

**CALERIE DXA Data Management Procedures
Version 2.0
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How whole body soft tissue results will be used in CALERIE

- Adherence calculations

“To analyze %CR over different intervals, we will use two versions of the intake/balance method, based on the relationship,

$$EI = EE + \Delta ES,$$

where EE is average daily energy expenditure during the period of interest, and ΔES is the change in body energy stores during the period of interest. ... ΔES will be estimated by calculating the change in energy stores (measured by DEXA) from the beginning to the end of the interval, divided by the duration of the interval in days.”

- Primary Aim #2. Reduced resting metabolic rate (RMR) corrected for changes in body composition.

“RMR and TEE will be analyzed in relation to changes in body composition measures (e.g., FFM) over time, and a different model will be applied. Body composition is known to be correlated with RMR, and differences between the two treatment arms are expected. Thus, body composition must be considered as a time-dependent confounder. Robins [272] demonstrated that including a time-dependent confounder as a covariate in a regression model will give rise to inconsistent estimators of the parameters. The approach of Rochon [273,274] will therefore be applied for this analysis instead. “

- Total and regional body composition changes as outcomes.
- In general, the focus in CALERIE is on change in parameters, rather than cross-sectional (baseline) levels
- Models will generally be adjusted for clinic site - and thus for scanner differences.

Adherence calculations

- Use scale weight, not DXA Total Mass, to calculate FM and FFM

Protocol specifies use of Scale Weight (not DXA Total Mass) and %FAT (from DXA) to calculate FM and FFM, used to estimate delta energy stores (ΔES)

“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 “*

Correction of total body %FAT, FFM and FM

- STEP 1: The WB scans have all been re-analyzed in the current (Apex) Hologic software. This version corrects the problem in older Hologic software of under-estimating fat mass (and over-estimating lean mass). (Schoeller et al. Am J Clin Nutr 2005).
- STEP 2: Apply longitudinal correction at each clinic based on the WB phantom, if needed, to %FAT. The first longitudinal report (thru Feb 2009) did not recommend any correction factors for %FAT. A final report will be prepared when all participants scans have been completed. The CALERIE QA Committee (or steering committee) will then decide whether to apply any recommended longitudinal corrections.
- STEP 3: Calculate $FFM_{\text{scale weight}}$ and $FM_{\text{scale weight}}$ from corrected %FAT and scale weight.
- As a check on quality control, any DXA Total Mass and scale weight measurements that were obtained on a participant on the same day will be compared and reviewed to identify any questionable outliers for scale weight.
- We are NOT recommending a correction across clinics (cross calibration) based on the WB phantom, circulated at the start of CALERIE. The **Site Z** scanner has a different hardware configuration (W versus A), and we lack confidence that the phantom cross cal results will reliably translate into in vivo differences. We DO recommend that models be adjusted for scanner (or clinic).
- Parameters that will be available for data analyses: Scale weight, $FFM_{\text{scale weight}}$, $FM_{\text{scale weight}}$, and %FAT (with longitudinal correction if needed). To avoid confusion regarding the parameters to use in data analyses, the values output directly from DXA (Total mass, %FAT, FFM, FM) will not be available in primary study datasets.
- FFM and FM parameters will be calculated by the CoC.

Changes in body composition, for RMR calculations and as an outcome

- For consistency with the total body FFM and FM values that will be used for adherence calculations, body composition parameters for these other purposes in CALERIE should also be calculated using scale weight (not DXA total mass) and corrected %FAT (from DXA).
- Corrections outlined above will be used

Calculation of lean soft tissue mass

- Lean soft tissue mass is calculated by subtracting bone mineral content (Total BMC) from FFM.
- Total BMC values will be longitudinally corrected, if needed. (See section below on bone parameters.) Decision on the need for correction will rest with the CALERIE QA Committee.

Correction of regional %FAT, FFM and FM

Changes in regional body composition, e.g. changes in FM or FFM of the arms, are not listed as a primary or secondary outcome, but are likely to be of interest to investigators. Hologic provides Total Mass and %FAT (and other parameters) by region. For example, Total Mass of the Arms and %FAT of the Arms are available.

Regional values will be corrected as follows:

- Apply any recommended longitudinal correction, based on the WB phantom, to Total Mass and %FAT for each region. Re-calculate regional FFM and FM.
- To derive regional lean soft tissue mass (LSTM), apply any longitudinal corrections, based on the WB phantom, to Total BMD and Bone Area for each region. Re-calculate Total BMC for each region. Calculate lean soft tissue mass as LSTM = FFM-BMC.
- Decisions on what longitudinal corrections to apply will rest with the CALERIE QA Committee.
- Scale weight will not be considered in correcting the regional parameters. Note that the sum of the regional total mass values will equal whole body total mass, but will not necessarily equal the scale weight.
- Data available in the primary (public) datasets: Regional total mass, FFM, FM and %FAT.

