CORONARY ARTERY RISK DEVELOPMENT IN YOUNG ADULTS (CARDIA) STUDY – ECHOCARDIOGRAPHY READING CENTER

I. BACKGROUND

The Coronary Artery Risk Development in Young Adults (CARDIA) Study started as a study of the distribution and evolution of risk factors for cardiovascular disease during young adulthood in black and white men and women. At Year 25 participants will be 43-55 years old, when risk factors and subclinical abnormalities become more prevalent and clinical events begin to emerge. CARDIA offers the opportunity to address aspects of the development and progression of subclinical vascular, ventricular, and pulmonary function abnormalities that cannot be addressed in older cohorts.

The study, which began recruitment in 1985, has completed 7 examinations over 20 years in a cohort of 5,115 men and women aged 18-30 years in four communities. Participants were initially sampled from the total population, selected census tracts or, in the case of one Center, the membership of a large health plan. The original cohort had approximately equal representation by blacks and whites, men and women, those aged 18-24 and 25-30, and those with no more than a high school education and more than a high school education. The baseline examination (Year 0) was conducted over a 14-month period during 1985-86. The examination consisted of questionnaires on sociodemographic characteristics, health behaviors, and psychological factors; an exercise treadmill test; resting electrocardiography; a diet history assessment; anthropometry; pulmonary function testing; and resting blood pressure. Fasting blood measurements included total cholesterol and its subfractions, insulin, glucose, liver enzymes and other serum chemistry measurements, and hematology.

Six additional examinations have been completed every 2-5 years, including a Year 20 examination completed in 2006. Repeat measurements on traditional risk factors, including plasma lipids, blood pressure, anthropometry, smoking behavior, physical activity, and pulmonary function testing (except Years 7 and 15) have used the same methods at each examination to assess age and secular trends in these factors during young adulthood. In selected years, additional measurements have been made, including a treadmill exercise test at baseline and Year 7; diet history at baseline, Year 7, and Year 20; cardiovascular reactivity measurements in Year 2; echocardiography at Year 5 and in a subset at Year 10; ambulatory blood pressure monitoring (in a subset) at Year 5; skin reflectance and assessment of the experience of discrimination and other psychosocial measures and urine sodium and creatinine in Year 7; glucose tolerance testing and microalbuminuria in Year 10 and Year 20; coronary CT scan in Year 15 and Year 20; and carotid intima media thickness in Year 20.

Retention of the surviving cohort was 90, 86, 81, 79, 74, and 72 percent at each of the respective follow-up examinations. Cohort members are contacted every six months to obtain information on vital status and current residence. Every other six-month contact also includes speaking with the participant to ascertain information on current smoking status, major illness or injury, and hospitalizations.

CARDIA ECHOCARDIOGRAPHY READING CENTER

A. Scientific Objectives

The Year 25 Examination and continued follow-up of the CARDIA study shall address the following five objectives:

1. Assess the impact of timing and varying levels of risk factors throughout young adulthood on the development of subclinical ventricular, vascular, and pulmonary function abnormalities in mid-life

   CARDIA will study the impact of traditional and novel risk factors acquired throughout young adulthood on the development of subclinical abnormalities in mid-life. Predictors of changes in left ventricular structure and function (measured by echocardiography) will be examined. Several subclinical vascular abnormalities will be identified, including early cerebral vascular abnormalities (manifested by cognitive decline and white matter disease), lower extremity arterial perfusion (measured by ankle-brachial index), arterial stiffness (measured by pulse wave velocity), and microalbuminuria. Changes in pulmonary function from young adulthood to mid-life will also be characterized.

2. Examine young adult antecedents and consequences of obesity and the longitudinal relationships and interactions among adiposity, insulin resistance, and inflammation

   CARDIA will study the genetic, biological, behavioral, and psychosocial factors that predict obesity, as well as the impact of obesity on the development of subclinical and early clinical abnormalities. The differential associations between visceral, subcutaneous, and intermuscular fat on insulin resistance and inflammation will also be examined.

3. Identify determinants and trajectories of subclinical disease development in women during menopause transition compared to men of similar age

   CARDIA will study subclinical disease development in the context of menopause transition. Changes in menstrual patterns over time will be evaluated for associations with increasing risk factor incidence and subclinical disease. The determinants and trajectories of subclinical disease development in women during menopause transition will be compared to men of similar age, as will comparisons between pre- and post-menopausal women of similar age.

4. Further assess the basis for racial differences in subclinical disease development

   CARDIA will assess the basis for differences between blacks and whites in the development of subclinical ventricular, vascular, and pulmonary function abnormalities. Racial differences in predictors and their varying consequences on the development of subclinical abnormalities will be explored.

5. Provide a platform for in-depth ancillary studies in cardiovascular and other areas

   CARDIA will continue to replenish and further enrich its rich repository of data and specimens to allow additional in-depth ancillary studies on how changes that occur in young adulthood contribute to the development of cardiovascular and other abnormalities in mid-life, and how these changes differ by race, sex, and other factors.

The final protocol (including any additional scientific objectives and measurements) will be developed by the CARDIA investigators in collaboration with the NHLBI Project Office, and will be reviewed and approved by NHLBI in consultation with the existing CARDIA Observational Studies Monitoring Board (OSMB).

The study will be a platform for in-depth ancillary studies that are funded outside of the current contract. These studies will be operationally integrated into the main study, and the data will be shared across both types of studies, per current CARDIA and NIH data-sharing policies. The study's data will be provided to interested investigators through a defined process that encourages maximum data utilization but that protects participant confidentiality.

The study will also continue to serve as a training ground for junior investigators, who will work with senior investigators and be provided with guidance on conducting research.

B. Study Operations

All surviving and willing members of the CARDIA cohort will be followed up by the Field Centers and included in the Year 25 Exam during 2010-2011 (approximately 12 months in duration). It is estimated that approximately 3600 participants will be examined. Participants will be contacted every 6 months to ascertain vital status and change in address; every other 6-month contact includes speaking with the participant to characterize new clinical events and other changes in health status.

A timeline for the study is provided in Table 1. A list of exam components is provided in Table 2.

Collaborating centers will include the four current Field Centers, a Coordinating Center, and an Echocardiography Reading Center. The Coordinating Center will establish Reading Centers for Electrocardiogram (ECG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Pulmonary Function, and laboratories. Principal Investigators from each of the 6 collaborating centers plus any relevant large subcontracts as determined by the NHLBI Project Office, and the NHLBI Project Officer form the CARDIA Steering Committee. The chair of the Steering Committee serves through a subcontract with the Coordinating Center.

Table 1. Timeline* for CARDIA Year 25 Exam

Activity	Time period
Protocol development	Start of this contract period – March 15, 2010
**OMB clearance package preparation	June 1, 2009 – October 1, 2009 (4 months)
Protocol review by NHLBI And CARDIA OSMB	March 15, 2010 – April 1, 2010 (3 weeks)
Staff training for Echocardiography	April 2, 2010 – May 1, 2010
Staff training for all other measures	April 15, 2010 – May 1, 2010 (2 weeks)
Pilot testing	May 3, 2010 – May 10, 2010 (1 week)
Year 25 Exam	June 1, 2010 – May 31, 2011 (12 months)
Close-out	October 1, 2012 – September 30, 2013 (12 months)

*Note: Timeline is accurate to within 2 months.

**Note: It is possible that the OMB Clinical Exemption under which the study currently operates will remain in effect during the renewal but this is not guaranteed.

C. Examination Components

The Year 25 Exam shall collect the following list of components, which may be modified during protocol development. The final protocol as approved by the NHLBI in consultation with the OSMB shall constitute the final content and schedule of the data to be collected.

Table 2. List of Year 25 Exam components

- Consent
- Demographic information
- Anthropometry
- Blood pressure
- Smoking history
- Medical history, including medications
- Cognitive assessment
- Questionnaires, including perimenopause, behavioral factors related to weight gain and weight loss, and physical activity
- Fasting phlebotomy for whole blood, serum, plasma, and DNA collection
- 2-hour oral glucose tolerance test
- Spot urine collection for albumin and creatinine
- Pulmonary function
- Ankle-brachial index
- Peripheral pulse wave velocity
- Electrocardiogram
- 2-D echocardiography
- CT of the abdomen and mid-thigh for fatty liver identification and body composition
- Brain MRI (in a subset)

D. Laboratory Measures

Year 25 Exam shall collect the following specific types or classes of measurements. The final protocol for lab measurements will be determined by the Steering Committee. The Laboratory Committee will coordinate proposals and incorporation of new assays over time, based on scientific priorities and costs.

1. Established clinical measures of metabolism, renal function, and lipid metabolism, including glucose, insulin, HbA1c, 2-hour oral glucose tolerance test, creatinine, cystatin C, and a lipoprotein panel.
2. Biomarkers that are putative risk factors for cardiovascular and pulmonary disease measured from blood samples, including but not necessarily limited to measures related with adiposity and markers of immune and inflammatory response.
3. Urine creatinine and albumin.
4. Other measures that will further understanding of the development of atherosclerosis and other forms of cardiovascular disease, and other related conditions.
5. Collection and storage of DNA, serum, plasma, and urine.

