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

4.1. 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, issues related to quality control monitoring by the Coordinating Center and the SEARCH laboratory, and site visits. Quality control procedures for Retinopathy (eye exam), SphygmoCor, and Neuropathy (MNSI) are included in their corresponding sections.

4.2. 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 trial. 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. A summary is provided for standardized study equipment as approved by the SEARCH Executive Committee.

Table 4-1 - SEARCH Registry and/or Cohort Visit Equipment Table

Study Component	**Recommended Equipment**	**Minimum Standard**	**Suggested Vendor** (others can be used at clinic discretion)
Height	Wall-mounted stadiometer	Portable Road Rod™ or Mobile Mount™ stadiometer	www.mckesson.com www.seca.com
Weight	SECA scale model 770 or 876	Digital scale with the capacity to measure within 0.1kg of body weight up to 150 kg and to 0.2 kg for weights > 150 kg	www.mckesson.com

Study Component	Recommended Equipment	Minimum Standard	Suggested Vendor (others can be used at clinic discretion)
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	**www.miami-med.com** **www.allheart.com**
	Calibration device (needs calibration check annually)	Netech DigiMano digital pressure and vacuum meter Part no. 200-2000IN	**www.netechcorporation.com** 1-800-547-6557
Stethoscope	Stethoscope with a diaphragm side and a pediatric bell side	Stethoscope with a diaphragm side and a pediatric bell side	**www.stethoscope.com**
Waist circumference	Fiberglass tape measure - BMS-8 for waists <150cm	For persons with waist circumference <150 cm: a non-stretch, non-tension fiberglass tape with increments at least 0.1 cm	**www.chponline.com**
	Steel tape measure for waists >150cm - Anthropometric Tape - Rosscraft 08730	For persons with waist circumference ≥ 150 cm: a non-tension flexible steel tape with increments at least 0.1cm	**www.quickmedical.com**
Centrifuge	Centra CL2 by A. Daigger	Centrifuge that has a swing bucket rotor and spin speed of 3500 rpm	**www.thermo.com** **www.fishersci.com**
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	**www.compactappliance.com** **www.amazon.com**

Study Component	Recommended Equipment	Minimum Standard	Suggested Vendor (others can be used at clinic discretion)
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	Purchased by CoC
	Laptop - Latitude E6410	Laptop - Latitude E6410	Purchased by the CoC
Heart function and cardiac autonomic neuropathy	AtCor SphygmoCor CVMS-CPVH	AtCor SphygmoCor CVMS-CPVH	Purchased by the CoC
	Conmed Cleartrace Electrodes - 1700-030 or 1700-005	Standard ECG electrodes with clip on connectors	Ordered by the site using the WFU account. Phone: 1-800-765-8375 Reference WFU Account #: 449 490 PO #: 2011018781
	Toshiba L670-EZ1711 laptop	Toshiba L670-EZ1711 laptop	Purchased by the CoC
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)	**www.sci-supply.com** **www.amazon.com** **www.middelta.com**
Urine collection (First morning void and spot sample)	Urine cups, antiseptic wipes, biohazard bag USPS flat rate box to mail urine cup	Urine cups, antiseptic wipes, biohazard bag USPS flat rate box to mail urine cup	Ordered through CBL **https://shop.usps.com** (10/11)

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 study Coordinating Center at periodic intervals.

4.3. DATA QUALITY

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. Written responses to any items on the questionnaires/forms should be legible. Confirmation of review is documented at the end of each form.

The data entry screens will be designed to mirror the paper data collection forms to the extent possible allowing a smooth flow from item to item minimizing data entry error. Verification of participant identifiers and visit numbers will be incorporated into the data entry system, in addition to gross range checking of fields.

Prior to entering data, each data entry person will be required to complete the certification module. This requires that each individual enter a standardized data set into the certification system. Once these data are entered, an overall quality score will be given. An established minimum acceptable score of 100% accuracy must be obtained prior to entering SEARCH study data. Once this score is attained, the individual will be provided access to the "live" SEARCH site to enter data.