Artifacts

- Artifacts are graded based on the tissue results they are likely to affect (bone and/or soft tissue) and the severity of the possible effect (1=negligible effect; 2=possible regional effect; 3=possible whole body effect). Artifacts assessed as level 1 severity, such as the core temperature pill appearing on the DXA scan, do not require any action and will not be identified in the final dataset.
- For severity level 2, regional bone and/or soft tissue values that might be affected by the artifact will be set to missing. Total values will be retained. For example, a participant with metal in the right arm will have right arm BMD, BMC and Bone Area set to missing; whole body values for BMD, BMC and Bone Area will be retained.
- For severity level 3,
 - Bone and/or soft tissue values in affected region will be set to missing.
 - If the artifact was present throughout the trial, total body values will be retained so that longitudinal changes can be calculated. If the artifact was not present throughout, appropriate action will be decided on a case-by-case basis by the CALERIE QA Committee or designated working group.
- These corrections will be applied by the UCSF DXA QA Center.
- A separate spreadsheet will be provided to the CoC, indicating the reason that any scan values were set to missing.

Date discrepancies: DLW dosing and DXA whole body scan dates differ

- If these dates differ, the DXA results used to calculate adherence will not coincide with the DLW results for energy expenditure.
- At baseline and at Month 6, 2 whole body DXA scans are obtained on each participant. At these visits, the average of the 2 DXA scans will be used to determine

FFM and FM at baseline (or Month 6) for the adherence calculations. At baseline DXA scans are obtained 28 days apart (two 14-day DLW measurements). At Month 6, they are 14 days apart (one 14-day DLW measurement). The first DXA scan should coincide with the DLW dose. The second scan should coincide with the final urine collection. (At baseline this is the final urine collection for the second DLW measurement.) Thus, the average of the 2 scans will provide an estimate of FFM and FM during the DLW testing period, i.e. from DLW dose to final urine collection.

If the DXA scans do not coincide with the DLW dose and final urine collection:

- If they are both within 14 days of the first or last date of the DLW testing period, the average result of the 2 scans will be used.
- If one DXA scan is within 14 days of the first or last date of the DLW testing period and one is outside, the measurement that occurred within the 14-day period will be used and the other scan result will be ignored for these calculations.
- If neither DXA scan is within 15 days of the start or end of the DLW testing period, the appropriate value to use will be decided on a case-by-case basis, before analyses are begun.
- At all other visits, 1 whole body DXA scan is obtained. The scan should coincide with the DLW dosing date.
 - If the scan was not obtained at DLW dosing, but was obtained before the final urine collection (i.e. during the DLW testing period), the scan results can be used.
 - If the scan was not obtained during the DLW testing period, but was obtained within 15 days of the period, it can be used.
 - If the scan was obtained more than 15 days before or after the testing period, the appropriate value to use will be decided on a case-by-case basis, before analyses are begun.

Date discrepancies Scale weight not available on the same day as DXA whole body scan

- If scale weight was not obtained on the whole body DXA date, the ability to use scale weight, in place of DXA Total Mass, is compromised.
- As of September 2010, there were 9 WB scans obtained on a date without scale weight available. 7 of these had a weight within 1-3 days. One had a 13 day gap, the other had a 28 day gap between the DXA and weight measurements.
- If the scale weight was obtained on a different day than the whole body DXA, the scale weight can be used if the scan was within 7 days of the DXA. The closest scale weight, in time, should be used.
- In the rare cases when the closest scale weight was obtained 8 days or more before or after the DXA, the DXA Total Mass should be used.

Bone (Hip, spine, forearm, whole body) results

How DXA bone measurements will be used in CALERIE

- BMD changes as outcome.
- For whole body, Total BMC will be used to calculate lean soft tissue mass from FFM ($FFM - BMC = \text{lean soft tissue mass}$)
- The focus in CALERIE is on change in parameters, rather than cross-sectional (baseline) levels
- Models will generally be adjusted for clinic site - and thus for scanner differences.

Correction of BMD for hip, spine, forearm, whole body

- STEP 1: Apply longitudinal correction at each clinic based on the spine phantom, if needed, for hip, spine, forearm BMD, and based on the whole body phantom for whole body BMD.
- STEP 2: For Whole Body results only, apply any longitudinal corrections to Total Bone Area and then recalculate Total BMC .
- We are not recommending a correction across clinics (cross calibration) based on the spine, hip and linearity phantoms, circulated at the start of CALERIE as cross scanner differences are not important for longitudinal changes. We DO recommend that models be adjusted for scanner (or clinic).

Artifacts

- For artifacts that affect whole body bone measurements, see previous section.
- Artifacts that affect spine, hip or forearm:
 - Spine scans: Affected vertebral levels are excluded from DXA results. If at least two levels are evaluable, the scan will be acceptable and the evaluable levels will be retained in the data. A scan that only includes one evaluable vertebral level will be considered unacceptable and will not be included in the DXA dataset.
 - Hip and forearm scans: If an artifact is present at baseline, the opposite hip (forearm) was scanned. If an artifact is introduced during the trial, the hip (forearm) is no longer scanned.

