CALERIE

UCSF DXA Quality Assurance Center
Manual of Procedures
(Chapter 16)

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PURPOSE OF MOP

This Manual of Procedures describes the activities of the DXA QA Center for the CALERIE study. These activities include the training, certification and monitoring of the DXA operators at the clinical sites; the receipt of study data from the CALERIE clinics; analysis of DXA scans; maintenance of a central DXA database; monitoring and analysis of scanner performance; periodic reports; and regular data transfers to the CALERIE Coordinating Center (CoC).

GOALS OF CENTRALIZED QUALITY ASSURANCE

The goal of the QA Center is to maintain a high level of precision and accuracy in the DXA measurements obtained during the CALERIE study. Sources of error in multicenter studies of body composition and bone density using DXA include variability in equipment between centers and over time, and variability in scan acquisition and analysis technique between operators. Our quality assurance program aims to reduce these sources of error through:

- study-specific procedures, and operations manual
- central on-site operator training, certification and technical support
- standards for, and monitoring, operator performance
- central analysis of scans
- cross-calibration of densitometers at the clinical centers
- standards for, and monitoring, longitudinal machine performance
- standardized data transfer procedures
- centralized DXA data management

GENERAL STUDY INFORMATION

The UCSF DXA QA Center maintains a centralized database of all DXA scans for the CALERIE study. All scans will be analyzed on a single workstation using Hologic software version 12.6.

CERTIFICATION OF DXA OPERATORS

All operators are required to read and understand the Hologic User's guide, attend the on-site training for this study and receive a satisfactory review of certification scans. Completion of the Hologic training course is also required but can be waived at the discretion of the QA Center. ISCD certification is required for the chief operator and recommended for other operators.

Certification scans are sent to the UCSF QA Center for all DXA operators participating in the CALERIE Study. Each operator must send printouts of 5 example scans done at each skeletal site. Upon successfully demonstrating proper acquisition procedures and satisfying the other requirements, the UCSF QA Center will issue an approval notification, certifying the operator to scan for CALERIE.

ON SITE TRAINING OF DXA OPERATORS

On site training will be provided for up to 4 DXA operators at each clinical site before the baseline visit. Training will include a review of basic Hologic procedures and instruction in the specific requirements of the CALERIE study.

PRECISION ASSESSMENT OF DXA OPERATORS

The chief operator at each clinical site will perform a precision assessment at the beginning of CALERIE for whole body scans. Thirty participants will be scanned twice for whole body by the chief operator. In between scans, the participant will get off the scanner table so that s/he is re-positioned for the second scan. The QA Center will provide detailed instructions to each clinical site. After the scans are analyzed at the QA Center, the QA Center will calculate the precision for each chief operator.

GENERAL BACKUP AND FILING PROCEDURE

Study information and data are stored in the DXA QA lab (room 5779). The following materials are filed by clinical site and in chronological order:

1. Correspondence
2. Forms related to scanner performance:
    a. Spine Phantom QC Plots,
    b. QC Data Transmittal Forms,
    c. Whole Body Air Scan QC Worksheets,
    d. Repair/Service/Upgrade logs and worksheets
    e. Hologic service reports
3. Optical disks with participant scan data
4. Participant Scan Logs
5. Excessive Bone Loss correspondence

DATA SHIPMENT/RECEIPT PROCEDURE

Participant scans will be sent on a daily basis during the baseline visits. For all subsequent visits, scans will be sent on a weekly basis. Each shipment will include:

1. Participant Scan Log
2. Participant scans on traveling media.

The QA Center will maintain a file of the Participant Scan Logs to track these shipments of participant scans.

Quality control data will be sent on a monthly basis. These shipments will include:

1. QC Data Transmittal Form
2. Spine Phantom QC Plots. A printout of the most recent plots of the QC database (spine BMD, BMC, and AREA).
3. Export of QC data (label the disk with site name, date and QC Data
4. Whole body phantom scans and "air" scans on CD/disk.
5. Copy of Whole Body Air QC Scan Worksheet.
6. Repair/Service/Upgrade logs and worksheets. Copy of any Hologic service reports for that time period.