E. Event Ascertainment

Follow-up will be performed by the Field Centers for morbidity (acute myocardial infarction, angina, stroke, heart failure, atrial fibrillation; peripheral vascular disease; chronic obstructive pulmonary disease); mortality; and any cardiovascular disease interventions received. In addition, all hospitalizations will be identified and data collected on discharge diagnoses. All participants, including those who have refused participation and unequivocally expressed the desire not to be re-contacted, will be followed through the Social Security Death Index and other commercial databases as appropriate. The types of data to be collected for event ascertainment include: Dates of deaths and hospitalizations; Interview data from participants; Hospital discharge diagnosis and ICD codes; Data collected from hospital inpatient and outpatient records.

The CARDIA protocol and Manual of Operations for event ascertainment shall be refined to include standardized procedures and forms for data abstraction by the abstractor(s) from the Coordinating Center. Events will be classified in a standard manner and consistent with current CARDIA practice, as developed by the Morbidity and Mortality Committee. Refinements to the protocol and Manual of Operations for event ascertainment shall to the extent possible be comparable to other NHLBI-sponsored large cohort studies such as the Multi-Ethnic Study of Atherosclerosis (MESA).

F. Mentoring Junior Investigators

Each Field Center will provide formal and/or informal training opportunities for junior or inexperienced investigators (assistant professors, fellows, and students). This includes but is not limited to the junior investigator working on data analyses and publications and serving on study subcommittees. Sites are encouraged to apply for supplements from existing NIH programs or include CARDIA experiences in existing training programs.

II. GENERAL REQUIREMENTS AND TASKS

Note: Throughout this statement of work, the terms "Contractor" and "Echocardiography Reading Center" are used interchangeably.

The Echocardiography Reading Center shall:

1. Participate in the CARDIA Steering Committee, the Imaging Committee and Quality Control Committee, as appropriate.
2. Develop the protocol for the acquisition and reading/information abstraction of the echocardiograms to be performed as part of the CARDIA Year 25 Exam.
3. Determine comparability of the proposed CARDIA Year 25 echocardiographic measurement to that from the Year 5 Exam by performing repeat measures of about 200 videotaped Year 5 echocardiographic studies plus 10% blind duplicates of the Year 5 echocardiographic studies.

4. Propose a plan to assess 20-year changes in echocardiographic measurements, particularly left ventricular structure and function, in the CARDIA cohort.
5. Convert the videotaped echocardiograms obtained from the CARDIA Y5 and Y10 Exams into digital electronic files and copy onto DVDs for secure archival storage.
6. Train and certify Field Centers' echocardiography technicians according to protocol.
7. Train and certify echocardiography readers at the Reading Center according to protocol, as well as orient professional staff from the Coordinating Center and NHLBI Project Office who have quality assurance responsibilities
8. Conduct a pretest of the Year 25 echocardiography protocol, including quality assurance activities, during the pilot testing phase of the Year 25 Exam, in collaboration with the CARDIA Coordinating and Field Centers.
9. Perform readings/information abstractions of echocardiograms in a timely manner during the pilot phase and throughout the Year 25 Exam period.
10. In collaboration with the Steering Committee, provide advice on the development of clinical alert values for reporting results to participants.
11. In collaboration with the Coordinating Center and Field Centers, provide timely reporting of clinically significant results to participants.
12. Track the receipt, reading, and storage of echocardiograms
13. Develop and implement long-term archiving and storage of echocardiograms and timely creation of backup copies.
14. Visit CARDIA Field Centers during the early phase of the Year 25 Exam and as needed, in support of quality assurance efforts of the study.
15. Participate actively in data analysis, presentation, and publication using the echocardiographic data.
16. Prepare and submit technical and financial reports as specified herein.

II. SPECIFIC REQUIREMENTS AND TASKS, IN PHASES

A. During the entire contract period, the Contractor shall:

1. Designate key personnel* to lead and manage the study who have the appropriate qualifications. (*Note: The NHLBI Project Office must approve key personnel.)
    a. A principal investigator with:
        i. Training and experience in echocardiography and cardiovascular epidemiology
        ii. Demonstrated excellence as a manager and collaborator

b. Co-investigator(s)** knowledgeable in scientific areas relevant to the study and skilled in echocardiography protocol design and data analysis (**Include the designation of one co-investigator who is qualified to temporarily serve in the place of the principal investigator as needed.)

2. Provide other staff, which may include the following:
   a. Investigator(s)
   b. Project manager
   c. Echocardiography readers
   d. Data management staff

3. Participate in and designate staff to participate in the Steering Committee, Imaging Committee, and Quality Control Committee, as appropriate.

4. Participate in various administrative activities to include, but not be limited to: visiting field centers as needed in support of quality assurance activities; preparing reports for the Steering Committee, Imaging Committee, Quality Control Committee, and Observational Study Monitoring Board.

5. Prepare and submit regular technical and financial reports, including the following:
   a. Semi-annual progress reports that describe main operational activities during the period, general progress in each activity, problems encountered and how they were resolved, an accounting of personnel (include levels of effort and changes during the period), and scientific productivity.
   b. Quarterly Staffing Report: Table containing a list of all current staff (name, position, administrative group, level of effort, and change in effort) and an explanation of any staffing changes.
   c. Periodic financial reports, as required by NIH, specific to your institution.

B. During the period before the Year 25 Exam (March 1, 2009 through May 10, 2010):

1. Develop, at the direction of the Steering Committee and in collaboration with the Imaging Committee, the Year 25 Exam protocol for performing the echocardiography examination at each Field Center, as well as the reading and information abstraction of the echocardiographic images at the Echocardiography Reading Center. The protocol will specify the techniques to measure the following measurements* and should aim to not exceed 30 minutes of participants' time during the examination (*Note: The list of measurements is subject to modification after the Echocardiography Reading Center contract is awarded, as a result of protocol development in collaboration with the Imaging Committee, Steering Committee, and NHLBI Project Office):
   a. Left ventricular structure and function (systolic and diastolic),
   b. Left atrial and aortic root dimensions,

c. Trans-mitral and aortic flow velocities,

d. Pulmonary artery systolic pressure, and

e. Echocardiography-based clinical diagnosis (e.g. mitral valve prolapse, hypertrophic cardiomyopathy, mitral and aortic regurgitation, etc.),

[NOTE TO OFFERORS: Other potential echocardiographic characteristics of interest may be proposed by the contractor. For any such proposed measurements, the offeror should provide in its response to this Request for Proposal the following information:

i. The additional participant time needed for the technician to obtain the measurement(s) during the examination.

ii. The additional costs required for the Echocardiography Reading Center (e.g. additional efforts and materials needed to read and archive the scans, etc).

2. Advise and assist the Field Centers in the purchasing of echocardiographic machines and equipment

3. Determine comparability of the proposed Year 25 echocardiographic measurement to that from the Year 5 Exam. This includes performing repeat measures of about 200 videotaped echocardiograms and 10% blind duplicates of studies from the Year 5 Exam. The videotapes will be selected at random by the CARDIA Coordinating Center. Tasks related to this comparability study include, but are not limited to, the following:

   a. Perform the measurements according to protocol and transmit all data to the Coordinating Center by September 30, 2009.

   b. Assist in analysis of comparability study and provide summary of findings and recommendations for any further re-readings or analyses to the Steering Committee by December 1, 2009.

   c. Assess and control intra- and inter-individual variability in reading protocol during the comparability study, and propose modification of this protocol as needed.

   [Note: The Year 5 protocol and manual of operations can be found at http://www.cardia.dopm.uab.edu/pdf/D10800.PDF; http://www.cardia.dopm.uab.edu/pdf/D10712.PDF; and http://www.cardia.dopm.uab.edu/pdf/D10709.PDF]

4. Propose a plan to assess 20-year changes in echocardiographic measurements, particularly left ventricular function and structure, in the CARDIA cohort.

5. Convert the videotaped echocardiograms from the CARDIA Y5 and Y10 Exams into digital electronic files. [NOTE TO OFFERORS: For planning purposes, estimate that about 4400 echocardiographic studies from the Year 5 Exam are present on ~ 320 VHS tapes; about 1751 echocardiographic studies from the Year 10 Exam are present on ~125 VHS tapes.]

