SEARCH 4 MOP
Section 3 - Quality Control
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3. Quality Control

3.1. OVERVIEW

Study-wide quality control is the ultimate responsibility of the SEARCH centers/sites and the Coordinating Center. The SEARCH study Project Manager at each center must be familiar with SEARCH study requirements and schedule clinic activities to allow adequate time for study personnel to carry out their responsibilities while meeting quality standards. This section will address issues related to equipment and quality control monitoring by the Coordinating Center and the SEARCH laboratory and reading centers. This section will also address training and certification procedures and requirements.

3.2. EQUIPMENT

The SEARCH study investigators have standardized certain equipment for the trial as well as providing minimum requirements for remaining equipment. Standardization (and the attendant maintenance and calibration of the equipment) assures a level of reliability (repeatability and accuracy) across SEARCH study centers. Each center is responsible for the proper operation and maintenance of equipment used in the SEARCH study. Some of the equipment is subject to standard calibrations and inspections (e.g., scales). It is suggested that responsibility for monitoring these standards be assumed by a specific individual, either the Project Manager or a designated Quality Control Officer. All staff should report any real or suspected equipment problems to that individual promptly. See Table 1 for a summary of standardized study equipment.

Table 1 - SEARCH Registry and/or Cohort Visit Equipment Table

Study Component	Recommended Equipment	Minimum Standard
Height	Wall-mounted stadiometer	Portable Road Rod™ or Mobile Mount™ stadiometer
Weight	SECA scale model 770 or 876	Digital scale with the capacity to measure within 0.1 kg of body weight up to 150 kg and to 0.2 kg for weights > 150 kg
Blood pressure	Welch-Allen Tycos aneroid manometer 767 and corresponding cuff or W. Baum, Co. cuff	Welch-Allen Tycos aneroid manometer 767 and corresponding cuff or W. Baum, Co cuff
	Calibration device (needs calibration check annually)	Netech DigiMano digital pressure and vacuum meter Part no. 200-2000IN

Study Component	Recommended Equipment	Minimum Standard
Stethoscope	Stethoscope with a diaphragm side and a pediatric bell side	Stethoscope with a diaphragm side and a pediatric bell side
Waist circumference	Fiberglass tape measure - BMS-8 for waists <150 cm	For persons with waist circumference <150 cm: a non-stretch, non-tension fiberglass tape with increments at least 0.1 cm
	Steel tape measure for waists >150 cm - Anthropometric Tape - Rosscraft 08730	For persons with waist circumference ≥ 150 cm: a non-tension flexible steel tape with increments at least 0.1 cm
Centrifuge	Centra CL2 by A. Daigger	Centrifuge that has a swing bucket rotor and spin speed of 3500 rpm
Specimen Freezer	Engel15	Any device that can freeze and store specimen at -4^{o} C, is not frost-free, and will not allow specimen to thaw
Retinal photography	Canon CR-1, Mark II Retinal Cameras Canon EOS 50D (15.1mp) digital backs RICS software	Canon CR-1, Mark II Retinal Cameras Canon EOS 50D (15.1mp) digital backs RICS software
	Laptop - Latitude E6410	Laptop - Latitude E6410
Heart function and cardiac autonomic neuropathy	AtCor SphygmoCor CVMS-CPVH	AtCor SphygmoCor CVMS-CPVH
	Conmed Cleartrace Electrodes - 1700-030 or 1700-005	Standard ECG electrodes with clip on connectors
	Toshiba L670-EZ1711 laptop	Toshiba L670-EZ1711 laptop
Echocardiography	Equipment as approved by Dr. Urbina	Equipment as approved by Dr. Urbina
Peripheral neuropathy (MNSI)	c128Hz tuning fork Tromner or Queen Square reflex hammer 10g monofilament (calibrated)	c128Hz tuning fork Tromner or Queen Square reflex hammer 10g monofilament (calibrated)

All standard maintenance should be documented by date in a permanent log at the study center. Problems and solutions should also be recorded. Copies of calibration records must be kept on file. The log and calibration records will be inspected during periodic site visits, or copies may be requested by the SEARCH Coordinating Center at periodic intervals.

3.3. DATA QUALITY

The goal in SEARCH 4 is for participants and/or their parents to complete the questionnaires using the online data entry tool developed by the Coordinating Center. Questionnaires completed online in advance of the clinic visit must be reviewed with the participant and/or parent at the clinic visit, particularly for items that are incomplete. A query tool is available to identify questions and/or modules that need verification at the time of the visit.

Some participants, however, may prefer to complete the questionnaires on paper. In this case, paper data collection forms will be printed from the data entry system. Clinical center personnel are asked to review all of the participants' questionnaires and data collection forms prior to ending each clinic visit. Forms must be completed neatly and accurately, and every question should be answered or marked as a known missing (-9) if the participant refuses to answer. Written responses to any items on the questionnaires/forms should be legible.

In addition to data entry of participant questionnaires, staff will also enter other data collection forms (e.g., physical exam). The data entry system will check data as it is entered using a series of 'data queries.' For example, verification of participant identifiers and visit numbers will be incorporated into the data entry system, in addition to range checking of fields. Data fields will be programmed to allow for fixed responses or immediate alerts when unusual values are entered. Staff will respond to queries as they occur during the data entry process; occasional data entry queries will be generated throughout the study.

Finally, the Coordinating Center will regularly perform internal comparisons of the entered data to detect missing records or suspicious or invalid data. These comparisons will include logical consistency checks of data within and across forms/questionnaires and across visits of the cohort participants.

3.4. QUALITY CONTROL FOR CENTRAL LABORATORY

Quality control procedures are carried out at the central laboratory and regularly reported to the Quality Control Committee. Quality monitoring will be conducted internally (within the laboratory) and externally.