Clinical sites will send all shipments using a next business day delivery system that provides a tracking number for each mailing. During the baseline and 6-month visits, shipments will be sent "next business day air" for delivery by 10AM.

The QA Center will log the receipt of each monthly shipment of quality control data and the contents of the shipment into a DXA QA tracking database.

If any items are missing from a packet, the DXA QA Center will notify the clinic using the DXA QA Data Action Form.

DATA TRANSFER TO HOLOGIC WORKSTATION

1. Participant scans will be downloaded from CD/super disks to the Hologic workstation where they will be analyzed.

2. Quality control data (spine phantom scans, WB phantom scans) will be downloaded to the Hologic workstation on a monthly basis.

3. Traveling copy media will be returned to the clinical sites for reuse.

DXA PARTICIPANT SCAN ANALYSIS PROCEDURE

1. Participant scans will be reviewed for quality of acquisition. Any problem will be noted on the Participant Scan Log. If an action is required by the clinic, the DXA QA Specialist will complete a DXA QA Action Form.
    a. Sites will be notified immediately if any scans need to be reacquired. The DXA QA Specialist will telephone the chief operator at the clinic and will also fax a copy of the DXA QA Action Form. Comments and suggestions for acquiring the scan again will be included on this form.

b. During the baseline and 6-month visits, clinics will be notified of the need for a repeat scan within one working day of receipt of the scans (for packets that are received at the DXA QA Center by 10AM).
c. At subsequent visits, clinics will be notified within five working days (one week) of receipt of the scans.
d. Scans that are acceptable but not optimal will be noted on the Participant Scan Log. A copy will be sent to the DXA operator with suggestions to improve acquisition on future scans.

2. All scans will be analyzed using standard analysis procedures as described in the Hologic User's Guide.

3. All follow up scans will be analyzed using the Compare feature. The Compare feature allows comparison of the current scan to the baseline scan using the same size, shape and location of the ROI (region of interest) as was used on the baseline scan.

4. Scans will be analyzed using version 12.6 of the Hologic software. Any changes to this software at the QA Center will require the approval of the CALERIE Coordinating Center.

5. Information on each scan will be entered into the DXA QA tracking database, including any feedback to the DXA operator or requests for a repeat scan.

LOW BMD & EXCESSIVE BONE LOSS (EBL) REVIEW AND NOTIFICATION PROCEDURE

BMD of the spine and hip will be measured by DXA at the Baseline, 6 (CR), 12, and 24 month visits. The UCSF DXA QA center will check for low bone density or excessive bone loss. When low bone density or excessive bone loss is confirmed, the QA center will notify the clinical study coordinator, the chief DXA operator, and the CALERIE CoC by faxed letter (Appendix B, page 2) with a copy of the participant's scan(s) attached.

At baseline, low bone density is defined as a BMD of the total hip, femoral neck, or total spine equal to or less than a T-score of -2.3.

At follow-up visits that include hip or spine scans, any participant who has a BMD T-score at the total hip or total spine less than -2.5, as determined by the UCSF DXA QA Center, will have the intervention permanently discontinued. The QA Center will notify the DXA chief operator and the CALERIE Study Manager at the clinical center and the CALERIE CoC using the Notification of Low BMD or Excessive Bone Loss (EBL) form (Appendix B) of low bone density in such cases. The QA Center will include copies of the relevant scans with the notification.

In addition, for the 6-month, 12-month and 24-month hip and spine scans the QA Center will evaluate bone loss compared to baseline. Any participant who experiences a decrease in BMD at the total hip or total spine of 10% or greater from the baseline during the study as determined by the QA Center will have the scan repeated within one month. A repeat scan will not be required at the 24-month visit. The QA Center will complete the Data Action form (Appendix B) to notify the DXA chief operator and CALERIE Study Manager at the clinical center that a second scan should be acquired. If the second scan confirms the original findings, the QA Center will confirm EBL and the participant will have the intervention permanently discontinued. The QA Center will notify the DXA chief operator and the CALERIE Study Manager at the clinical center and the CALERIE CoC using the Notification of Low BMD or Excessive Bone Loss (EBL) form (Appendix B). The QA Center will include copies of the relevant scans with the notification.