6. Provide advice on language pertaining to the Year 25 echocardiography examination to be included in the informed consent document.
7. In collaboration with the Steering Committee, provide advice on the development of a graded alert system that identifies which abnormalities seen on the echocardiograms will be reported to the study participants, and in what form.
8. In collaboration with the Quality Control Committee, design quality control measures for performing the echocardiographic examinations at the Field Centers and reading of echocardiograms at the Echocardiography Reading Center. The goals should be to ensure reproducibility both for a given technician (i.e. limit intra-individual variability) and between technicians (i.e. limit inter-individual variability) at various Field Centers, as well as to ensure reproducibility both within and between readers at the Echocardiography Reading Center.
    a. Develop quality assurance procedures and performance standards to ensure that studies from each echocardiography technician at each Field Center and the readings of the study echocardiograms at the Echocardiography Reading Center conform to protocol requirements. Include in the plan procedures for assessment and control of inter- and intra-technician variability, as well as inter- and intra-reader variability.
    b. Develop protocol for performing a subset of blind duplicate echocardiographic studies at each Field Center, to be read as blind duplicates at the Echocardiography Reading Center. Compare results of blind duplicates to original studies in a timely manner as specified in the study protocol, and provide feedback to technicians on a regular basis.
    c. Develop protocol for performing the re-reads of a subset of blind duplicate echocardiographic studies at the Echocardiography Reading Center. Compare results of blind duplicates to original studies in a timely manner as specified in the study protocol, and provide feedback to readers on a regular basis.
9. Prepare and present to the Steering Committee two Echocardiography Manuals of Operation: one for measurement (reading) of echocardiography data for the Echocardiography Reading Center and one for performing the echocardiography examination for the Field Centers. Both the draft and final forms of these Manuals of Operations shall be submitted to the Steering Committee for approval prior to training clinic staff. These Manuals of Operations shall be web-friendly for posting on the CARDIA internal website for use by the Field Centers, the Coordinating Center, and the Project Office.
10. Train and certify Field Centers' echocardiography technicians according to protocol. This will include the initial training, certification, and orientation in the pilot testing phase, any necessary recertification, and the training, certification, and orientation of new technicians and quality assurance due to staff turnover.

11. Train and certify echocardiography readers at the Echocardiography Reading Center according to protocol. This will include the initial training, certification, and orientation in the pilot testing phase, any necessary recertification, and the training, certification, and orientation of new readers and quality assurance staff due to turnover.
12. Orient, as necessary, professional staff from the Coordinating Center with quality assurance responsibilities and the NHLBI Project Office according to the reading and information abstraction protocol.
13. Participate in the pilot testing for the Year 25 Exam. The pilot test will occur after training is complete, consisting of performing all of the components of the Year 25 Exam according to the draft Manual of Operations, in at least 9 volunteers per Field Center who are not study participants. The pilot tests also are to include transmission of echocardiographic images to the contractor, who shall read the images according to protocol. The contractor shall also participate in transmitting the abstracted echocardiographic data to the Coordinating Center. Results will be reviewed by the Steering Committee.
14. Redesign and implement changes in protocol, as recommended by the Imaging Committee and approved by the Steering Committee, based on pilot testing results.
15. Assist the Coordinating Center in making final modifications to the Manual of Operations based on the pilot test results at the direction of the Steering Committee.
16. Deliver the following to the Coordinating Center:
    a. The Field Center and Reading Center Protocols and Manual of Operations: draft at least 8 weeks prior to start of Year 20 pilot examination and final at least 4 weeks prior to start of Year 20 examinations.
    b. Training materials for echocardiography technicians and the Coordinating Center at least 6 weeks prior to the technicians' training session.
    c. Pilot test results (raw data) and written evaluation and recommendations, within 14 days of receipt of Field Center images.
    d. Reading Center Results Data transmitted electronically within 14 days after receipt of images from the Field Centers.
    e. Quality control data, monthly beginning on July 1, 2010 and ending 1 month after end of exam.
    f. Reading Center Status Reports for distribution to the SC, monthly
        1. Prior to exam: Describe status of protocol, Manual of Operations, training materials, training plans
        2. During pilot and exam: Describe number of images received from Field Centers, number read (monthly and cumulative), quality assessment of the echocardiography technicians, summary of feedback to technicians if

applicable, number of scans reread for quality control, any problems identified and proposed solutions

C. During the Year 25 Exam period (June 1, 2010 through May 31, 2011),

1. Work cooperatively with other study centers, including Field Centers, Coordinating Center, Reading Centers, Laboratories, and the NHLBI Project Office staff in all relevant aspects of study development and execution.

2. Perform readings/information abstractions of echocardiographic measurements throughout the CARDIA Year 25 exam period. Enter and transmit abstracted information from the study's echocardiograms into a computer, using software designed in cooperation with the Coordinating Center, and transmit the data to the Coordinating Center within 14 days of receipt of the echocardiographic images. The Reading Center must notify the Coordinating Center in advance of, and the Coordinating Center must agree to, any proposed changes in the data transfer format during the exam cycle.

3. Assist in the analysis and interpretation of the echocardiographic data, the report of the results to the Steering Committee, and the design and implementation of any necessary corrective actions.

4. In collaboration with the Quality Control Committee, the Field Centers, and the Coordinating Center, implement quality control measures for the acquisition of echocardiograms at the Field Centers and reading of echocardiograms at the Echocardiography Reading Center. Ensure both within- and between-technician reproducibility at various Field Centers. Ensure both within- and between-reader reproducibility at the Echocardiography Reading Center. Monitor performance to ensure uniformity of data collection among all Field Centers throughout the data collection period and report results of this monitoring to the Steering Committee:

   a. Implement quality assurance procedures and performance standards to ensure that echocardiogram technicians at each Field Center and echocardiogram readers at the Echocardiography Reading Center conform to protocol requirements. This includes assessing and control of inter- and intra-technician variability, as well as inter- and intra-reader variability.

   b. Implement the protocol for performing a subset of blind duplicate echocardiographic studies at each Field Center, to be read as blind duplicates at the Echocardiography Reading Center. Compare results of blind duplicates to original studies in a timely manner as specified in the study protocol, and provide feedback to technicians on a regular basis.

c. Implement the protocol for performing the re-reads of a subset of blind duplicate echocardiographic studies at the Echocardiography Reading Center. Compare results of blind duplicates to original studies in a timely manner as specified in the study protocol, and provide feedback to readers on a regular basis.

d. Transmit quality control data to the Coordinating Center according to specifications of the study protocol.

e. Participate in the analysis and interpretation of the quality control data.

f. Perform site visits of the four Field Centers during the first 4-6 weeks of the Year 25 exam and later as needed in support of quality control monitoring by the Coordinating Center. Prepare site visit reports within 21 days of site visit; the reports shall be delivered to the Field Center, the Project Office, and all other members of the site visit team.

g. Orient, as necessary, professional staff from the Coordinating Center with quality assurance responsibilities and the NHLBI Project Office according to the reading and information abstraction protocol.

h. Perform any necessary recertification and the training, certification, and orientation of new echocardiography technicians and readers due to staff turnover

5. Assist the Field Centers and Coordinating Center in generating clinical reports provided to the Field Centers for prompt reporting to participants, along with appropriate clinical recommendations (such as for clinical follow-up).

6. Track the receipt, reading, and storage of echocardiograms.

   a. Develop and implement methods to assure complete and accurate transfer of echocardiograms between the Field Center and the Echocardiography Reading Center, including receiving the echocardiograms from the Field Centers, verifying that the number of echocardiograms received matches the number sent according to logs from the Field Centers, and resolving discrepancies with the Field Centers. To ensure that scans were received for each participant who had an echocardiogram, transmit weekly to the Coordinating Center an electronic list of IDs for participants for whom echocardiograms were received that week. Work collaboratively with the Field Centers and Coordinating Center to resolve discrepancies.

   b. Develop and implement methods to assure complete and accurate transfer of all data to the Coordinating Center. Data transmission will occur on a regular basis, approximately weekly or as agreed upon in protocol development. The content and format of data transmitted will be developed in collaboration with the Coordinating Center. The reading and transferring of the data shall occur within 14 days of the Echocardiography Reading Center's receipt of the echocardiographic images.

c. To ensure that all activities have been performed for each participant's data, maintain an electronic tracking database to include: date scan received from the Field Centers; date read and reader ID; scan quality assessment; reread dates and reader ID if appropriate; date of transmission to Coordinating Center; and location of original and backup copy if appropriate. Share database with Coordinating Center upon request.

d. Develop and implement long-term archiving and storage of echocardiograms and timely creation of backup copies.

7. Provide raw data to NHLBI Project Office, upon request

D. During the period following the Year 25 Exam (June 1, 2011 through September 30, 2013),

1. Participate in scientific activities, including the preparations of abstracts and manuscripts for presentations and publications using results of the echocardiography data.

2. Submit draft abstracts and manuscripts to the Publications and Presentations (P&P) Committee and through the CARDIA Coordinating Center to NHLBI for review prior to submitting to scientific meetings or journals. The abstracts shall be submitted to the P&P Committee and Coordinating Center at least 2 weeks prior to submission to scientific meetings, and the manuscripts at least 6 weeks prior to submission to scientific journals.

3. Provide accepted publications emanating from the Field Center within two weeks of publication, for a data base to be managed by the Coordinating Center.

4. At the end of the contract period (plan for last 6 months of contract period), propose a plan, in collaboration with Steering Committee and the NHLBI, for the long-term storage of the archived echocardiographic images.

5. A final report, due September 30, 2013, documenting and summarizing the results of the entire contract work, including salient results, recommendations and conclusions based on both the general experience and the individual viewpoint of the Field Center.

THIS IS THE END OF THE ECHOCARDIOGRAPHY READING CENTER'S STATEMENT OF WORK. BELOW ARE THE COORDINATING AND FIELD CENTERS' STATEMENTS OF WORK TO ASSIST THE OFFERORS IN DEVELOPING THEIR RESPECTIVE PROPOSALS. ALSO ATTACHED IS A STATEMENT ON ANCILLARY STUDIES.