3.4.1. Internal Quality Control

Internal quality control procedures include functional and calibration checks of instrumentation as well as monitoring:

- Assay performance of quality control pools with each run of specimens for each analyte;

- Assay performance of blind split duplicate specimens;
- Accuracy of lipid measurements by comparison with reference methods;
- Computer-generated error lists; and
- Specimen turnaround times.

3.4.2. External Quality Control

External quality control procedures include participation in:

- the College of American Pathologists quality assurance program for inter-laboratory comparison (e.g., lipids, HbA_{1C});
- the NHLBI-Centers for Disease Control and Prevention quarterly lipoprotein standardization program (lipids), or participation in other professionally supported peer survey programs.

Blind split specimens are also exchanged and compared with reference, gold standard, or long-established methods.

3.4.3. Quality Control Data and Graphs

Performance in assay of quality control pools by the various methods is determined and monitored using the database application's quality control functions. Target values have been established for pools; statistics relative to target values are calculated monthly along with Levy-Jennings graphs, and these data are analyzed by operators and by the laboratory director. Trends are noted and calibrations are made as necessary.

3.4.4. Long-Term Drift

Lyophilized quality control pools have been prepared to address the issue of drift in long-term studies. Pools are prepared in bulk at -70°C. These are assayed monthly in multiple replicates to monitor any changes taking place in assays.

3.4.5. Blind Splits

Blind split analyses are not routinely performed for SEARCH 4.

3.4.6. Periodic Reports

Periodic reports are submitted to the Quality Control Committee summarizing performance in assay of internal quality control, laboratory proficiency survey materials and/or reference materials, and long-term drift monitoring. Additionally, data on the number of samples received by clinical site, number of samples contained in long-term storage, and turn-around times between samples being obtained and arriving at the laboratory are provided to the Quality Control Committee.

3.5. QUALITY CONTROL FOR RETINOPATHY IMAGING

3.5.1. Image Quality

Photographers will provide the first assessment of image quality, a big advantage of digital imaging. This initial review of images allows for the immediate assessment of image quality and the opportunity to retake the images before the subject leaves the camera imaging area. Additionally, reading center staff will continuously monitor image quality throughout the study. Initially, all images will be reviewed by reading center staff and feedback will be provided to the photographers in cases that warrant critique. A telephone call or e-mail will be used, detailing problems and suggesting improvements. Once the study is underway, image quality reports will be generated from the photograph readers' evaluations of all images and sent to the Coordinating Center as well as each site Project Manager for distribution. The Imaging Consultant will review a small percentage of the images, and feedback will be provided to the photographers in cases that warrant critique. In cases where problems with image quality persist, the additional training in the form of a site visit may be recommended.

3.6. CARDIAC & VASCULAR QUALITY CONTROL

3.6.1. General

a. Variability between observers will not be assessed as one observer will perform only 3 measures during one 'True' visit. There will be no repeat 'QC' measures since heart structure does not change from day to day, hence most variability is in reading, not obtaining the ultrasound images.

b. Variability within a visit:

   i. 3 readings of each measure are obtained at a single visit;

   ii. Variability among these measures will be assessed soon after study initiation and then every 6 to 12 months.

c. Variability between visits will not be performed since between visit variability in Search3 was acceptable and within visit variability, which can be assessed more frequently, in Search3 was sufficient to identify observers needing retraining.

d. Between center variability: can stratify by center or control for center in models.

e. Variability between readers: only 1 reader will be employed. If 2 readers are used, readers will re-read 10 of the other reader's studies on a yearly basis.

f. All QC calculations should be performed **OVERALL** and stratified by **SITE**.

3.6.2. Cardiac

a. From excel with name QUERY (from Digiview) calculate CV (overall & by site) for the following variables.

i. LVM: Reliability of LV mass measurement in Ohio shows ICC of 0.96 and 0.84 for intraobserver and interobserver variability and coefficient of variability for LVMI on blind duplicate readings of 7% within limits set by national guidelines.

   A. IVSd (MMODE_IVSdDimension , MMODE_IVSdDimension_2 , MMODE_IVSdDimension_3)

   B. LVIDd (MMODE_LVIDdDimension , MMODE_LVIDdDimension_2 , MMODE_LVIDdDimension_3)

   C. LVPWd (MMODE_LVPWdDimension , MMODE_LVPWdDimension_2 , MMODE_LVPWdDimension_3)

ii. Tissue Doppler imaging (diastolic function)

   A. E wave (DOPPLER_MVEVelVelocity , DOPPLER_MVEVelVelocity_2 , DOPPLER_MVEVelVelocity_3)

   B. A wave (DOPPLER_MVAVelVelocity , DOPPLER_MVAVelVelocity_2 , DOPPLER_MVAVelVelocity_3)

   C. E' septal (DOPPLER_MVEaSEPTVelocity , DOPPLER_MVEaSEPTVelocity_2 , DOPPLER_MVEaSEPTVelocity_3)

   D. A' septal (DOPPLER_MVAaSEPTVelocity , DOPPLER_MVAaSEPTVelocity_2 , DOPPLER_MVAaSEPTVelocity_3)

   E. E' lateral (DOPPLER_MVEaLATVelocity , DOPPLER_MVEaLATVelocity_2 , DOPPLER_MVEaLATVelocity_3)

   F. A' lateral (DOPPLER_MVSaLATVelocity , DOPPLER_MVSaLATVelocity_2 , DOPPLER_MVSaLATVelocity_3)

iii. Strain, Strain Rate and EF from STRAIN excel (from Tomtec) is only read once. Distribution of key variables will be examined for clinical and statistical outliers periodically and significant outliers will be re-read and the 2nd reading used. Distribution will be examined for the following variables:

   A. Strain (first tab of excel): GLS in 4 CHAMBER view (column M), average LONG time to peak strain in 4 CH in % (column AD)

B. Strain Rate (second tab of excel): average LONG SR 4 CH (column L), average LONG time to peak SR 4 CH in % (column AB)

C. Ejection Fraction (fifth tab of excel): SV (column H), EF (column I).

b. Adjudication of outliers:

i. LVM & Doppler (Digiview)

A. CoC to provide ID, 3 raw values, mean, differences (1-2, 1-3, 2-3) for all Digiview values with CV > 10

B. Sonographer will examine images to determine

C. If image is poor, will DELETE that parameter (keep other measures for that subject)

D. If visual inspection of the MEAN value seems unlikely, that portion of the echo will be re-read copying over previous values and saved in Digiview to be captured with the next Digiview Query

E. If visual inspection of (or one quick measure that is not saved so as not to overwrite original readings) the MEAN seems plausible, original readings will be retained.

ii. Strain

A. CoC will supply ID of all studies with parameters outside of the range in the strain editing table

B. These will be adjudicated by the sonographer:

1. POOR quality image: set all parameters to missing

2. ADEQUATE image quality will be re-read and second reading will be used.

3.6.3. Arterial Stiffness

a. Augmentation Index

i. General: Only the main outcome variable should be assessed for reproducibility (AIx is C_AGPH_HR75 in the SphygmoCor PWA *.txt files).

A. Wilkinson who is well respected in this technique did not quote CV or ICC but published mean differences between AIx recordings of up to 5.4% (AIx is measured in %).

B. Urbina published reproducibility (within visit) from her cohort study of T2DM vs obese and lean controls and found ICC between 0.7 and 0.9.

C. Unpublished data from July 2013 from SEARCH 3 show ICC average ranged from 0.75 to 0.87 depending on site.

ii. QC report the number (overall & by site):

A. With errors:

1. Missing: C_AGPH_HR75 = 9999
2. Inconclusive = 'Yes'
3. Simulation = 'Yes'
4. SUB_TYPE NE 'RADIAL'

B. Out of range: C_AGPH_HR75 <-30 or >+30

C. Widely variable: AIx differences > 25 (1 vs 2, 1 vs 2, 2 vs 3)

D. Operator Index

1. < 65 (delete as poor quality)
2. 65-74 (borderline for screenshots to be evaluated)

E. P_QC_PH

1. < 70 (delete as poor quality)
2. 70-79 (borderline for screenshots to be evaluated)

F. P_QC_PHV

1. > 10 (delete as poor quality)
2. 5-10 (borderline for screenshots to be evaluated)

G. P_QC_DV

1. > 10 (delete as poor quality)
2. 5-10 (borderline for screenshots to be evaluated)

H. P_QC_SDEV

1. > 10 (delete as poor quality)
2. 5-10 (borderline for screenshots to be evaluated)

b. Pulse Wave Velocity

i. General: Only the main outcome variable should be assessed for reproducibility (PWV carotid-femoral in the SphygmoCor PWV *.txt files).

A. Sutton-Tyrell published overall reliability coefficient of 0.77 for PWV in the elderly.

B. In unpublished data from 2007, Ohio measured ICC of 0.90 similar to published studies. These data were later published with a larger data from a cohort of T2DM with obese and lean controls and demonstrated CV of <7%.

C. Unpublished data from July 2013 from SEARCH 3 show CV ranged from 8 to 11% depending on site.

ii. QC report the number (overall & by site):

A. With errors:

1. PWV missing
2. A_SUBTYPE NE 'CAROTID'
3. B_SUBTYPE = 'CAROTID' (should be Distal, Femoral or Radial)

B. Out of range:

1. Femoral or Distal > 10 or < 3
2. Radial > 12 or < 5

C. Widely variable: PWV differences > 0.5 (1 vs 2, 1 vs 2, 2 vs 3). This is a conservative cut-point since in Urbina's HTN study, mean difference (N=113) = 0.08 m/sec.

D. A_DEVIATION_DT

1. > 15 (delete as poor quality)
2. 10-15 (borderline for screenshots to be evaluated)

E. B_DEVIATION_DT

1. > 15 (delete as poor quality)
2. 10-15 (borderline for screenshots to be evaluated)

F. PTT_SD

1. > 15 (delete as poor quality)

2. 10-15 (borderline for screenshots to be evaluated)

G. PWV_DIST (for femoral only) <300 or > 600

3.6.4. Autonomic Tone

a. Heart Rate Variability.

i. General: Only the main outcome variable should be assessed for reproducibility (RMSSD, PNN50, LF power, HF power in the SphygmoCor PWV *.txt files).

A. Batten & Urbina published reproducibility of HRV from 24-hour Holter monitor recordings with CV all < 5%.

B. Unpublished data from July 2013 from SEARCH 3 show ICC average ranged from 0.5 to 0.75 depending variable and on site.

ii. QC report the number (overall & by site):

A. With errors:

1. HRV missing
2. NUMBER_PULSES <350 or >1200
3. MEAN <500 or > 1500

B. Out of range:

1. SDANN > 60 or <=0
2. SDNN > 200 or < 5
3. RMSSD > 250 or < 3
4. PNN50 > 85 or < 0.5
5. LF_POWER_NORMALISED > 80 or < 10
6. HF_POWER_NORMALISED > 95 or < 8
7. LF/HF RATIO > 10 or < 0.1

3.7. QUALITY CONTROL FOR ECHOCARDIOGRAPHY

There will be no repeat echocardiography studies for quality control purposes since heart structure does not change from day to day, hence most variability is in reading, not obtaining the ultrasound images. Furthermore, there is significant cost and burden associated with a repeate study. However, three readings of each measure are obtained at a single visit. Variability among these measures will be assessed soon after study initiation and then every 6 to 12 months. Only the main outcome variable will be assessed for reproducibility (IVSd, LVIDd, LVPWd). Reliability of LV mass measurement in Ohio shows ICC of 0.96 and 0.84

for intraobserver and interobserver variability and coefficient of variability for LVMI on blind duplicate readings of 7% within limits set by national guidelines. CV may be examined on E, A, e' and a' and global longitudinal strain and strain rate from the 4-chamber view.