Any participants who experience a decrease in BMD greater than or equal to 5% and less than 10% at the total hip or total spine from baseline to Month 6 or baseline to Month 12 will have their BMD of both the hip and spine measured by DXA at Month 18. The QA Center will complete the Data Action form (Appendix B) to notify the DXA chief operator and CALERIE Study Manager at the clinical center that the additional scans will be acquired at Month 18. If the decrease in BMD from baseline to Month 18 is greater than or equal to 10% for either scan, the participant will have the scan repeated within one month and the same procedure for notification/confirmation will be followed as for Month 6 and Month 12.

Visit	T-Score	EBL
Baseline	Report if T-score ≤ -2.3 at: Femoral neck Total hip OR Total spine	N/A
6-month	Report if T-score <-2.5 at: Total hip OR Total spine	Request a second scan if visit scan shows loss greater than 10% from baseline at total hip or total spine If second scan shows loss greater than 10% from baseline, report confirmed EBL based on second scan If BL/6M BMD decreases greater than or equal to 5% but less than 10% at total hip or total spine, request that both a hip and spine scan be acquired at 18M.
12-month	Report if T-score <-2.5 at: Total hip OR Total spine	Request a second scan if visit scan shows loss greater than 10% from baseline at total hip or total spine If second scan shows loss greater than 10% from baseline, report confirmed EBL based on second scan. If BL/12M BMD decreases greater than or equal to 5% but less than 10% at total hip or total spine, request that both a hip and spine scan be acquired at 18M.
18-month		Request a second scan if scan shows loss greater than 10% from baseline at total hip or total spine If second scan shows loss greater than 10% from baseline, report confirmed EBL based on second scan.
24-month	Report if T-score <-2.5 at: Total hip OR Total spine	If visit scan shows loss greater than 10% from baseline at total hip or total spine, report EBL without the second scan

The first scan will be retained as the official visit scan; the second scan will only be used to confirm EBL.

A finding of low bone density or excessive bone loss should be reported by the clinical study coordinator as an adverse event (AE).

The DXA QA Center will provide notification of low bone density or EBL within five working days (one week) of receipt of the scans.

DATA TRANSFER TO SAS

Participant scan data and whole body phantom scan data will be processed, analyzed and saved to a centralized database on the Hologic workstation. The data from the analyzed scans will be exported to create a MS Access format file (dbexport.mdb). Spine phantom QC data will also be saved on the Hologic workstation to an MS Access format file called QCexport.mdb. These Access files are then copied to a password protected internal network. The data are imported to SAS by the data manager using a standard SAS function.

Note that the Access database generated by Hologic for the participant scan results does not include a T-score. The T-score will be available on the hard copy of the analyzed participant scan and in the electronic version of the analyzed scan, but will not be part of the main DXA scan result dataset maintained in SAS. Using the data provided by the DXA QA Center, T-scores can be generated by the CoC, using various available reference databases, as a check on the safety review, if desired. It may not be possible to exactly duplicate the Hologic calculations.

DXA SCAN EDITS

The participant scan data in SAS are reviewed once a month. The checks include: Outliers, duplicate scans, valid/correct ID numbers, all skeletal sites included, subregions complete (WB, spine, hip, forearm), correct scan mode, T-score <-2.3 (at total spine, total hip, or femoral neck at BL) or T-score <-2.5 (at total spine or total hip at follow-up). Additional checks at follow-up visits include: Scan mode consistent across visits, same side (hip, forearm), vertebral levels consistent, EBL. Queries are generated for the DXA QA Specialist and/or CoC. If corrections are needed to resolve the query, the data are corrected in the Hologic dataset on the workstation. Resolution of data queries and any data corrections or re-analysis of scans will be documented in the CALERIE study binder maintained by the DXA QA Specialist.