CARDIA ECHOCARDIOGRAPHY READING CENTER

ATTACHMENTS:

1.a. Statement of Work for Coordinating Center (which includes work scopes for establishing the ECG Reading Center, CT Reading Center, Brain MRI Reading Center, Pulmonary Function Reading Center, and laboratories).

1.b. Statement of Work for Field Centers.

2. Ancillary Studies

Attachment 1.a.: STATEMENT OF WORK – COORDINATING CENTER

III. BACKGROUND

The Coronary Artery Risk Development in Young Adults (CARDIA) Study started as a study of the distribution and evolution of risk factors for cardiovascular disease during young adulthood in black and white men and women. At Year 25 participants will be 43-55 years old, when risk factors and subclinical abnormalities become more prevalent and clinical events begin to emerge. CARDIA offers the opportunity to address aspects of the development and progression of subclinical vascular, ventricular, and pulmonary function abnormalities that cannot be addressed in older cohorts.

The study, which began recruitment in 1985, has completed 7 examinations over 20 years in a cohort of 5,115 men and women aged 18-30 years in four communities. Participants were initially sampled from the total population, selected census tracts or, in the case of one Center, the membership of a large health plan. The original cohort had approximately equal representation by blacks and whites, men and women, those aged 18-24 and 25-30, and those with no more than a high school education and more than a high school education. The baseline examination (Year 0) was conducted over a 14-month period during 1985-86. The examination consisted of questionnaires on sociodemographic characteristics, health behaviors, and psychological factors; an exercise treadmill test; resting electrocardiography; a diet history assessment; anthropometry; pulmonary function testing; and resting blood pressure. Fasting blood measurements included total cholesterol and its subfractions, insulin, glucose, liver enzymes and other serum chemistry measurements, and hematology.

Six additional examinations have been completed every 2-5 years, including a Year 20 examination completed in 2006. Repeat measurements on traditional risk factors, including plasma lipids, blood pressure, anthropometry, smoking behavior, physical activity, and pulmonary function testing (except Years 7 and 15) have used the same methods at each examination to assess age and secular trends in these factors during young adulthood. In selected years, additional measurements have been made, including a treadmill exercise test at baseline and Year 7; diet history at baseline, Year 7, and Year 20; cardiovascular reactivity measurements in Year 2; echocardiography and ambulatory blood pressure monitoring (in a subset) at Year 5; skin reflectance and assessment of the experience of discrimination and other psychosocial measures and urine sodium and creatinine in Year 7; echocardiography (in a subset) in Year 10, glucose tolerance testing, and microalbuminuria in Year 10 and Year 20; coronary CT scan in Year 15 and Year 20; and carotid intima media thickness in Year 20.

Retention of the surviving cohort was 90, 86, 81, 79, 74, and 72 percent at each of the respective follow-up examinations. Cohort members are contacted every six months to obtain information on vital status and current residence. Every other six-month contact also includes speaking with the participant to ascertain information on current smoking status, major illness or injury, and hospitalizations.

A. Scientific Objectives

This renewal will fund continued follow-up and examination of the CARDIA study to address the following five objectives:

6. Assess the impact of timing and varying levels of risk factors throughout young adulthood on the development of subclinical ventricular, vascular, and pulmonary function abnormalities in mid-life

   CARDIA will study the impact of traditional and novel risk factors acquired throughout young adulthood on the development of subclinical abnormalities in mid-life. Predictors of changes in left ventricular structure and function (measured by echocardiography) will be examined. Several subclinical vascular abnormalities will be identified, including early cerebral vascular abnormalities (manifested by cognitive decline and white matter disease), lower extremity arterial perfusion (measured by ankle-brachial index), arterial stiffness (measured by pulse wave velocity), and microalbuminuria. Changes in pulmonary function from young adulthood to mid-life will also be characterized.

7. Examine young adult antecedents and consequences of obesity and the longitudinal relationships and interactions among adiposity, insulin resistance, and inflammation

   CARDIA will study the genetic, biological, behavioral, and psychosocial factors that predict obesity, as well as the impact of obesity on the development of subclinical and early clinical abnormalities. The differential associations between visceral, subcutaneous, and intermuscular fat on insulin resistance and inflammation will also be examined.

8. Identify determinants and trajectories of subclinical disease development in women during menopause transition compared to men of similar age

   CARDIA will study subclinical disease development in the context of menopause transition. Changes in menstrual patterns over time will be evaluated for associations with increasing risk factor incidence and subclinical disease. The determinants and trajectories of subclinical disease development in women during menopause transition will be compared to men of similar age, as will comparisons between pre- and post-menopausal women of similar age.

9. Further assess the basis for racial differences in subclinical disease development

   CARDIA will assess the basis for differences between blacks and whites in the development of subclinical ventricular, vascular, and pulmonary function abnormalities. Racial differences in predictors and their varying consequences on the development of subclinical abnormalities will be explored.

10. Provide a platform for in-depth ancillary studies in cardiovascular and other areas

    CARDIA will continue to replenish and further enrich its rich repository of data and specimens to allow additional in-depth ancillary studies on how changes that occur in young adulthood contribute to the development of cardiovascular and other abnormalities in mid-life, and how these changes differ by race, sex, and other factors.

The final protocol (including any additional scientific objectives and measurements) will be developed by the CARDIA investigators in collaboration with the NHLBI Project Office, and will be reviewed and approved by NHLBI in consultation with the existing CARDIA Observational Studies Monitoring Board (OSMB).

The study will support in-depth ancillary studies that are funded outside of the current contract. These studies will be operationally integrated into the main study, and the data will be shared across both types of studies, per current CARDIA and NIH data-sharing policies. The study's data will be provided to interested investigators through a defined process that encourages maximum data utilization but that protects participant confidentiality.

The study will also continue to serve as a training ground for junior investigators, who will work with senior investigators and be provided with guidance on conducting research.

B. Study Operations

All surviving and willing members of the CARDIA cohort will be followed up and included in the Year 25 Exam during 2010-2011 (approximately 12 months in duration). It is estimated that approximately 3600 participants will be examined. Participants will be contacted every 6 months to ascertain vital status and change in address; every other 6-month contact includes speaking with the participant to characterize new clinical events and other changes in health status.

A timeline for the study is provided in Table 1. A list of exam components is provided in Table 2.

Collaborating centers will include the four current Field Centers, a Coordinating Center, and an Echocardiography Reading Center. The Coordinating Center will establish Reading Centers for Electrocardiogram (ECG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Pulmonary Function, and laboratories. Principal Investigators from each of the 6 collaborating centers plus any relevant large subcontracts as determined by the NHLBI Project Office, and the NHLBI Project Officer form the CARDIA Steering Committee. The chairman of the Steering Committee serves through a subcontract with the Coordinating Center.

Data analysis, publications, and cohort follow-up for morbidity and mortality will occur throughout the contract period. The total contract period is 5 years.

Table 1. Timeline for CARDIA Year 25 Exam

Activity	Time period
Protocol development	October 1, 2008 – March 15, 2010 (16 months)
OMB clearance package preparation	June 1, 2009 – October 1, 2009 (4 months)
Protocol review by NHLBI And CARDIA OSMB	March 15, 2010 – April 1, 2010 (3 weeks)
Staff training	April 15, 2010 – May 1, 2010 (2 weeks)
Pilot testing	May 3, 2010 – May 10, 2010 (1 week)
Year 25 Exam	June 1, 2010 – May 31, 2011 (12 months)
Follow-up of cohort for morbidity and mortality	October 1, 2008 – September 30, 2013 (60 months)
Close-out	October 1, 2012 – September 30, 2013 (12 months)

Note: It is possible that the OMB Clinical Exemption under which the study currently operates will remain in effect during the renewal but this is not guaranteed.

Note: Timeline is accurate to within 2 months.

C. Examination Components

Data to be collected are approximated by the following list of components, which may be modified during protocol development. Unless there is a strong rationale, procedures should be

similar to those used for previous data collections in CARDIA. The final protocol as approved by the NHLBI in consultation with the OSMB shall constitute the final content and schedule of the data to be collected.

Table 2. List of Year 25 Exam components

- Consent
- Demographic information
- Anthropometry
- Blood pressure
- Smoking history
- Medical history, including medications
- Cognitive assessment,
- Questionnaires, including perimenopause, behavioral factors related to weight gain and weight loss, and physical activity
- Fasting phlebotomy for whole blood, serum, plasma, and DNA collection
- 2-hour oral glucose tolerance test
- Spot urine collection for albumin and creatinine
- Pulmonary function
- Ankle-brachial index
- Peripheral pulse wave velocity
- Electrocardiogram
- 2-D echocardiography
- CT of the abdomen and mid-thigh for fatty liver and body composition
- Brain MRI (in a subset)

D. Laboratory Measures

The following specific types or classes of measurements will be made. The final protocol for lab measurements will be determined by the Steering Committee, The Laboratory Committee will coordinate proposals and incorporation of new assays over time, based on scientific priorities and costs.

