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GLOBAL PUBLIC HEALTH

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TO: HCHS/SOL Quality Control Committee
CC: Yasmin Mossavar-Rahmani, SOLNAS PI
Sanjay R Patel, Sueño PI

FROM: Daniela Sotres-Alvarez, HCHS/SOL Coordinating Center
DATE: January 25, 2012

RE: HCHS/SOL Quality Control Report, January 2012

MEMORANDUM

This report includes:

- QC status reports for two HCHS/SOL Ancillary Studies:
    - Nutrition & Physical Activity Assessment Study (SOLNAS)
    - Sueño Study (Sleep)
- Recommendation from the Central Lab and HCHS/SOL Coordinating Center to statistically adjust insulin values measured before Oct 29, 2009 using a manual non-automated ELISA method with the new automated immunoassay method using the Roche Elecsys 2010 analyzer.

In the next QC report we will include a QC plan for the abstraction and adjudication of events being prepared by the Coordinating Center and the Endpoints Ascertainment and Classification Committee.

Quality Control Management
for Nutrition & Physical Activity Assessment Study (SOLNAS)

Yasmin Mossavar-Rahmani, Principal Investigator
Albert Einstein College of Medicine

January 17, 2012

The study is designed to enroll 476 participants from HCHS/SOL. The primary aims of this ancillary study are as follows:

Aim 1. To compare energy and protein data from the 24-hr dietary recall to the gold standard biomarkers Doubly Labeled Water (DLW) for energy and urinary nitrogen for protein in the HCHS/SOL study; to compare physical activity energy expenditure data from study questionnaires to the Actical (an accelerometer for measuring physical activity), DLW and indirect calorimetry.

Aim 2. To contrast measurement error properties of: (i) the 24-hr dietary recall; (ii) the 24-hr dietary recall with the addition of the Food Propensity Questionnaire (FPQ) (iii) HCHS/SOL Physical Activity Questionnaire; (iv) the Multi-Cultural Food Frequency Questionnaire (formerly known as Tufts University Food Frequency Questionnaire.) [Of the four HCHS/SOL sites, the Bronx site which consists primarily of Puerto Rican & Dominican participants will be the only site testing this questionnaire.]

Aim 3. To use the fitted measurement error model to produce calibrated intake and physical activity measures on the full HCHS/SOL cohort for use in analyses of clinical outcomes. For this population, clinical outcomes of interest include cardiovascular disease and self-reported diabetes.

So far approximately 351 participants have been recruited and three sites are scheduled to complete the primary study (119 participants/site) by 1/31/12.

Tools used to monitor quality control include:

1. Manual of Operations
2. Local Tracking System
3. Specimen Shipment Tracking
4. Management Report
5. Bi-weekly conference calls with minutes distributed afterwards
6. Communication with updates as needed

1. **Manual of Operations (MOP**)

   The manual has detailed instructions on performing the study and quality control measures for specimen collection including 5% blinded sub-sample of specimens (blood and urine) collected for quality control. Information relating to collection of specimens is on p. 101, 102 and 112 of the MOP. Information relating to collection of the 24 hr recalls is also covered on section 10, p.iii-viii and modeled after the parent study. In addition Dr. Wong at the Baylor College of Medicine performs quality control measures on the

quality of the Doubly Labeled Water (DLW) collection by examining the correlation coefficients of the DLW turnover rates.

2. **Local Tracking System**
   Developed by the Bronx site, this system offers real-time information on participants' progress in the study enabling study coordinators to determine whether participants have completed the visits, whether sample distribution characteristics such as weight and Hispanic/Latino background is on target and whether study enrollment is proceeding in a timely manner.
3. **Specimen Shipment Tracking** developed by the SOLNAS-Data CC at UNC allows shipment of specimens from sites to Reading Centers (Baylor College and Central Lab) with minimal data entry.

4. **Monthly Management Report** by UNC-Data CC
   This report provides overall statistics by site on recruitment, participant accrual projections and data completion. It also includes queries to correct errors related to incorrect or missing data.

5. **Bi-weekly conference calls** with staff allow quick dissemination of important updates. These pertain to quality control issues and enrollment.

Examples of Quality Control measures in action: changing recruitment site and showing excellent specimen collection:

Based on sub-optimal enrollment report from the San Diego site given a decision was made in December 2011 to move the study recruitment site to the parent study site. Recruitment started Saturday, Jan. 14, 2012 at the San Diego parent study site (Chula Vista) with four visit 1s, and one visit 2 completed on that day alone. Nine visit 1s are scheduled the week of 1/16/12. Given that only 14 participants were recruited at the previous site in the last six months, this pace of recruitment in one day alone is significant and bodes well for successful recruitment for this site. We anticipate completing recruitment at this site by May 1, 2012.