During the baseline visit, repeat whole body scans will be sent for the precision assessments. The first of each pair of scans will be retained in the SAS dataset as the official participant scan. Occasionally, an operator may send two scans because of concerns regarding the best method of acquisition. The operator will flag these scans and

comment on the reason for a repeat scan in the accompanying Participant Scan Log. After review and consultation with the operator, the QA Center will make a final decision on which scan to retain.

QUALITY CONTROL OF SCAN ANALYSIS

The DXA QA Specialist assigned to CALERIE will complete a precision assessment at the beginning of the study. Every four months, a random sample of the analyzed scans will be reviewed.

QUALITY CONTROL OF SCANNER PERFORMANCE - OVERVIEW

Scanner performance is monitored to identify problems that may arise during the study. If a problem persists, this will trigger a request from the clinical site for a service call by a Hologic field engineer. The methods used to monitor scanner performance are described in the following table. In addition, the spine phantom and whole body (WB) phantom scan results are analyzed at the end of each study visit to assess scanner performance over time and to recommend correction factors for the participant scan results if appropriate. At the beginning of the study, a cross-calibration is performed to identify differences in scanners across study sites.

Scan of:	Frequency:	Identify problems with scanner performance:	End of Visit analysis
Spine phantom	Daily	Daily review by operator. Outlier value triggers service call. Checked by QA Center monthly.	Longitudinal
Hologic tissue bar	Weekly	Required by Hologic scanner. Checks calibration for soft tissue measurements. Failure triggers service call. Not monitored by the QA Center.	NA
WB "air" scan	Weekly	Weekly review by operator. Outlier value triggers service call. Checked by QA Center monthly.	NA
WB phantom	Weekly	QA Center reviews plots visually once a month.	Longitudinal
Cross-cal phantoms	Once at baseline		Baseline cross-cal

QA CENTER MONITORING OF SCANNER PERFORMANCE

The activities of the QA Center to identify problems with scanner performance will be carried out on a monthly basis:

1. The hard copies of the spine phantom plots will be reviewed for any shifts or trends.
2. The WB "air" scan is loaded into the scan database and the global HiBone SD of the scan is determined. The WB Air Scan Worksheet sent by the clinic operator is reviewed. A SD >2 for the global SD or for any of the ten levels recorded at the clinic triggers an investigation.
3. The WB phantom scans will be analyzed at the QA Center. A plot of the WB phantom scans will be generated from the SAS dataset and reviewed for any visually evident shifts or trends.
4. Clinical sites will be contacted if any problems are noted that cannot be explained by the Hologic service (field engineer) report.
5. Performance and results of the scanner performance monitoring described above are entered into the DXA QA tracking database.

ANALYSIS OF QC PHANTOM DATA TO ASSESS LONG-TERM LONGITUDINAL SCANNER PERFORMANCE

The goal of the analysis of longitudinal phantom data is to determine whether significant deviations in long-term scanner performance have occurred. Where appropriate, correction factors may be generated from the data and applied to participant scan results.

Longitudinal performance of the scanners will be assessed using spine and WB phantom data at the end of the baseline, 12-month and 24-month visits.

Analysis of the spine and WB phantom scan results starts with a visual review of the plots and the calculation of the coefficient of variation for the DXA parameters. CUSUM analysis is then used to detect changes in scanner performance. This method has been shown to be a sensitive and specific procedure for evaluating QC data (Lu et al., J Bone Miner Res 11:626, 1996). Statistically significant change points identified by CUSUM are compared against a threshold for clinical significance (e.g., 0.5%/year for spine). The change points that meet the criteria of clinical significance are then compared with the scanner records for maintenance and repairs in an effort to identify the cause of any shifts. Once the phantom data are divided into intervals using the CUSUM technique, linear regression of the data in each interval may be used to identify statistically significant drifts ($p < 0.05$).

Based on the results of the analyses described above and a review of the scanner records, a correction factor may be recommended for the participant scan data.

SYSTEM CROSS-CALIBRATION PROCEDURE

The purpose of this procedure is to test the relative performance of the DXA scanners at multiple clinics. Where appropriate, these data can be used to generate correction factors to improve the pooling of participant data across sites. The cross calibration will be performed once at baseline during the study.