6. Established clinical measures of metabolism, renal function, and lipid metabolism, including glucose, insulin, HbA1c, 2-hour oral glucose tolerance test, creatinine, cystatin C, and a lipoprotein panel.
7. Biomarkers that are putative risk factors for cardiovascular and pulmonary disease measured from blood samples, including but not necessarily limited to measures related with adiposity and markers of immune and inflammatory response.
8. Urine creatinine and albumin.

9. Other measures that will further understanding of the development of atherosclerosis and other forms of cardiovascular disease, and other related conditions.
10. Collection and storage of DNA, serum, plasma, and urine.

E. Event Ascertainment

Follow-up will be performed for morbidity (acute myocardial infarction, angina, stroke, heart failure, atrial fibrillation; peripheral vascular disease; chronic obstructive pulmonary disease); mortality; and any cardiovascular disease interventions received. In addition, all hospitalizations will be identified and data collected on discharge diagnoses. All participants, including those who have refused participation and unequivocally expressed the desire not to be re-contacted, will be followed through the Social Security Death Index and other commercial databases as appropriate.

Table 3. Types of data to be collected for event ascertainment

Dates of deaths and hospitalizations
Interview data from participants
Hospital discharge diagnosis and ICD codes
Data collected from hospital inpatient and outpatient records

New to this renewal will be the addition of centralized data abstractor(s) from the Coordinating Center. The CARDIA protocol and Manual of Operations for event ascertainment shall be refined to include standardized procedures and forms for data abstraction by the abstractor(s).

Events will be classified in a standard manner and consistent with current CARDIA practice, as developed by the Morbidity and Mortality Committee. Refinements to the protocol and Manual of Operations for event ascertainment should to the extent possible be comparable to other NHLBI-sponsored large cohort studies such as the Multi-Ethnic Study of Atherosclerosis (MESA).

F. Mentoring Junior Investigators

Each Field Center will provide formal and/or informal training opportunities for junior or inexperienced investigators (assistant professors, fellows, and students). This includes but is not limited to the junior investigator working on data analyses and publications and serving on study subcommittees. Sites are encouraged to apply for supplements from existing NIH programs or include CARDIA experiences in existing training programs.

IV. GENERAL REQUIREMENTS AND TASKS

Throughout the period of performance, the Contractor shall provide appropriate senior personnel with expertise in cardiovascular epidemiology, clinical and subclinical cardiovascular disease, longitudinal studies, laboratory measurements, pulmonology, body composition imaging,

statistics, bioinformatics, statistical methods development, bioinformatics, statistical genetics, and administrative management to:

A. Establish and manage an ECG Reading Center, a CT Reading Center, a Brain MRI Reading Center, a Pulmonary Function Reading Center, laboratories, and other consultants and subcontracts, as necessary.

B. Manage subcontract for the Steering Committee chairman.

C. Coordinate the establishment of the Emerging Science Committee (ESC), which consists of experts in imaging, laboratory medicine, women's health, lipid metabolism, genetics, and other disciplines as appropriate. The ESC will participate in protocol development and in analysis, interpretation, and publication of study data. The Committee shall participate in Steering Committee meetings and conference calls on a regular basis and otherwise be incorporated into study operations.

D. Participate actively in the study as members of the Steering Committee and other study committees.

E. Coordinate development of the study protocol by the Steering Committee.

F. Oversee development of and coordinate Field Center staff training and certification and pilot testing.

G. Oversee central administrative aspects of participant recruitment/retention and participant satisfaction assurance.

H. Monitor implementation of the study protocol by the Field Centers, Reading Centers, and laboratories, in accordance with the study timelines (Table 1 above).

I. Facilitate and coordinate the tracking of regular follow-up contact of participants

J. Facilitate and coordinate the collection of data on clinical events and classification thereof. Provide a centralized abstractor to abstract event data from medical records, death certificates, and other relevant materials received from the Field Centers.

K. Perform administrative duties to support productive collaboration among the study centers and the NHLBI Project Office.

L. Provide relevant computers, scanners, and other standardized equipment to the Field Centers for performing examinations, collecting data, and communicating data to the Coordinating Center and Reading Centers.

M. Maintain study databases.

N. Direct quality assurance and quality control programs.

O. Conduct statistical analyses for quality assurance, and scientific publications and presentations.

P. Create databases for investigators and the scientific community and support data sharing.

Q. Contribute to new scientific developments within the study and work collaboratively with all centers to support young investigators in training.

R. Direct shipment of samples to NHLBI Repository at the end of the contract period, or as directed by NHLBI.

S. Prepare and submit technical and financial reports.

V. SPECIFIC REQUIREMENTS AND TASKS

A. Designate key personnel to lead and manage the study who have the appropriate qualifications and provide other staff to support the function of the study.

1. A principal investigator with the following:
    a. Training and experience in cardiovascular epidemiology
    b. Demonstrated excellence as a manager and collaborator
    c. Experience successfully managing the coordination of multi-center cohort studies.
2. Co-investigator(s)* knowledgeable in scientific areas relevant to the study and skilled in study design and data analysis

    (* Include the designation of one co-investigator who is qualified to temporarily serve in the place of the principal investigator as needed.)

    Note: The NHLBI Project Office must approve key personnel.
3. Other staff, including but not limited to:
    a. Project directors and mangers
    b. Investigators
    c. Analysts
    d. Operations staff
    e. Events ascertainment coordinator
    f. Events abstractor
    g. Computer specialists
    h. Publications and Presentation Committee coordinator
    i. Ancillary studies manager/coordinator
    j. Website manager
    k. Secretary/administrative staff

B. Establish and manage a CT Reading Center, a Brain MRI Reading Center, an ECG Reading Center, a Pulmonary Function Reading Center, laboratories, and other consultants and subcontracts, as necessary.

1. Identify qualified sources or justify providing a contract to a previously-used source; provide Statement of Work and Deliverables; negotiate and award contracts, taking into account technical capabilities and cost; and manage contract. Coordinate with the NHLBI Project Office, as appropriate, for all phases of this work.

2. Specifically identify a CT Reading Center that will oversee the acquisition and reading of CT scans of abdomen and mid-thigh on all Year 25 Exam CARDIA participants for the evaluation of fatty liver and body composition (Required components: abdominal subcutaneous and visceral adipose and average Hounsfield units (HU); total abdominal muscle and average HU; total abdominal intramuscular adipose; thigh subcutaneous adipose and average HU; thigh intramuscular adipose and average HU; and total thigh muscle area and average HU. Optional measurements: psoas and paraspinal intramuscular adipose and average HU; and intramuscular adipose and average HU of specific muscle groups in the thigh):

   a. The tasks of the CT Reading Center shall include, but are not limited to:

      i. Coordinate, at the direction of the Steering Committee and in collaboration with the Coordinating Center, Field Centers, Imaging Committee, and other experts to be named by the Project Officer, the development of protocols for CT examinations for body composition at each Field Center and reading and information abstraction of the resulting CT scans at the Reading Center, in accordance with the study protocol. This protocol should be developed so that data from each center will be comparable with that from other centers, even accounting for variation in the CT machines between centers and over time, and should address the question of standardizing the protocol for density composition measures of muscle and adipose. The protocol should be consistent with that used in other studies that have examined abdominal and thigh composition.

      ii. Train, certify, and monitor performance of Field Center technicians according to the scanning protocol. This will include training and certification of initial and new technicians due to turnover, site visiting the four Field Centers during the first 4-6 weeks of the Year 25 exam and later as needed in support of quality control monitoring of the Coordinating Center, and orientation training to scanning protocol methods for professional staff from the Coordinating Center with quality control responsibilities.

iii. Train, monitor, and certify CT readers at the Reading Center according to the reading and information abstraction protocol. This will include initial training, certification, and orientation in the pilot testing phase and training, certification, and orientation of new readers and quality control staff due to turnover. It will also include orientation of professional staff from the Coordinating Center with quality control responsibilities.

iv. Conduct a pilot test of the CT protocols, including monitoring and evaluation for quality control, during the protocol development/pilot testing phase, in collaboration with Field Centers and the Coordinating Center.

v. Track the receipt, reading, and storage of CT scans.

vi. Perform readings and information abstractions of CT measurements, including studies from the pilot phase, the Year 25 examination period, and re-reads for quality control during the examination. Provide a radiologist to evaluate for potentially serious medical problems and to offer appropriate clinical recommendations (such as for clinical follow-up).

vii. Enter and edit results from CT measurements using software designed in cooperation with the Coordinating Center, and transmit the data to the Coordinating Center in a timely manner.

viii. Generate and provide to the Field Centers reports for prompt reporting to participants, along with appropriate clinical recommendations (such as for clinical follow-up) as needed.

ix. Participate in various other activities including participating in the Steering Committee, Imaging Committee, and other subcommittees as necessary, and participating in data analysis and preparation of reports and manuscripts using the CT data.

b. In addition to managing the CT Reading Center, the Coordinating Center's tasks include, but are not limited to:

i. Assure that the CT Reading Center has a plan to oversee training of technicians for performing abdominal and thigh CT scans. Oversee technician training; consider incorporating this training into the overall Field Center training. Assist with compilation of materials for a Manual of Operations detailing procedures relevant to the CT acquisition, quality control and analysis

ii. With the selected CT Reading Center and in collaboration with the Steering Committee and NHLBI Project Office, develop a QC system that covers the images and CT scanner, and that will ensure protocol compliance by the CT Reading Center.

iii. Assure that the CT images are sent to the CT Reading Center for detailed reading and analysis according to the protocol approved from the Steering Committee and NHLBI Project Office.

iv. In consultation with the Field Centers and the CT Reading Center, develop a graded alert system that identifies which, if any, abnormalities seen on CT will be reported to the study participants, and in what form.

v. Assure that clinical reports are appropriately generated by the CT Reading Center and provided to the Field Centers for prompt reporting to participants, along with appropriate clinical recommendations (such as for clinical follow-up).