3.8. QUALITY CONTROL FOR MICHIGAN NEUROPATHY SCREENING EXAMINATIONS

The MNSI is a well validated tool used to identify signs of distal symmetrical peripheral neuropathy. Developing a method to ensure uniform administration of the MNSI examination, and especially inter-examiner reproducibility of the MNSI, is challenging given that many of the MNSI measures are somewhat objective. Appropriate training, certification, and re-certification of personnel who will be performing the MNSI assessments are critical.

Assessment of MNSI quality includes:

Quarterly review of MNSI examination data by the MNSI Reading Center

- The Coordinating Center will send the MNSI RC a file containing examination results for all MNSI examinations completed in the quarter for the blind duplicates (every 10th participant) and any record that has reported "other" abnormal findings for foot appearance.
- For duplicates, the Coordinating Center will also produce a report of concordance for each abnormality.
- The MNSI RC will review the file, especially looking at reporting of "other" abnormal findings for foot appearance.
- The MNSI RC will notify the Coordinating Center and individual examiners of any concerns related to inappropriate findings being identified as MNSI abnormalities, and may request corrections to the Case Report Form.
- The MNSI RC will track the frequency and types of inappropriate abnormalities recorded, as well as record of the examiners responsible and may provide summary reports to the Coordinating Center or individual site leaders if there are excessive or repeated errors noted.

3.9. COORDINATING CENTER ACTIVITIES

Quality assurance will be a major activity of the Coordinating Center throughout the study. Activities will include arranging for training/retraining of clinical center staff in data collection procedures, and monitoring data entry activities.

Monitoring of the SEARCH study data will take place at the Coordinating Center. These activities include data control and report generation. Some of the monitoring and quality control reports will be transmitted to the centers for immediate action and attention; other quality control and monitoring reports will be generated regularly for the Quality Control Committee and bi-annually for the Observational Study Monitoring Committee (OSMB).

Examples of these reports include:

- Recruitment yields at each clinical center
- Summaries of certifications
- Summaries of training and re-training sessions
- Deviations from protocol
- Missed visits, refusals, lost to follow-up
- Errors in collection, labeling, storage, shipping of laboratory specimens or other materials to central reading centers
- Quality control reports generated by the central reading centers.

3.9.1. Changes in the Protocol

Changes in the Protocol may need to be made periodically. When this is required, the Coordinating Center will update the protocol and informed consent template, if appropriate, with the corrected/revised information and notify the clinical centers so that the centers may submit the amendments to their local IRBs. A revision log will be maintained as the first page of the protocol.

3.9.2. Changes in the Manual of Procedures (MOP)

Changes in the MOP may need to be made periodically. When this is required, a notification will be sent to all clinical centers. When obsolete pages/sections are removed from the manual, they should be labeled as "***obsolete"*** and archived based on local IRB regulations. If a major procedural or design problem occurs, the Steering Committee will be asked to make a recommendation, the change will be made as above, and the Steering Committee will be asked to approve these changes at their regularly scheduled meeting.

3.9.3. Quality Control Committee

The Quality Control Committee (QCC) will be responsible for monitoring all aspects of data quality in the cohort study and the registry study, including physical and laboratory measurements, questionnaire data, and data entry. The QCC will also monitor recruitment and retention as well as all adverse events that occur in the study. The QCC will report to the Study Group, the Steering Committee, and the Observational Study Monitoring Board, on a regular basis. The QCC will consist of representatives across the clinical centers, the laboratory and reading centers, and the Coordinating Center.

3.10. SITE VISITS

Site visits may be performed if consistent departures from the Protocol and Manual of Procedures are detected. Virtual site visits may be considered as an option. Retraining may be done as needed.

3.11. TRAINING OF SEARCH PERSONNEL

3.11.1. Training

Key clinic staff from each clinical site will be trained at the initial SEARCH study central training session. A train-the-trainer model will be used, i.e., key staff trained at the central training session will be responsible for training and re-training other staff members at their local sites. Certification and re-certification are required in order to assure that SEARCH personnel have a clear understanding of the SEARCH study Protocol and Manual of Procedures (MOP) and for standardization of procedures at all centers. Procedures for visit data collection and laboratory measurements are carefully outlined in Sections 10-13.

3.11.2. Certification

Certification is required of SEARCH personnel performing activities described below and listed in Table 2. SEARCH personnel are required to complete certification prior to obtaining SEARCH study measurements in a specific area. The Project Manager (or designee) at each clinical site is responsible for documenting that each of the certification tasks has been completed by all data collection staff. The Coordinating Center will have a continually updated list of certified personnel on the SEARCH website to assist sites along with an indication of the date of certification and deadlines for re-certification.

Based on the train-the-trainer model, certified personnel will train new individuals at their centers. Training slides and web-based information will be provided to each center to use for training purposes. Each trainer must certify that SEARCH study personnel meet the same requirements as listed in each following section of the MOP. All certification measures are based on each SEARCH study personnel's data being compared to the 'standard' for agreement.