Regarding quality control measures for the bio-specimens, applying the quality control parameters for the Doubly Labeled collection, Dr. Wong states on the 10/7/11 study PI call that: "The excellent correlation coefficients for the turnover rates indicated that the samples were collected properly" (from call minutes).

Summary of Quality Check Procedures for Sueño* HCHS/SOL *Ancillary Study:

Sanjay R Patel, Principal Investigator
Harvard Medical School/ Brigham and Women's Hospital (BWH)

January 19, 2012

Study Description:

Sueño HCHS/SOL Ancillary Study was designed to assess the prevalence of poor sleep habits in a Hispanic-American population, identify predictors of poor sleep patterns, and define the impact of poor sleep on health consequences including obesity, diabetes, hypertension, and cardiovascular disease by measuring objectively sleep for a week (actigraphy watch) in a subgroup of 2200 participants of the parent HCHS/SOL study. The recruitment period is October 2010 – December 2013 to recruit 550 participants from each of the four field sites. As of January 2012, overall 425 subjects have been recruited.

At the Reading Center:

Field sites are asked to do a cursory evaluation of actigraphy data upon return of the actigraphs. If studies are clearly inadequate, they invite the participant to repeat the study with clarification of instructions to improve results. When an Actigraphy file is initially received at the Sleep Reading Center (BWH), the file is reviewed within 72 hours to determine whether minimum criteria for a valid study are met. If the Actigraphy file is determined to be of insufficient quality, the field site is notified so the participant can be re-contacted to assess willingness to repeat the study. The Reading Center also submits a Study Failure form to the field site to provide a reason for study failure and provide feedback to field site staff regarding ways to eliminate this type of failure in the future. In addition, study failure rates are quantified by site on monthly reports from the Data Coordinating Center and reviewed on monthly conference calls with Study Coordinators as well as monthly Steering Committee calls. Of the first 413 participants with actigraphy reviewed, 17 (4.1%) had a failed actigraphy on first attempt, well below the 10% expected rate. Of these 17, 12 agreed to wear the device again with a second failure occurring in only 3 (25%).

The sleep data (both actigraphy and sleep diary) collected then undergoes more rigorous scrutiny at the Reading Center with completion of an Actigraphy Quality Form. The general purpose of this form is to indicate the level of confidence that the sleep intervals set on a participant's actigraphy file are an accurate reflection of the participant's actual sleep habits. The participant's Daily Sleep Log is scored on this form as "Reliable" if it aided in the confidence of the placement of the sleep intervals, "Unreliable" if it did not aid, and "Missing" if no sleep log was received. For each day, the Time in Bed (time when it was thought the participant intended to sleep) and the Time Out of Bed (time when it was thought the participant woke up) are assigned grades. A grade of "1: Unreliable" indicates that the time set was a guess/approximation. In contrast, a grade of "3: Mostly Reliable" indicates that the interval set is likely the actual time the participant intended to sleep or wake up. Naps are similarly graded. All scoring is done by a single actigrapher dedicated to the Sueño study. Once a week, the Sueño PI reviews scoring and grading of all studies received in the prior week with the Study Actigrapher to ensure high quality scoring and consistency in grading. Quality scoring is summarized quarterly by site and if outliers are identified, these are reviewed with the site PI and study coordinator with specific recommendations to improve study quality. Of the first 405 subjects with usable actigraphy data, only 3 Sleep Logs (0.7%) have been classified as "Missing" and 18 (4.4%) as "Unreliable". In terms of Time in Bed and Time Out of Bed for each night, only 212 out of 6418 intervals (3.3%) have received an "Unreliable" score.

Errors in data quality are also tracked by actigraphy device used. Devices associated with multiple studies containing minor errors or any study containing a major error are immediately shipped to the manufacturer for battery replacement or more substantive repairs and/or replacement.

At the Data Coordinating Center:

