the calculation of short term adherence at months 6, 12, 18 and 24. For month 6 two calculations of adherence will be performed, one using the DXA estimates for change in body energy stores, and the other using estimates of changes

in body energy stores derived from daily body weight assessments. For the 12, 18 and 24 month assessments only 1 estimate of adherence will be generated, using the daily body weight assessments.

18.3.2 Long term TDEE

- For calculations of long term adherence between two consecutive DLW periods (e.g. Baseline to Month 6, Month 6 to Month 12), average TDEE will be estimated by the average of the two TDEE's from the two 14-day DLW periods.

- For intervals spanning more than two DLW periods, (e.g. Baseline to Month 12), the average daily TDEE will be estimated by the weighted average of the TDEE's of each component interval, weighted by the duration of each component interval:

  $\mathbf{TDEE_p\ (kcal/day) = \Sigma_i\ [}d_i\ \mathbf{x\ (\ TDEE_{i1} + TDEE_{i2})/2\ ]\ /\ \Sigma}\ d_i$ **,** where

  - i indexes each component interval within the composite interval of interest,
  - $TDEE_{i1}$ (kcal/day) is the TDEE from the DLW period at the start of component interval i,
  - $TDEE_{i2}$ (kcal/day) is the TDEE from the DLW period at the end of component interval i,
  - d_i (days) is the duration of each component interval, defined in 18.4.

18.4 Duration of Long Term intervals

For both component and composite intervals, the interval duration is defined as :

d_i = interval end date – interval start date, where interval start date is the

- date of intervention start if the interval starts at baseline

- midpoint of of the starting of the 14-day DLW period if the interval starts after baseline. (typically this would be day 7 of the DLW period as long as the DLW period is 14 days)

Interval end date is the midpoint (day 7) of the ending 14-day DLW period

For example, if the period of interest is M6 to M12, the duration would be:
Day 7 of M12 DLW period – Day 7 of M6 DLW period

18.5 Delta Energy Stores for Long Term Adherence

For the long term adherence, average daily changes in energy stores from the beginning to the end of the interval will be calculated using standard coefficients and fat mass (FM) and fat free mass (FFM) from DEXA and clinic weight measures. Whether

the interval of interest spans two or more DLW periods, only the DEXA measurements at the first and last DLW periods of the interval will be used to determine delta energy stores.

At each DEXA assessment, FM and FFM are calculated by:

- FM (kg) = % Body Fat (from DEXA) x Clinic Weight (kg)
- FFM (kg) = Clinic Weight – FM

Baseline FM (FFM) will be estimated by the average of the two FMs (FFMs) during the baseline period.

Month 6 FM (FFM) will be estimated by the average of the two FMs (FFMs) during the month 6 DLW period.

For Months 12, 18 and 24, the FM and FFM from the single DEXA assessment will be used.

Changes in FM and FFM from the beginning to the end of the interval are calculated as:

- $\Delta FM\ (kg) = FM_{end} - FM_{start}$
- $\Delta FFM\ (kg) = FFM_{end} - FFM_{start}$

Where FM_{start} , FFM_{start} , FM_{end} , $FFM_{end,}$ denote the FM and FFM at the start and end of the interval, respectively.

Using standard coefficients for energy content per kg of FM and FFM, the average daily change in energy stores is calculated as:

ΔES_p (kcal/day) = [(9300 x ΔFM) + (1100 x ΔFFM)] / duration of interval in days

where duration of interval in days is defined in section 18.3.

18.6 Delta Energy Stores for Short Term Adherence

Two different methods can be used to estimate delta energy stores for short term adherence during each 2-week DLW period, using DEXA measures or regression of clinic or daily home weights.

18.6.1 Short term Delta Energy Stores using changes in FM and FFM

This analysis is analogous to the calculation of delta energy stores for long term adherence, using the DEXA assessments at the beginning and end of the 2-week DLW period at month 6.

As in the long term method, FM at each DEXA assessment will be calculated by multiplying the % Body Fat from DEXA with the clinic weight at the time of DEXA, and FFM will be calculated as the difference between clinic weight and FM.

- ΔFM (kg) = FM at the end of the14-day DLW period – FM at the beginning of the14-day DLW period

- ΔFFM (kg) = FFM at the end of the14-day DLW period – FFM at the beginning of the 14-day DLW period

ΔES_p (kcal/day) = [(9300 x ΔFM) + (1100 x ΔFFM)] / duration of interval in days

Usually, the duration of the interval will be 14 days. However, in the event of departures from 14 days, the actual duration will be used.

18.6.2 Short term Delta Energy Stores using regression of daily home weights

For each participant, a linear regression of the daily home weights (kg) during the 2-week DLW periods at months 6, 12, 18 and 24 against day will provide an estimate of the daily rate of weight change β(kg/day). Assuming 7,400 kcal per kg of weight change,

ΔES_p (kcal/day) = β x 7,400

A similar analysis will be performed using clinic weights.

18.7 Calculating expected future weight change for the Toolbox

Carl Pieper will fill this in.

Appendix

Various exploratory analyses will be done at the end of the study, or as data becomes available. These will include:

- Calculating the constant for energy content of weight change (currently using 7,400 kcal/kg). Factors that may influence the energy content of weight change, including stage of CR, gender and PAL will be explored in these analyses.
- Calculating RQ based on participant self-reported dietary intakes and taking into account rate of change in body energy stores during the same period. (currently using RQ=0.86)
- Adjusting FM and FFM for changes in body water. Currently we assume that the energy content of FFM change is 1.1 kcal/g. However, if the hydration of FFM is different from the expected value of 73%, the energy content of FFM may be different from anticipated. We currently assume based on Phase 1 data that changes in hydration will result in negligible changes in energy content of FFM.

Adherence calculations may be re-calculated to reflect results from these exploratory analyses.