3. Manage an MRI Reading Center that will oversee training of technicians and acquisition and reading of brain MRIs on a subset of Year 25 CARDIA participants (n=600). The MRIs from this sub-study will be used to describe the brain, including but not limited to structure, pathology, and energetics. To obtain these descriptions of the brain, selected sequences such as FLAIR, Diffusion Tensor, T1, T2* scan or MR Spectroscopy will be performed on 600 Black and White men and women who are part of the CARDIA cohort. A short battery of tests of cognitive function will be administered in conjunction with the MRI.

   a. The MRI Reading Center shall, in collaboration with the CARDIA Steering Committee, NHLBI Project Office, and other experts to be named by the Project Office, perform tasks that include, but are not limited to:

      i. Develop a protocol for the *acquisition* of brain MRI data. The protocol shall maximize the reliability of measures of anatomical and functional variables of the brain, including but not limited to regional volumes, white matter lesions, infarctions, microbleeds and glucose utilization. The protocol should be so designed as to allow comparisons with data collected in other large population based MRI series including the ACCORD-MIND trial on diabetics.

      ii. Develop a plan to oversee training of technicians for performing brain MRIs on this subset.

      iii. Develop an *analysis plan* for processing, reading, or grading the scans; interpretation of the MR images; implementation of the analysis; and data entry into a database. The protocol should have a high level of reproducibility of readings and allow for comparisons with other large

MRI population based studies. Plan for periodic blind re-readings of measurements and retraining and establish intra- and inter-rater reliability for each type of scan within 6 months of planned start of study.

iv. Track the receipt, reading, and storage of MRI scans.

v. Enter and edit results from MRI measurements using software designed in cooperation with the Coordinating Center, and transmit the data to the Coordinating Center in a timely manner.

vi. Contribute to scientific aspects of the study, including data analysis and manuscript preparation

b. In addition to managing the MRI Reading Center, the Coordinating Center's tasks shall include, but are not limited to:

i. Select from the CARDIA database a cohort of 600 subjects to be included in the MRI sub-study, with characteristics defined in consultation with NHLBI Project Office..

ii. Assure that the MRI Reading Center has a plan to oversee training of technicians for performing brain MRIs on this subset. Oversee technician training; consider incorporating this training into the overall Field Center training. Assist with compilation of materials for a Manual of Operations detailing procedures relevant to the MRI acquisition, quality control and analysis.

iii. With the selected MRI Reading Center and in collaboration with the Steering Committee, NHLBI Project Office, and other experts to be named from the Project Office develop a QC system that covers the images and MRI scanner, and that will ensure protocol compliance by the MRI Reading Center.

iv. Assure that the brain images are sent to the MRI Reading Center for detailed reading and analysis according to the protocol approved from the Steering Committee and NHLBI Project Office.

v. In consultation with the MRI Reading Center, develop a graded alert system that identifies which, if any, abnormalities seen on MRI will be reported to the study participants, and in what form.

vi. Assure that clinical reports are appropriately generated by the MRI Reading Center and provided to the Field Centers for prompt reporting to participants, along with appropriate clinical recommendations (such as for clinical follow-up).

vii. In collaboration with the Steering Committee, NHLBI Project Office, and other experts to be named by the Project Office develop a short

battery of cognitive function tests of memory, processing speed and working memory, as well as a short questionnaire of depressive symptomatology. The protocols should be so designed as to allow comparisons with data collected in other large population based studies, including the ACCORD-MIND trial on diabetics. The protocol shall include but not be limited to a plan for: training and certification over the period of the sub-study; quality control of testing booklets; scoring test results; and data entry into a database. The protocol should have a high level of reproducibility and be simple and standard enough for lay persons to administer. Propose clinical alerts for the test results and a method to disseminate the results to the participants.

4. Specifically identify an ECG Reading Center that will oversee the acquisition and reading of ECGs on all Year 25 Exam CARDIA participants, using methods that are comparable to those used in previous CARDIA exams. The tasks shall include, but are not limited to:
    a. Develop protocol for acquiring ECGs from participants at the Field Centers and transmitting them to the ECG Reading Center.
    b. Develop a training protocol for technicians from all Field Centers.
    c. Oversee training; consider incorporating this training into the overall Field Center training.
    d. Participate in a pilot test of the ECG protocol during the study's pilot-testing phase, in collaboration with the Field Centers and Coordinating Center
    e. Develop and implement a quality control program, including certifying and monitoring performances of Field Center technicians according to the ECG acquisition protocol.
    f. Oversee acquisition and the reading of ECGs to obtain the following measures:
        i. ECG abnormalities related to ischemia, left ventricular hypertrophy, left atrial enlargement, arrhythmias (particularly atrial fibrillation), and conduction abnormalities
        ii. Heart rate variability
    g. Provide physician(s) to evaluate for potentially serious abnormal ECG findings and to offer appropriate clinical recommendations (such as clinical follow-up).
    h. Track the receipt, reading, and storage of ECGs.
    i. Enter and edit results from ECGs using software designed in cooperation with the Coordinating Center, and transmit the data to the Coordinating Center in a timely manner.

j. Generate and provide to the Field Centers reports for prompt reporting to participants, along with appropriate clinical recommendations (such as for clinical follow-up) as needed.

k. Contribute to scientific aspects of the study, including data analysis and manuscript preparation

5. Specifically identify a Pulmonary Function Reading Center that will oversee the acquisition and reading of pulmonary function tests on all Year 25 Exam CARDIA participants, using methods that are comparable to those used in the CARDIA Year 20 Exam. The tasks shall include, but are not limited to:

   a. Develop protocol for acquiring pulmonary function testing from participants and transmitting the data to the Pulmonary Function Reading Center. If bronchodilator challenge is proposed as an addition to the testing, justification should be provided.

   b. Develop training protocol for technicians from all Field Centers.

   c. Oversee training, including the incorporation of this training into the overall Field Center training.

   d. Develop and implement a quality control program.

   e. Participate in a pilot test of the pulmonary function protocol during the study's pilot-testing phase, in collaboration with the Field Centers and Coordinating Center

   f. Provide physician(s) to establish criteria for abnormal findings and to offer appropriate clinical recommendations (such as clinical follow-up).

   g. Track the receipt, reading, and storage of pulmonary function testing data.

   h. Ensure transmission of pulmonary function data from the Reading Center to the Coordinating Center in a timely manner.

   i. Contribute to scientific aspects of the study, including data analysis and manuscript preparation

6. Identify and manage the Central Blood and Urine Repository, the DNA Laboratory, and all other laboratories for laboratory measures and specimens to be collected in the CARDIA Year 25 Exam (See Section I.D. for list of laboratory measurements). The tasks shall include, but are not limited to:

   a. The laboratories shall develop and perform laboratory analyses of blood, urine, and DNA samples collected.

      i. In collaboration with the Steering Committee, Laboratory Committee, and NHLBI Project Office develop protocols for the Year 25 Exam laboratory components.

ii. For all laboratory measures that have been previously collected in CARDIA, use comparable methods unless otherwise justified.

iii. Include quality control measures to assure accuracy of measurements over time. Monitor and report quality control measurements at least biannually. Investigate and act to correct apparent errors in measurements.

iv. For planning purposes, estimate 5% repeat measurements and samples for quality control of assays.

v. Participate in comparability studies as deemed appropriate and necessary by the Steering Committee.

vi. As requested by the Coordinating Center, contribute to the training and certification of Field Center laboratory technicians.

vii. Participate in a pilot study that will include receipt of a specified number of specimens from the Field Centers to test the Year 25 exam protocol for collecting and shipping samples. The samples must be analyzed and the results sent to the Coordinating Center no later than 14 days after receipt of Field Center's specimens.

viii. Assist Field Centers in establishing alert values as appropriate.

ix. Assist Field Centers in reporting clinical values to participants in a timely manner.

x. Contribute to scientific aspects of the study, including data analysis and manuscript preparation.

b. The DNA Laboratory shall also maintain a repository of extracted DNA and blood cells from which DNA may be extracted; create standard dilutions of DNA; and retrieve, aliquot, and distribute selected DNA specimens to qualified investigators, under the direction of the Coordinating Center.

c. The Central Blood and Urine Repository shall maintain a repository of blood and urine specimens; and retrieve, aliquot, and distribute selected specimens to qualified investigators, under the direction of the Coordinating Center.