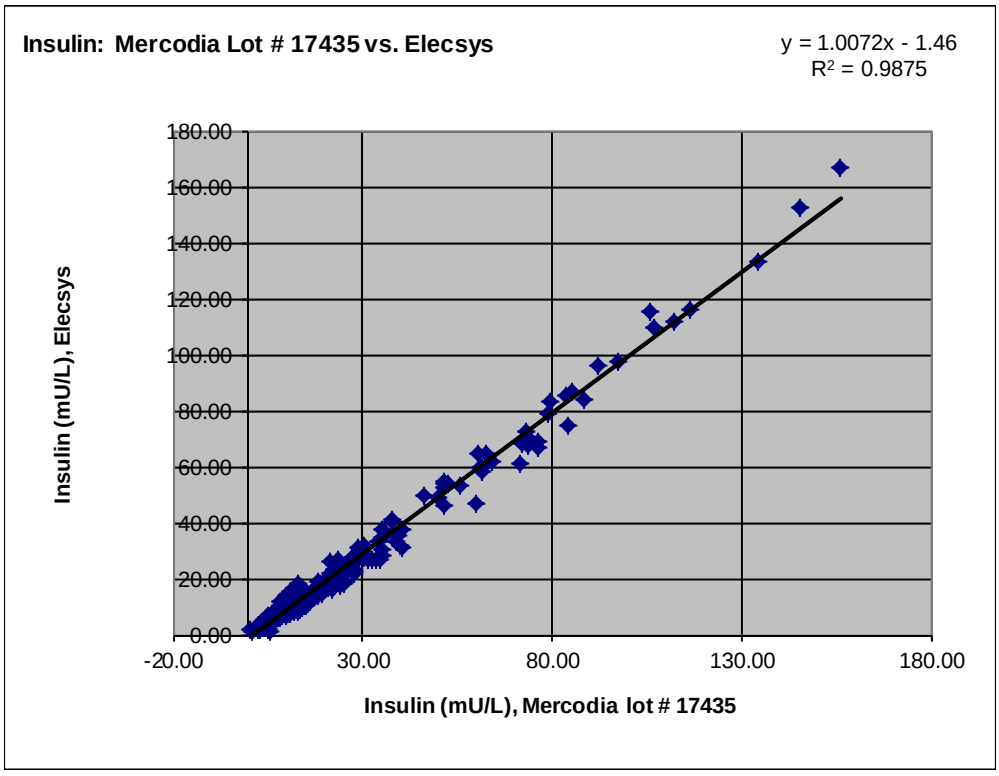
The management report includes overall statistics by site on recruitment, participant accrual projections and data completion. Queries for data inconsistencies across forms and a Missing Items Report are generated monthly based on missing forms and missing data from each form entered into the Data Management System. As of January 2012, the proportion of missing forms studywide was only 0.3% of 4057 forms and the overall proportion of missing items was only 0.3%.

HCHS/SOL Insulin Assay Change

HCHS/SOL Central laboratory changed the insulin assay from an ELISA method to the Roche Elecsys automated immunoassay method effective October 29, 2009 for all their studies including HCHS/SOL, CARDIA and MESA.

The Central Lab worked with the Coordinating Center to decide whether it was necessary to use an adjustment factor for insulin values measured before October 29, 2009. The Central Lab conducted an internal study to compare the two measurements in a sample of 346 specimens collected over 8 days. Specimens were from NHANES, METS, COATS, CAMP and HCHS/SOL. The correlation between the two methods is very high (r=0.99) with a linear regression line of y = 1.0072x - 1.46. Further, the slope is significantly different from one and the intercept from zero. Thus, the insulin values measured before October 2009 using the old ELISA method were, on average, 1.46 units lower than values measured later using the new Roche Elecsys automated immunoassay method.

We recommend adjusting statistically insulin values measured before October 29, 2009 to the newer Roche values prior to releasing the data for analyses. The new Roche method was chosen as a reference in HCHS/SOL since most of the measurements have been performed using the new Roche method and it is likely that any HCHS/SOL insulin measurements in the future will also be done using the Roche method.



HCHS/SOL Insulin Assay Change

Methods Details

Insulin – Mercodia Method

Insulin is measured in serum using a solid phase two site enzyme-linked immunosorbent assay (ELISA) from Mercodia (Uppsala, Sweden). It is based on the direct sandwich technique in which two monoclonal antibodies are directed against separate antigenic determinants on the insulin molecule. Specimen, control, or standard is pipetted into the sample well followed by the addition of peroxidase-conjugated anti-insulin antibodies. During incubation, insulin present in the sample binds to anti-insulin antibodies bound to the sample well, while the peroxidase-conjugated anti-insulin antibodies will also bind to the insulin at the same time. After washing to remove unbound enzyme-labeled antibodies, 3,3'5,5'-tetramethylbenzidine (TMB)-labeled substrate is added and binds to the conjugated antibodies. Acid is added to the sample well to stop the reaction, and the colorimetric endpoint is read on a microplate spectrophotometer set to the appropriate light wavelength. The Mercodia Insulin ELISA kit is calibrated against 1st International Reference Preparation 66/304. The laboratory CV is 8.4%.

Insulin – Elecsys

Insulin is measured in serum or EDTA, heparin or citrate plasma on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation) using a sandwich immunoassay method (Roche Diagnostics, Indianapolis, IN 46250). In the first incubation, the patient sample reacts with a biotinylated monoclonal insulin-specific antibody and a monoclonal insulin-specific antibody labeled with a ruthenium complex to form a sandwich complex. During the second incubation, streptavidin-coated microparticles are added and the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The microparticles are then captured magnetically and unbound substance is removed. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. This method is standardized using the 1st International Reference Preparation WHO Reference Standard 66/304. The Roche reported CV is 2.6% at a level of 6.36 µU/mL and 2.8% at a level of 20.9 µU/mL.