3.11.3. Physical Examination

3.11.3.1. **Anthropometry**

Anthropometry is the study of the measurement of the human body in terms of the dimensions of bone, muscle and adipose (fat) tissue. This measure can help in providing critical information regarding the presence of obesity and its relationship to diabetes. SEARCH personnel will be instructed on the use of anthropometric equipment pertinent to the study (see Section 10 for more complete information) and compliant with minimum specifications. See Table 1 (above) for the *minimum* equipment required for these measures.

SEARCH study personnel will be trained on the principles and concepts of measurement as well as the location of measurement sites/landmarks and be requested to provide evidence of understanding by correctly completing multiple

measurements under the guidance of a trained person who is knowledgeable of SEARCH procedures. Staff members are required to read and become familiar with the SEARCH Protocol and Manual of Procedures for anthropometric measurements followed by the hands-on activities provided at the training session.

3.11.3.2. **Blood Pressure**

Each data collector will be trained and certified to perform all data collection tasks. Blood pressure measurements will be made using an aneroid manometer and appropriately sized cuffs for the person being measured. The certification procedure includes training the research staff at each center in the techniques and process of performing the actual measurements. During this training the actual methodology, recording of results, equipment calibration, and potential sources of error will be demonstrated.

Each site will identify a trainer. Designated trainers will be responsible for training and certifying new staff members. Certification will involve training related to Korotkoff sounds 1 and 5. Instructions will be provided regarding cuff selection and application, measurement sites, and terminal digit bias.

3.11.3.3. **Acanthosis Nigricans**

Acanthosis nigricans is an eruption of the skin characterized by hyperpigmentation and velvety cutaneous thickening that can occur on any part of the body but characteristically affects the axillae, the posterior portion of the neck, the groin, the antecubital and popliteal surfaces and the umbilicus. Acanthosis nigricans is now recognized as a sign of insulin resistance. Insulin resistance, however, can occur in the absence of acanthosis nigricans. A higher prevalence of acanthosis nigricans is found in ethnic populations with darker skin than lighter skin. Studies in children and adolescents demonstrated that the neck was most significantly affected and always involved when other areas of the body have acanthosis nigricans. In a field study, the anatomical area that proved to be the most reproducible was the neck. Changes in texture must be present to identify acanthosis nigricans.

Acanthosis nigricans can be a difficult sign for the untrained person to detect. Training will provide in-depth presentation of cases of acanthosis nigricans in children. Slides will be provided to centers for use in training and retraining center personnel. Based on an education program previously conducted by Burke and colleagues (1999), personnel will be provided with literature to review as background information, slides depicting acanthosis nigricans in children, and will be expected to pass a visual examination determining the presence or absences of acanthosis in 61 cases.

3.11.3.4. **Laboratory Specimen**

Instructions for obtaining and processing laboratory specimen will be provided by SEARCH Laboratory personnel from Northwest Lipid Laboratories (see Section 13 for details). Certification specimens are sent to the SEARCH Lab in the same manner as those specimens obtained from SEARCH participants.

3.11.4. Primary Certification for Retinal Photography

Each photographer taking fundus images will need to become certified before taking images for the study. The initial group of photographers will receive didactic and hands-on training at a centralized training. Each site will receive assistance from Synemed to install and configure their camera system after which time site photographers should practice taking images and prepare image sets for submission to the OERC for certification. Certification begins with the completion of the Photographer Certification Request Form (Section 12). This form will be used in lieu of the SEARCH Image Inventory Batch Form and will be submitted along with images of 10 eyes (5 right eyes and 5 left eyes, F1 and F2 of each) imaged following the study protocol. A photographer is fully certified after submitting satisfactory quality images of 10 eyes taken on non-study volunteers and the form is signed and sent to the Coordinating Center by the OERC. These images must show proper field definition (Fields 1 and 2 of each eye, 20 images total), proper exposure, alignment and focus. Photography certification subjects will be given a unique 8-digit subject ID number. It will begin with CERT and the next number will be a number one through 5. The last 3 digits will be the photographer's 3 digit initials (i.e., CERT1ABC is the first person imaged for this photographer and CERT2ABC is the second person etc.). The OERC will confirm certification to the Coordinating Center who will notify the photographers at each site or will provide helpful feedback requesting the submission of additional images to resolve a problem and complete certification.

Small pupil aperture (SPA) feature usage -- should not be used for certification photos, as it should be the photographer's best images. We will not accept certification images using the SPA feature. You may practice using this feature, in the event that for a subject it is necessary, but it should not become routine. Remember, it is in the study's best interest to NOT use this feature.

3.11.5. Primary Certification for SphygmoCor

Each staff member responsible for SphygmoCor measures will need to be certified before completing measurements on study participants. Certification includes attending in-person training (or equivalent), detailed review of the MOP, and completion of SphygmoCor measures on three volunteers repeated on two separate days. Measures will be sent to the Coordinating Center for evaluation. If the readings are consistent, the Coordinating Center will notify the site that certification is complete. If one or more

readings are inconsistent, the Coordinating Center will ask the site to send screen shots of the tracings to Elaine Urbina (elaine.urbina@cchmc.org). Dr. Urbina will review the screen shots and send individualized feedback to the site about how to adjust the technique to get more consistent readings. The certifier must repeat certification measures and transmit new readings to the Coordinating Center for evaluation.

3.11.6. Primary Certification for MNSI

The MNSI is a brief physical examination involving 1) inspection of the feet for deformities, dry skin, hair or nail abnormalities, callous or infection, 2) semi-quantitative assessment of vibration sensation at the dorsum of the great toe, 3) grading of ankle reflexes and 4) monofilament testing. All components of the MNSI are done on each foot.

All SEARCH staff performing the MNSI must be trained, and then certified. Previously trained and certified SEARCH staff must be observed correctly performing and scoring the MNSI twice by an already certified SEARCH staff member, or other approved MNSI trainer to be re-certified. SEARCH staff who have not been previously trained and certified must be observed correctly performing and scoring the MNSI three times by an approved trainer (or other MNSI certified SEARCH staff) to obtain initial certification.