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. Data fields will be programmed to allow for fixed responses or immediate alerts when unusual values are entered. Web-based quality control reports will be generated quarterly and reviewed by the Protocol Oversight Committee and available for the Steering Committee. When inconsistencies are detected, the clinical center will be notified through edit reports, and will be asked to verify, if possible, some entries. Prompt action with these verification requests is essential for an efficient quality control system.

4.4. QUALITY CONTROL FOR CENTRAL LABORATORY

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

4.4.1. Internal Quality Control

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

- Temperature-dependent equipment and water quality;
- 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.

4.4.2. External Quality Control

External quality control procedures include participation in:

- the College of American Pathologists quality assurance program for inter-laboratory comparison (lipids, chemistries, apolipoproteins, urinalysis, clotting factors, HbA_{1C}, and insulin);
- 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.

4.4.3. 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.

4.4.4. 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.

4.4.5. Blind Splits

Blind split analyses are routinely performed both internally and for specific studies. These will be performed for C-peptide on 10% of samples in the first 12 months of data collection. Reports will be sent to the POC committee. Additionally blind splits performed on other analytes, i.e., lipids, glucose, and HbA_{1C} will be shared with the LookAhead study that currently uses NWLRL for research purposes. These results will be sent to the CoC after review by the LookAhead Quality Control Committee.

4.4.6. Periodic Reports

Periodic reports are submitted summarizing performance in assay of internal quality control, laboratory proficiency survey materials and/or reference materials, e.g., College of American Pathologists and Centers for Disease Control and Prevention, performance in assay of blind

split duplicates, and long-term drift monitoring will be reported to the Protocol Oversight Committee. 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 Coordinating Center.

4.5. COORDINATING CENTER ACTIVITIES

Quality assurance will be a major activity of the Coordinating Center throughout the study. Activities will include:

- Training/retraining of clinical center staff in data collection procedures,
- 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 for the Steering Committee. Annually quality control reports are provided to the External Scientific Committee. For example, these reports will include data on:

- Recruitment yields at each clinical center
- Summaries of certifications
- Site visit summaries
- Unanticipated Occurrences
- Deviations from protocol
- Missed visits, refusals, lost to follow-up
- Adherence
- Errors in collection, labeling, storage, shipping of laboratory specimens or other materials to central reading centers

4.5.1. Changes in the Protocol

Changes in the Protocol may need to be made periodically. When this is required, the CoC will update the documents with the corrected/revised information and notify the clinical centers so that the centers may submit the amendments to their local IRB's.

4.5.2. 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.

4.5.3. Protocol Oversight Committee

The Protocol Oversight Committee (POC) will consist of representatives across the clinical centers, the Central Lab, the CoC. The POC will have co-chairs and voting members. Because of the nature of the committee's charge, the chair of POC will be the Director of the CoC. The committee will be responsible for reviewing aspects of the study protocol, including data quality control, adverse events, and recruitment and retention. The POC will also make recommendations to the Steering Committee on modifications to the study MOP and Protocol. The committee will report to the Study Group on a regular basis.

4.6. SITE VISITS

The Coordinating Center will arrange a site visit program to each center to promote communication, answer questions, and ensure that study procedures are understood and correctly carried out. The site visit program will provide a mechanism to encourage the effective and standardized delivery of recruitment efforts and the collection of appropriate and valid data within each of the SEARCH study clinic sites. Members of the site visit team will be selected by the Coordinating Center and will include personnel from the Coordinating Center along with one or more personnel from selected centers. Site visits may also be performed if consistent departures from the Protocol and Manual of Procedures are detected. Retraining may be done as needed during these visits, depending on the availability of staff.