Appendix 1: Recommended Corrections**SITE X (QDR #45927)****Correction Factors:****FOR TOTAL BODY and REGIONAL VALUES****Total BMD:**

- 1) For scans performed from 1/31/09-9/28/10, multiply BTOTBMD by 0.9884.
- 2) For scans performed from 9/29/10-6/21/11, multiply BTOTBMD by 0.9775.
- 3) For scans performed on or after 6/22/11, multiply BTOTBMD by 0.9827.

Total Area:

- 1) For scans performed from 6/9/08-12/2/09, multiply BTOTAREA by 1.0164 (extend previous correction through 12/2/09).
- 2) For scans performed from 4/21/10-7/15/10, multiply BTOTAREA by 1.0145.
- 3) For scans performed on or after 9/29/10, multiply BTOTAREA by 1.0179.

Total BMC:

After applying the corrections for Total BMD and Total Area, recalculate BTOTBMC using the formula $BTOTBMC = BTOTBMD * BTOTAREA$.

Total Percent Fat:

- 1) For scans performed from 1/31/09-8/13/09, multiply BTOTPF by 1.0118.
- 2) For scans performed from 2/19/10-6/14/10, multiply BTOTPF by 0.9945.
- 3) For scans performed from 8/30/10-1/11/11, multiply BTOTPF by 0.9927.
- 4) For scans performed from 1/12/11-12/11/11, multiply BTOTPF by 0.9825.
- 5) For scans performed on or after 12/12/11, multiply BTOTPF by 0.9923.

CALIBRATE WHOLE BODY VARIABLES TO SCALE WEIGHT

The CALERIE protocol requires use of Scale Weight rather than DXA Total Mass to calculate soft tissue variables. Calculations are as follows:

- 1) Use scale weight and %FAT to calculate Total Fat Mass (based on scale weight) and Total Fat Free Mass (based on scale weight).
- 2) Recalculate Total Lean Soft Tissue = Total Fat Free Mass (based on scale weight) – BTOTBMC. Use the corrected BTOTBMC (based on WB phantom).

The regional values are NOT recalibrated to Scale Weight.

FOR REGIONAL VALUES ONLY (including “Wbody sub total” values)**BMC, Area, BMD (for Region)**

Apply corrections above, for whole body bone-related values, to regional values for BMD, Bone Area and BMC.

Total Mass (for Region):

- 1) For scans performed from 7/16/07-7/15/08, multiply Regional Mass by 1.0032.

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- 2) For scans performed from 7/16/08-12/2/09, multiply Regional Mass by 1.0082 (extend previous correction through 12/2/09).
- 3) For scans performed from 4/21/10-9/28/10, multiply Regional Mass by 1.0030.
- 4) For scans performed from 9/29/10-6/21/11, multiply Regional Mass by 1.0050.
- 5) For scans performed on or after 9/24/11, multiply Regional Mass by 1.0042.

Total Fat (for Region):

After applying the corrections for Regional Mass and Regional Percent Fat, recalculate Regional Fat using the formula $FAT = (PF/100) * MASS$.

Total Fat Free Mass (for Region):

After applying the corrections for Regional Mass and Regional Fat, recalculate Regional Fat Free Mass (FFM) using the formula $FFM = MASS - FAT$.

SITE Y (QDR #80310):

Correction Factors:

Total BMD:

- 1) For scans performed from 8/12/08-9/7/10, multiply BTOTBMD by 1.0150 (extend previous correction through 9/7/10).
- 2) For scans performed from 9/8/10-11/29/10, multiply BTOTBMD by 1.0304.

Total Area:

- 1) For scans performed from 9/8/10-11/29/10, multiply BTOTAREA by 0.9746.

Total BMC:

After applying the corrections for Total BMD and Total Area, recalculate BTOTBMC using the formula $BTOTBMC = BTOTBMD * BTOTAREA$.

Corrections are not recommended for **Total Percent Fat**.

Correction Factors for REGIONAL VALUES (including “Wbody sub total” values)

Regional values should be corrected as follows (example using Right Arm):

- 1) Correct RARMBMD, RARMAREA, using correction factors from phantom (above). Recalculate RARMBMC (as above).
- 2) No correction is required for %FAT (RARMPF). Therefore, no corrections will be applied to RARMFAT or RARMFFM.
- 3) Recalculate RARMLEAN as RARMFFM - RARMBMC (corrected based on phantom).

Site Z (QDR #70570):

Correction Factors:

No corrections are recommended for the whole body variables for this scanner.

BOTH SCANNERS:

CALIBRATE WHOLE BODY VARIABLES TO SCALE WEIGHT

The CALERIE protocol requires use of Scale Weight rather than DXA Total Mass to calculate soft tissue variables. Calculations are as follows:

- 3) Use scale weight and %FAT to calculate Total Fat Mass (based on scale weight) and Total Fat Free Mass (based on scale weight).
- 4) Recalculate Total Lean Soft Tissue = Total Fat Free Mass (based on scale weight) – BTOTBMC. For **Site Y** use the corrected BTOTBMC (based on WB phantom). For **Site Z**, use BTOTBMC without correction.

The regional values are NOT recalibrated to Scale Weight.