Table 2. Certification Requirements

Certification Components	Initial Certification Requirements	
	Number	**Parameters**
Physical examination procedures		
Height	2 volunteers	*Note: If a site utilizes the RoadRod™ or Mobile Mount™ for this measurement, SEARCH personnel are to be certified using this instrument. If the site does not utilize the RoadRod™ or Mobile Mount™ SEARCH personnel are to be certified using a wall mounted stadiometer.* ▪ Each volunteer will be measured twice ▪ If measurements are not within **0.5 cm** of each other, a third measurement will be taken ▪ The mean of the two closest measurements will be used to determine the agreement with the mean of two measures taken by the 'gold standard' or the trainer ▪ Trainee and trainer measurement variance must be equal to or less than **1.0 cm**
Weight	2 volunteers	▪ Each volunteer will be measured twice. ▪ If measurements are not within **0.2 kg** of each other, a third measurement will be taken ▪ The mean of the two closest measurements will be used to determine the agreement with the mean of two measures taken by the 'gold standard' or the trainer. ▪ Trainee and trainer measurement variance must be equal to or less than **0.2 kg**
Waist circumference	3 volunteers	▪ Each volunteer will be measured four times – twice using the NHANES protocol and twice using the natural waist. ▪ If measurements are not within **1.0 cm** of each other, a third measurement will be taken ▪ The mean of the two closest measurements in each protocol will be used to determine the agreement with the mean of two measures taken by the 'gold standard' or the trainer. ▪ Trainee and trainer measurement variance must be equal to or less than **2.0 cm**

Certification Components	Initial Certification Requirements	
	Number	**Parameters**
Blood Pressure	2 volunteers PLUS Video recording	▪ Each trainee is to watch the blood pressure measurement training video developed by SEARCH prior to conducting blood pressure measurements. The video can be found on the SEARCH website under OPERATIONS >TRAINING MODULES. Since the video demonstrates blood pressure measured using a mercury manometer, it is not necessary to take the test. The purpose of watching the video is to learn about the difference between K-4 (muffling of sound) and K-5 (disappearance of sound). ▪ Demonstrate proper selection of cuff size and application ▪ Determine POP and MIL ▪ Demonstrate proper deflation rate (2-4 mm Hg/sec.) ▪ Each trainee is to evaluate the blood pressure of two volunteers ▪ Trainees are required accurately identify K1 and K5 readings within ± 6 mm/Hg of readings obtained by the trainer using a dual-headed stethoscope.
Acanthosis nigricans		▪ Read reference article in Appendix A ▪ Review set of 61 acanthosis nigricans slides on website under OPERATIONS >TRAINING MODULES. Classify a minimum of 57 slides correctly on web-based certification test. Test should be repeated until minimum score is obtained.
Laboratory procedures		
Blood draw, urine collection, processing and shipping	1 complete set (fresh and frozen) for both registry and cohort laboratory measures	▪ Review laboratory MOP (Section 11) and complete local training on laboratory procedures (by previously certified SEARCH staff) ▪ Submit one complete set of blood and urine samples (fresh and frozen) for registry visit measures and one complete set of blood and urine (fresh and frozen) for cohort visit measures. These can be drawn on two different volunteer subjects (not SEARCH participants). Note: If urine collection is not available, water can be sent in its place and should be noted on the shipment form so the lab does not analyze it.

Certification Components	Initial Certification Requirements	
	Number	**Parameters**
Diabetes Complications Testing		
Retinal photographs	Photographs of 10 eyes (5 right and 5 left eyes) (F1 and F2 of each)	▪ Complete and submit Photographer Certification Request Form (in lieu of SEARCH Image Inventory Batch Form) (See Section 12) ▪ Submit images of 10 eyes (5 right eyes and 5 left eyes, F1 and F2 of each) imaged to the OERC following the study protocol. ▪ A photographer is fully certified after submitting satisfactory quality images of 10 eyes taken on non-study volunteers and the form is signed and sent to the Coordinating Center by the OERC. ▪ Small pupil aperture (SPA) should not be used for certification photos.
SphygmoCor measurements	3 volunteers with repeat measures on two separate days	▪ Review MOP (Section 13) and training slides ▪ Complete SphygmoCor measures on three volunteers repeated on two separate days ▪ Transmit readings to the CoC, along with the certification worksheet. ▪ If measures are consistent, CoC will notify you that you are certified. ▪ If one or more measures are not consistent, the CoC will ask the site to send screen shots of the tracings for the volunteers with inconsistent readings to Elaine Urbina, elaine.urbina@cchmc.org ▪ After reviewing screen shots, Dr. Urbina will send individualized feedback about how to adjust technique to get more consistent readings ▪ Repeat certification measures and submit to the CoC for evaluation
Michigan Neuropathy Screening Instrument (MNSI)	3 volunteers	▪ Review MOP and training slides ▪ Complete MNSI on 3 volunteers in accordance with the detailed competency checklist (Section 3, Appendix B)
Neurocognitive testing		▪ Greta Wilkening will conduct initial training and certification at an in-person meeting.
Echocardiogram		▪ Echocardiograms will be performed by trained sonographers. Elaine Urbina will conduct initial training and certification of sonographers.

Note: for all components, the following tasks must be completed:

- Attendance at the SEARCH study centralized training session; training by someone who attended the centralized training session; or alternative training approved by

the SEARCH Steering Committee. If the primary trainer leaves the study site, the PI or his/her designee should contact the CoC to arrange for training a primary trainer.

- Required reading: Manual of Procedures and Protocol.