7. As necessary and as directed by the Project Office, provide consultant agreements or subcontracts for analyses using previously-collected data and any data collected subsequently, and other areas where specific expertise is needed.

C. Coordinate development of the study protocol by the Steering Committee.

1. Facilitate and coordinate development of the study protocols and Manuals of Operation for the following:

a. Field Centers operations
    i. Assure that guidelines and protocols are in place to promptly identify and refer clinically significant findings from the examinations for routine reports and recommendations to participants.
    ii. See Table 2 (under Section I.C.) above for list of examination components.
b. Reading Centers
c. Laboratory Centers
d. Quality Control
e. Events
f. Data Analysis
    i. Develop data documentation and manuals.
    ii. Provide guidance for data analysis, including handling unusual features of the dataset and recommending analysis methods.

2. Develop and finalize protocols.
    a. Circulate protocols to Steering Committee and NHLBI Project Office for review and develop Manuals of Operations.
    b. Finalize protocols and Manuals and post to web site.
    c. Periodically update protocols and Manuals as needed.

D. Oversee development of and coordinate Field Center staff training and certification and pilot testing.
    1. Make arrangements for central training of staff from all Field Centers approximately six weeks prior to the start of the Year 25 Exam. Plan for staff persons to attend from each Field Center, plus trainers and experts in the various components.
    2. Develop a program to certify technicians and maintain certification to assure high quality and standardized measurements across the Field Centers.
    3. Oversee pilot testing, analysis and review of the pilot results with the Steering Committee. Pilot testing is to be conducted after training is complete, and is to consist of performing the examination, according to the draft Manual of Operations, in at least 9 volunteers per Field Center, who are not study participants. The pilot tests are to include shipping blood samples to the appropriate laboratories and transmission of images and other data from the appropriate reading centers.

4. Oversee implementation of improvements in protocols and manuals based on the pilot study results.
5. Update staff on protocol changes.

E. Monitor implementation of the study protocol by the Field Centers, Reading Centers, and Laboratories, in accordance with the study timelines (Table 1 above),

1. Support the functions of the Steering Committee in all aspects of protocol implementation and scientific and operational management of the study.
2. In conjunction with the Steering Committee and Field Centers, develop and, to the extent possible, standardize methods of participant recruitment and retention across Field Centers.
3. Develop and implement a web-based tracking system for use by the Field Centers, to monitor number of contacts and outcomes of contacts.
4. Update the data collection and entry systems to allow Field Center staff to perform computer-assisted data entry and initial verification and correction of the entered data.
    a. Finalize data collection forms and distribute forms and software to the Field Centers to reproduce study forms. The forms should be developed in such a way as to facilitate Field Center staff to perform computer-assisted data entry and the initial verification and correction of the entered data.
    b. Provide software to the Field Centers for electronically entering medication data against a computerized database of medications.
5. Oversee data collection for the Year 25 Exam
    a. Monitor timeliness, completeness, and quality of all data collected.
    b. Report periodically to the NHLBI Project Office and Steering Committee and/or post results at least every two weeks on the web site.
    c. Report at least every two weeks to sites and centers on overdue, missing, or out-of-range data or other data irregularities.
    d. Provide weekly recruitment reports for the exam by center, race, and gender group (June 6, 2010 and weekly until 1 week after Year 25 exam ends), including number examined for each week, cumulative number examined, average number examined per week, number needed to reach target, and percent of target examined.
6. Prepare for use by the Field Centers reports on clinical information for participants and their physicians. Coordinate the efforts to ensure the reports are distributed in a timely matter (Note: Non-urgent findings from examinations should be reported within 4 weeks of examination. Urgent findings must be reported the same day or as clinically relevant and feasible.)

F. Facilitate and coordinate periodic follow-up contact of participants per protocol developed by the Steering Committee. Manage the data collected on clinical events and the classification of these events.

1. Coordinate Field Center follow-up contact of participants according to protocol.
2. Monitor data collection including timelines of collection and receipt of all reports, including final completed investigations. Notify Field Centers when reports are overdue.
3. Coordinate the activities of the Morbidity and Mortality Committee, which will be comprised of representatives from the Coordinating Center and Field Centers knowledgeable about nosology and clinical assessment of cardiovascular and related diseases.
4. In conjunction with the Morbidity and Mortality Committee, maintain standardized procedures to identify and classify morbid cardiovascular events (including myocardial infarction and other forms of coronary heart disease, stroke, heart failure, and atrial fibrillation), cardiovascular interventions, and all mortal events. Assure standardization of methodology and consistency of procedures over time with appropriate quality assurance activities.
5. Refine as needed, maintain, and oversee implementation of the protocol and Manual of Operations for Morbidity and Mortality Follow-up and Events investigations and reporting. The refinement shall include the addition of standardized procedures and forms for data abstraction by a centralized abstractor. Refinements should to the extent possible be comparable to other NHLBI-sponsored large cohort studies such as the Multi-Ethnic Study of Atherosclerosis (MESA).
6. Provide Coordinating Center staff to serve as centralized data abstractor(s) of medical records, death certificates, and other relevant materials received from the Field Centers.
7. Create and post on the CARDIA internal web site regular reports on the status of events investigations and the outcomes of final adjudicated events that have accrued in the study.

G. Perform administrative duties to support productive collaboration among the study centers and the NHLBI Project Office.

1. Facilitate meetings and communications among all Centers, subcontractors, and the NHLBI Project Office as necessary throughout the contract period.
2. Contribute leadership and membership as needed, as well as coordinate activities of the following committees: Steering Committee, Executive Committee, Morbidity and Mortality Committee, Laboratory Committee, Imaging Committee, Quality Control

Committee, Publications and Presentations Committee, Clinic Coordination and Retention Committee, Genetics Committee, Pulmonary Function Committee, and other subcommittees, as appropriate.

3. Update and document policies and procedures for all committees, as necessary.
4. Update Ancillary Studies procedures to be consistent with NIH data sharing policies, including the Limited Access Data Set policy (http://www.nhlbi.nih.gov/resources/deca/policy_new.htm) and other data sharing policies, such as for genome-wide association studies (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-094.html)
5. Facilitate communications among the subcommittees and the Steering Committee by organizing regular conference calls, maintaining web site communications, and otherwise facilitating dissemination of material and information among committee members. Incorporate subcommittee recommendations approved by the Steering Committee into study policies and Manuals of Operations.
6. For conference calls, distribute meeting materials and the agenda at least three working days prior to meetings, and record and distribute minutes within 5 working days.
7. Make arrangements for and convene regular (biannual) in-person meetings for the Steering Committee. Distribute meeting materials and the agenda two weeks prior to in-person meetings. Record and distribute minutes from in-person meetings to the Project Office within 10 working days.
8. Make arrangements for and convene regular in-person meetings (generally at the time and location of the Steering Committee meetings) and conference calls for the subcommittees, as necessary and proposed by the subcommittee chairs.
9. Arrange for and manage annual meetings of the CARDIA Observational Studies Monitoring Board (OSMB) as directed by the NHLBI Project Office; distribute meeting materials at least three weeks prior to meetings; make travel and meeting arrangements for OSMB members; and provide expense reimbursement to OSMB members.
10. Coordinate the Executive Committee review and approval process of ancillary study proposals. Specific tasks include, but are not limited to:
    a. Submit proposals approved by the Executive Committee to the OSMB Executive Secretary for OSMB review
    b. Generate Executive Committee approval letters for ancillary studies (within 1 week of approval)
    c. Maintain a log of all ancillary studies proposed, approved, or funded.
11. Utilizing state-of-the-art web design and content by employing appropriate expertise in this field, modify and maintain CARDIA web sites, including an external site for the

public and an internal site for study investigators and others, as necessary. The sites should contain, but not be limited to, the following:

a. Study description and timeline
b. Directory of investigators
c. Description of subcommittees
d. Manuals of Operations
e. Study Protocol and forms
f. Description and guidance for preparation and review of ancillary study proposals
g. Log of ancillary studies proposed, approved, ongoing, and completed
h. Newsworthy articles
i. Publications materials, including Abstracts and Published papers (or PubMed link to the paper), and papers in progress.
j. Guidance for preparation, submission, and review of paper proposals
k. Lists of Reading and Laboratory Centers and the NHLBI Project Office
l. Lists of examination components

12. Assist the NHLBI Project Office with development of the package for clearance by the Office of Management and Budget (OMB). The package should cover pilot testing and be submitted to OMB by October 1, 2009.

    Note: It is possible that the Clinical Exemption under which the study currently operates will remain in effect during the renewal but this is not guaranteed.

13. Provide continuously updated status of blood, urine, and DNA specimen repositories, as well as provide a summary report table annually for inclusion in the OSMB report.

14. Oversee development and implementation of standardized informed consents.

    a. In conjunction with the Steering Committee, coordinate development of standardized informed consent among the Field Centers.
    b. Assure inclusion of all required elements.
    c. Maintain a database on informed consent versions and participant responses, covering Exams from Years 0 to 25.
    d. Assure that samples and data bases are distributed in accordance with the expressed desires of participants in their signed informed consents.
    e. Post results of informed consent responses such that interested investigators may determine the availability of samples with appropriate consent.