One of the most valuable resources is SEARCH study personnel who collect study data. It is these individuals who have the experience and knowledge as well as a practical perspective to identify and help correct problems and/or variations in procedures that centers may be having. Before the visit, the centers will be sent a proposed agenda and a schedule will be worked out in advance. The Principal Investigator, Project Coordinator, and other key staff members, will be involved. Site visits will occur after experience has been gained with the first wave of participants. This will enable the site visitors to look at recruitment efforts, the methods of process and procedures, and any staffing problems clinics may be encountering. A schedule of site visits will be developed by the Coordinating Center in concert with the Steering Committee.

The site visit will be an ideal time for suggesting solutions for problems that are identified. It should be noted that outside visitors may not have better answers; however they may have different answers that may prove useful. Of equal importance will be the lessons that site visitors gain while watching other centers in action. The observational experience can enhance and increase the visitor's own skills at developing problem solving strategies and solutions. Consequently, the site and peer-review visits will be a time when the Coordinating

Center personnel, peers and center personnel review progress and problems, share what has/has not worked, and consider new strategies and solutions.

At the conclusion of each site visit, there will be a discussion between the Site Visit Team, the Principal Investigator and key study personnel summarizing issues raised during the visit. The Site Visit Team will prepare written reports on the activities of the site visit. A detailed report of the team's observations and recommendations that subsequently will be sent to the Principal Investigator of the site being reviewed and the Steering Committee.

4.6.1. Organization of the Site Visit

The site visits are designed to insure that each SEARCH study clinical site is recruiting appropriate individuals and collecting high quality data. Objectives for the site visitor are: a) to determine if the Protocol and Manual of Procedures are being followed, and if not, what measures should be taken to correct the problems; and b) to learn as much as possible from center staff about how to improve effectiveness in recruitment, collecting data, and facilitating a smooth clinic flow.

A key to a successful site visit is adequate preparation both from the Coordinating Center and clinic centers. The visits should serve to enhance communication throughout the study, and to personalize interchange among clinic staff and investigators.

<u>Questions for the Center Personnel</u>

During the site visit the visitor should seek answers to the following questions, review and discuss data reports provided by the coordinating center and explore any concerns or questions that arise.

a. Do clinics have an adequate number of appropriately trained staff members to provide for effective recruitment, data collection, and data entry?

b. Are personnel roles clearly defined and is there communication and interaction between the various working groups?

c. How information is shared, for example, changes in the MOP or Protocol?

d. What is the overall view of clinic flow?

e. The clinic tracking/scheduling system will be discussed and the following questions may be asked.

- What is the procedure followed when a participant does not show up for his/her appointment?
- How does the clinic keep track of where an individual is in the study flow so that the participant is scheduled within the appropriate window?
- How are problem participants handled?

During the site visit, the visitor may ask to follow a participant through an entire visit, observe a randomly selected interview and observe the collection of physical measurements. Questions will be asked about where records are kept and how participant confidentially is assured. A site visitor will conduct selected reviews to determine if appropriate consent forms are available and signed.

Protocol and Manuals

The following questions concerning study documentation should be answered during the course of the site visit.

a. Where is the MOP located? Do study personnel have easy access to it?

b. Do the Protocol and MOP have all the updates included?

c. What is the procedure for maintenance on equipment? Where are the quality control logs documenting that equipment is checked at appropriate intervals?

d. Where is the IRB approval document located? Has the IRB been informed of protocol changes?

e. A review of laboratory procedures and what OSHA regulations are being followed.

f. A review and discussion of data reports provided by the Coordinating Center, and exploration of any concerns or questions that arise. Possible items for discussion include: data edits, missing/delinquent forms, missed visits and protocol violations.

Preparation for the site visit will be valuable to the staff. Preparation should include:

a. Distribution of the site visit guidelines to all study personnel;

b. An explanation of the goals of the site visit to all study personnel;

c. A review of compliance with the guidelines during staff meetings prior to site visits; and

d. A self-evaluation of clinic strengths and weaknesses by each staff member in preparation for discussions with site visitor(s).

Post site-visit activities at the clinical center should include:

A staff meeting to debrief the clinical center staff regarding information and issues related to the site visit;

a. Review of the written site visit report when available;

b. Goal setting and planning based on site visit recommendations.