Attendance at central training is not sufficient for certification. Site personnel who attend the central training session must also complete all bulleted items above.

3.11.7. Recertification

Recertification of secondary personnel will be required 6 months and one year after initial certification, and then every two years thereafter. This will be carried out at each clinical center by the designated primary trainer.

Because designated primary trainers are responsible for re-certifying local personnel, primary trainers are considered re-certified whenever they conduct re-certification of secondary personnel.

The recertification processes will be consistent with procedures required for initial certification - that is, all criteria listed in Table 2 are to be repeated except for laboratory sample collection, diet interview, data entry, retinal photographs, and SphygmoCor measurements. These procedures will be monitored via other methods of quality control. The MNSI will require recertification on two individuals according to the MNSI certification checklist. Recertification for physical measurements and acanthosis will be completed as indicated in Table 3 below. *Note: Any SEARCH study personnel currently conducting study measurements that fails to recertify, will be suspended from taking measurements until recertification requirements are met.*

The Steering Committee, in consultation with the Quality Control Committee, will determine whether a central recertification session is necessary during the course of SEARCH 4.

Table 3 provides an overview of recertification requirements.

Table 3. Recertification Requirements

Recertification Components	Recertification Requirements for Secondary Personnel		
	N	Freq	Parameters
Physical Examination Procedures			
Height	2 volunteers	6 months 1 year then every 2 years	▪ Each volunteer will be measured twice. ▪ If measurements are not within **0.5 cm** of each other, a third measurement will be taken ▪ The mean of the two closest measurements will be used to determine the agreement with the mean of two measures taken by the 'gold standard' or the trainer. ▪ Trainee and trainer measurement variance must be equal to or less than **1.0 cm**
Weight	2 volunteers	6 months 1 year then every 2 years	▪ Each volunteer will be measured twice. ▪ If measurements are not within **0.2 kg** of each other, a third measurement will be taken ▪ The mean of the two closest measurements will be used to determine the agreement with the mean of two measures taken by the 'gold standard' or the trainer. ▪ Trainee and trainer measurement variance must be equal to or less than **0.2 kg**
Waist circumference	2 volunteers	6 months 1 year then every 2 years	▪ Each volunteer will be measured four times – twice using the NHANES protocol and twice using the natural waist. ▪ If measurements are not within **1.0 cm** of each other, a third measurement will be taken ▪ The mean of the two closest measurements in each protocol will be used to determine the agreement with the mean of two measures taken by the 'gold standard' or the trainer. ▪ Trainee and trainer measurement variance must be equal to or less than **2.0 cm**
Blood Pressure	2 volunteers	6 months 1 year then every 2 years	▪ Each trainee is to evaluate the blood pressure (single measurement) of two volunteers. Trainees are required to be within $\pm$ 6 mm/Hg of readings obtained by the trainer using a dual-headed stethoscope.
Acanthosis nigricans		6 months 1 year then every 2 years	▪ Review set of 61 acanthosis nigricans slides ▪ Classify a minimum of 57 slides correctly on web based certification test

Recertification Components	Recertification Requirements for Secondary Personnel		
	N	Freq	Parameters
Michigan Neuropathy Screening Instrument (MNSI)	2 volunteers	6 months 1 year then every 2 years	▪ Review MOP and training slides ▪ Complete MNSI on 2 volunteers in accordance with the detailed competency checklist

Appendix A: Acanthosis References

Acanthosis nigricans in obese patients: Presentations and implications for prevention of atherosclerotic vascular disease

Appendix B: MNSI Competency and Certification Checklist

Name of person to be certified: _____

SEARCH ID Number (if applicable): _____
Previously SEARCH MNSI Certified (circle)? Yes No
If yes, must be observed correctly performing MNSI on 2 people to be re-certified.
If no, must be observed correctly performing MNSI on 3 people to be certified.

Certification Examination # (circle): 1 2 3
Certification Examination Date: _____

Name and SEARCH ID Number of Observer: _____

Competency/Required Behaviors:	*Met*	*Not Met*	*Initials*
Explains procedure to patient			
1. *Examination of foot will be done* 2. *Not painful or invasive* 3. *Will use tuning fork on big toe (describes that will feel a "buzzing sensation"* 4. *Will measure reflexes by tapping on the back of the ankle* 5. *Will measure ability to feel light touch by touching the big toes with a filament, ("like a piece of fishing line")* 6. *Will take less than 10 minutes*			
Positions patient			
1. *On exam table or chair that is high enough for foot to be off the floor* 2. *Legs dangle freely from over the edge of the table or off the chair and are not crossed* 3. *Patient is relaxed*			
Prepares foot for examination			
1. *Gathers required equipment (Tromner or Queen's square reflex hammer, 10 gram calibrated monofilament, C128Hz tuning fork), examination recording form* 2. *Instructs participant to removes footwear and socks* 3. *Begins examination within 5 minutes of removing footwear*			
Examiner washes hands			
1. *Soap and water for at least 15 seconds*			