The UCSF QA center will distribute a set of cross calibration phantoms (spine, hip, block and whole body) to all sites with machine specific protocols. The phantoms used in the cross-calibration study will be scanned using the same procedures used to scan the study participants.

The QA center will analyze and archive all data from the cross-calibration procedure. For the spine, hip and whole body phantom, the mean, standard deviation and % CV will be calculated for each study site. One clinic will be selected as the "gold standard" site. Using ANOVA and Dunnett's test to account for multiple comparisons, the difference between the other two sites and this selected clinic will be determined. These data can be used to generate correction factors where appropriate. The block phantom results will be analyzed using linear regression to determine the linearity of BMD measurements on each scanner. All statistical analyses are performed in SAS.

REPORTS PROVIDED TO CALERIE

The DXA QA Center will provide regular reports to the CALERIE study regarding the status of the DXA participant scans and performance of the scanners. Reports will include:

1. Training and Certification of DXA Operators
    a. On site training (after completion of 3 sites)
    b. Certification status (6 months; updated in end of visit reports – see #5)
2. Monitoring of Participant Scans (Every 2 months during BL visit; updated in end of visit reports after BL)
    a. # completed scans
    b. # unacceptable scans
    c. Feedback provided to each operator on scan acquisition
3. Cross Calibration (BL)
4. Precision Assessment of DXA Operators (BL)
5. End of Visit Reports (BL, 12-mo, 24-mo)
    a. Participant scans - # completed, # unacceptable
    b. DXA operator certification and performance
    c. Longitudinal scanner performance (spine and WB phantoms)
    d. Scanner maintenance and repair records
    e. 6-mo visit will be included in the 12-mo report; 18-mo visit will be included in the 24-mo report.

Estimated Timeline for Reports

Report	APPROXIMATE date of report
1a. On site training	Dec 2006
1b. Certification status of operators at 6 mos	July 2007
2. Participant scans and operator performance – 2 , 4, 6, 8, 10, 12 mos. Then in end of visit reports.	March 2007 May 2007 July 2007 Sept 2007 Nov 2007 Jan 2008
3. Cross calibration	After phantoms circulated to 3 sites. June 2007
4. Precision assessment	After 30 ppts randomized at each clinic. Nov 2007
5. End of Visit reports	End of baseline. March 2008 End of 12-mo visit March 2009 End of 24-mo visit March 2010

DATA TRANSFERS TO/FROM CALERIE COORDINATING CENTER

The participant scan results will be transferred to the CALERIE CoC on a monthly basis. The data will be sent in an ascii file (pipe delimited). The format will be one record per participant per scan. Datasets will be cumulative. The QA Center will provide the CoC with a data dictionary or data definition table of the dataset including: variable name, label, type, length, format and format values. See Appendix C for an example of the data dictionary from another study. Change in the DXA parameters between visits will be calculated by the CoC. In addition, at the end of the baseline, 12-month and 24-month visits, a clean datafile of participant scan results will be transferred to the CoC.

The CoC will transfer the following data to the QA Center as a SAS dataset on a monthly basis for all participants currently enrolled in CALERIE:

Participant ID
DOB (or age at baseline)
Gender
Race/ethnicity
Any missed DXA scans reported by the clinics

Within 12 months after the last participant visit in CALERIE, the study archives will be transferred to the CALERIE CoC.

APPENDICES

[Appendices are in separate documents until the final versions of the forms and MOP are approved.]

APPENDIX A – CALERIE STUDY FORMS (Clinic to DXA QA Center)

1. Participant Scan Log
2. QC Data Transmittal Form
3. Hologic DXA Repair/Service/Upgrade Log
4. Whole Body Air QC Scan Worksheet

APPENDIX B - CALERIE STUDY FORMS (DXA QA Center to Clinic)

1. EBL Guidelines
2. Notification of low bone density/Excessive bone loss
3. DXA QA Data Action Form

APPENDIX C – DATA DICTIONARY

Initial list of variables for data transfers to CoC