2. Thoroughly dries hands *3. Apply gloves (optional)*			
Examines feet (visual and tactile) for deformities, infection, callus, dry skin, fissures, ulcers			
1. Top and bottom *2. Between toes* *3. Records findings for left and right foot.* *EXAMPLES of COMMON REPORTABLE DEFORMITIES: Hallux Valgus (bunion at great toe), Tailor's bunion (fifth toe bunion), overlapping toes, hammer toe, claw foot, Charcot joint ("rocker bottom foot").* *EXAMPLES OF REPORTABLE INFECTIONS: toenail infection (redness, drainage from around the nail bed), wound or other skin infections, cellulitis, gangrene, athlete's foot infection.* *Note: Onychomycosis, a common toenail fungal infection, should be captured as "other". Feel free to make note of actual findings, e.g., "Red macerated skin between toes with flaking and scaling c/w athlete's foot infection", or "second toe crosses third toe".* *DISTINGUISHING ULCERATION FROM OTHER TYPE OF WOUND: True neuropathic ulcers tend to occur over pressure points (e.g., over bony prominences, beneath calluses, on the plantar surface of the heel, or metatarsal heads – the "ball of the foot"), are quite often painless, are generally well demarcated and are usually more or less circular in shape. They penetrate through more than the epidermis, so that the dermis and often deeper sub-cutaneous tissue is visible. Ulcer margins often "thick" or whitish and there may be a whitish film or eschar that covers the central ulcerated area. The central area may also appear red and "beefy" (indication granulating tissue is filling in the ulcer as healing occurs). Ulcers generally persist for at least two weeks and are slow to heal. True neuropathic ulcers are not generally associated with a known traumatic injury (a cut from a sharp object, stepping on a piece of glass, these are common traumatic injuries that generally result in simple lacerations, epidermal abrasions or punctures to the skin. While an injury of this sort can develop into an ulcer, it should not be graded as such unless it clearly meets the description of a neuropathic ulcer outlined above. Simple lacerations, abrasions, thermal injuries, punctures and other traumatically injured feet are not graded on the MNSI, unless the wound is infected (mark infection on the form).*			

Performs reflex assessment			
1. *Has subject seated with leg/foot hanging relaxed and freely* 2. *Encourages subject to relax foot* 3. *Explains that examiner will lightly stretch foot upward, but participant should try to stay as relaxed as possible* 4. *Examiner slightly dorsiflexes foot, either with hand, or by placing foot on examiner thigh* 5. *Examiner identifies Achilles tendon on posterior ankle* 6. *Taps **firmly/briskly** on Achilles tendon while watching/feeling for foot response (brisk plantar flexion)* 7. *If no response, repositions foot and repeat* 8. *If no response, asks subject to perform Jendrassic Maneuver (grasps hands, pulls, grits teeth) while examiner elicits the response* 9. *Reminds subject to relax between attempts* 10. *If no response after at least two attempts, examiner stops and repeats procedure on the second foot* 11. *Records findings for each foot; Present, Present with Reinforcement (if response elicited with Jendrassic Maneuver) or Absent (no response)*			
Determines Vibration Perception			
1. *Explains procedure to patient – will apply a tuning fork to the top of the big toe. Participant will be asked to say "stop" when they no longer feel any vibration or "buzzing"* 2. *Demonstrates the feeling of the buzzing tuning fork on the hand of the participant* 3. *Positions the participant with the foot hanging freely (not supported by floor or examiner hand)* 4. *Identifies the DIP joint on the great toe by bending the toe* 5. *Asks the participant to close his or her eyes* 6. *Applies the tuning fork (non-vibration) to the joint and tells the participant "that is the feeling of the tuning fork without any vibration"* 7. *Strikes the tuning fork against a solid object or examiner's hand to start vibration* 8. *Holds the vibrating fork by the stem* 9. *Re-applies the tuning fork to the DIP joint and asks the participant to confirm that they feel the "buzzing" or vibration. If they do not feel the*			

vibration, examiner verifies with his or her own hand whether or not fork is vibrating, then re-strike the hammer and re-apply 10. *Uses only a finger or two against the tip of the big toe to stabilize the foot during vibration assessment* 11. *Confirms that the participant feels the vibration and then ask them to say "stop" when they no longer feel any vibration or "buzzing"* 12. *As soon as the participant says "stop" moves the tuning fork (still held by the stem) to his/her own finger (DIP of the thumb or first finger)* 13. *Times with a watch or clock with a second hand, the number of seconds that the examiner feels vibration* 14. *Scores the vibration correctly* *A. If examiner feels the vibration on his/her finger for less than 10 seconds after patient says "stop", then records score as "present"* *B. If examiner feels the vibration on his/her finger for longer than 10 seconds, scores as "reduced"* *C. If participant is not able to detect any vibration from the tuning fork, and examiner confirms that positioning was correct and vibration was present, the score marked is "absent"* 15. *Repeats assessment for other foot*			
Determines Monofilament Perception			
1. *Explains procedure to subject; "I am going to lightly touch your big toe with this filament- it's a thin piece of nylon, sort of like fishing line"* 2. *Pre-stresses the filament on the participant's hand to demonstrate the feeling of the filament* 3. *With each application, the filament bends to a "c" shape and each application lasts about 1 second* 4. *Positions the participant with the foot hanging freely* 5. *Supports the foot to be tested with the examiner's hand (sole of foot in palm of hand (or, can have sole of foot resting on a firm surface, e.g., carpeted floor , or stool, as long as the surface is not overly cool or warm)* 6. *Instructs the subject to close his or her eyes and to say "yes" if they feel the filament touching the toe* 7. *Applies the monofilament to the dorsum of the great toe, on the skin between the DIP and base of the nail*			

8. *Applies sufficient pressure to create a "c" shaped bend in the filament and the duration of application is about 1 second* 9. *Removes the filament and waits for the subject response* 10. *After the subject responds, waits a couple of seconds and reapply* 11. *Repeats the application process for a total of 10 applications. The duration of the pause between applications is staggered, and the examiner periodically checks to make sure that the subject still has his or her eyes shut.* 12. *Records the number of correctly identified filament touches. If 8 or more are correctly identified, the response is "present", if 1 to 7 are correctly identified, the score is "reduced" and if none of the applications are correctly identified, "absent" is marked.* 13. *Repeats the process for the second foot.* 14. *If the subject does not respond to the first or second touch, the examiner has the patient open his or her eyes, and reviews the instructions again, while testing on the hand. Then, resume testing on the foot.*			