Note: CARDIA has a Certificate of Confidentiality for DHHS Funded Studies that should be noted in the informed consent forms.

H. Provide relevant computers, scanners, and other standardized equipment to the Field Centers for performing examinations, collecting data, and communicating data to the Coordinating Center and Reading Centers.

1. Investigate, purchase, distribute, and coordinate utilization of appropriate common computer and other equipment among all centers, as relevant.
2. Coordinate utilization and upgrades, as necessary.

I. Maintain study databases.

1. Prepare data sets of examination results within 4 months of the end of Year 25 Exam.
2. Maintain updated Morbidity and Mortality events data on a monthly basis.
3. Prepare documentation for distribution to investigators and the NHLBI Project Office and outside collaborations, per NIH data sharing policies and with appropriate protections for participant privacy and assuring that only qualified investigators have access. (Procedures for gaining access to the data by investigators will generally be through the manuscript proposal procedures or through an NHLBI-administered program.)
4. Provide data documentation to eligible users upon request
5. Provide updates with corrections to or clarifications of the database as necessary and maintain a record of these corrections or clarifications for future use.
6. Include data from examinations, interviews, follow-up data, imaging measurements and results, and laboratory measurements, morbidity and mortality data, and from all substudies and ancillary studies. (Note: Ancillary studies should provide data within 12 months of completion of data collection and editing.)
7. Maintain data on quality control measurements.
8. Provide to NHLBI Project Office raw data without individual identifiers whenever difficulties arise with the database, or on request.

J. Direct quality control and quality assurance programs

1. The Quality Control Committee shall be chaired or co-chaired by a staff member from the Coordinating Center.
2. In conjunction with the Quality Control Committee and relevant subject matter experts within CARDIA:
    a. Prepare a plan to monitor the quality of all data in a timely manner.

b. Include all questionnaire, interview, morbidity and mortality follow-up, laboratory, and imaging measures.

c. Generate monthly quality control reports for examination and interview data, including a data completeness report (i.e., data received at the Coordinating Center matches those sent by a Field or Reading Center and all data received at a Reading Center matches those sent by a Field Center).

d. Generate monthly quality assurance reports for technician certification and equipment calibration.

e. Develop and oversee implementation of recommendations to correct errors in a timely manner.

f. Where warranted, provide for approximately 5% blind duplicate measurements within an examination cycle (e.g., certain biochemical laboratory-based and imaging measures).

g. Include assessment and control of measurement temporal drift within and between examination cycles for each laboratory and reading center measurement, as feasible and necessary.

h. Include assessment of stability of stored laboratory specimens.

i. Assess on an ongoing basis and provide annual reports to the Steering Committee and to the OSMB including a review of collected data. Verify completeness, timeliness, reliability, and accuracy of collection and coding. Include comparisons of measures of distribution of values between the Field Centers and/or technicians/instruments as appropriate to the measurement method. Include development and modification of standards to identify outlying values, and initiate and coordinate separate review of these observations for accuracy with the appropriate Field, Reading, and Laboratory Center.

j. When necessary, appropriate, and feasible, develop and implement plans for comparability studies when technologies or assays have changed over time or differ across centers.

k. Maintain logs of data received, edit checks conducted, and identified errors; pursue missing data and correctable errors by communication with Field, Reading, and Laboratory Centers within three weeks of receipt and review of data; and develop, maintain, and modify an audit trail for all data entry and data correction activities, including electronically transferred data.

l. Monitor scheduled maintenance of equipment at Field Centers in collaboration with appropriate Reading Centers and Central Laboratory.

m. Establish QC activities for scanned data.

n. Coordinate initial certification and maintain ongoing retraining and recertification of performance capabilities of Field Center staff and Reading Center staff through centralized and localized training appropriate to the Center.

o. Coordinate and participate in periodic site visits to the collaborating centers as needed. (Plan to visit to each Field Center and Reading Center and, if necessary, Laboratories in first 2 months of the Year 25 Exam).

K. Conduct statistical analyses for quality assurance and scientific publications and presentations.

1. Perform centralized data analyses.
2. Support, via consultation, collaborating Centers in local analyses.
3. Develop statistical methods, as needed, to analyze new types of data.
4. Review analyses performed outside of the Coordinating Center for appropriateness.
5. Maintain a list and insofar as possible, repository of public presentations made using CARDIA data by the investigators.
6. Generate periodic reports on the status of publications and presentations, at least biannually for the Steering Committee and OSMB.
7. Maintain a database on paper proposals and manuscripts in progress.
8. Analyze data in a timely fashion for the presentation and publication of study results.
9. Provide statistical support for development and analysis of all quality assurance activities.
10. Provide timely responses to specific requests from the Project Office, Steering Committee, and OSMB.

L. Create databases for investigators and the scientific community and support data sharing, consistent with NIH policy, which may be found at http://www.nhlbi.nih.gov/resources/deca/policy_new.htm. (For policies on sharing genome-wide association data see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-094.html).

1. Limited access data will be released under this study. Limited access data refers to study data, with certain deletions and recoding, that are released to requesting institutions and investigators for specific purposes and with certain restrictions and conditions. Limited access data will be made available to the public in accordance with the NHLBI Policy for Distribution of Data (http://www.nhlbi.nih.gov/resources/deca/policy_new.htm) as revised on June 27, 2005. All changes to the policy are hereby incorporated by reference without further amendment to the contract.

a. For the Year 20 Exam: Limited access data sets shall be released by September 1, 2011 and annual updates containing additional data such as genotyping, morbidity, and mortality (each September 1 after data collection ends)

b. For the Year 25 Exam: Consistent with NIH policy or three years after the completion of the Year 25 Exam (whichever comes first) and annually, with updated events data, create limited access data sets with documentation.

c. Include all ancillary study data in the limited access data sets

Note: The limited access data sets will contain all the data deriving from an examination cycle or data collection activity, but may exclude raw data that is used solely for the purpose of creating summary or derived variables. It should exclude individual identifiers but include detailed documentation appropriate for independent use by an investigator external to the study and unfamiliar with details of the data. Participant privacy must also be assured by removing or modifying variables that could lead to individual identification.

Data will not be released if believed to be unreliable or invalid by the NHLBI Project Office. Delays in data release must be approved by the NHLBI Project Office.

2. Working with the NHLBI Project Office, publicize the existence of CARDIA data sets for use by qualified scientists outside of the CARDIA investigators.

M. In conjunction with the Publications and Presentations Committee,

1. Coordinate the proposal, development, and prioritization of study manuscripts, and monitor progress in completing manuscripts,

2. Coordinate the submission of CARDIA abstracts and manuscripts to NHLBI for review. Specifically, the Coordinating Center shall submit the abstracts and manuscripts to NHLBI on behalf of the authors and inform the authors of the outcome of the review.

   Note: Per current NHLBI policy, NHLBI reviews are required for CARDIA abstracts and papers before the authors may submit them to scientific meetings or journals.

3. Maintain an archive of proposed manuscripts, manuscript drafts, completed manuscripts and abstracts in print, in press, and in preparation, and

4. Supply reprints of published manuscripts upon request.

5. Oversee investigator utilization of Data Distribution Agreements, and track and manage files thereof.

N. Contribute to new scientific developments within the study and work collaboratively with all centers to support young investigators in training.

1. In collaboration with the other centers, or within the Coordinating Center, propose new ideas for analyses, testing, and scientific directions.
2. Propose new collaborations to achieve the goal of advancing new scientific objectives.
3. Support training of and providing experience for young investigators.
    a. Both at the Coordinating Center and at collaboration centers, provide assistance to develop new research projects
    b. Encourage young investigators to apply for programs to bring support for training
    c. Provide guidance in accessing the data set, proposing manuscripts, analyzing data, interpreting findings, preparing manuscripts, identifying next steps for research, and proposing ancillary studies

O. At the end of the contract period (Plan for last 6 months of contract period)

1. Direct and oversee shipment of biological samples to NHLBI Repository and/or other repositories as directed by NHLBI
2. Propose a plan, in collaboration with Steering Committee, for the long-term storage of archived images such as CT and MRI scans, ECGs, and spirograms

P. Prepare and submit technical and financial reports, including the following:

1. Quarterly progress reports that include descriptive information about the activities undertaken during the reporting period and those planned for future reporting periods. The Contractor shall report on:
    e. Main operational activities
    f. Problems encountered and how they were resolved
    g. An accounting of personnel, including levels of effort and changes during the period
    h. Progress report on the support of young investigators
    i. Modifications to any subcontracts
    j. Scientific productivity (note: during the period June 1, 2010 through September 30, 2013, also provide progress on abstracts and papers generated that pertains to each of the Year 25 scientific objectives)
2. Semi-annual status report on CARDIA abstracts and papers the Coordinating Center submitted to NHLBI for review. The report shall include, at a minimum:

a. Date of receipt of the abstract/paper by the Coordinating Center
b. Date of submission to NHLBI
c. Title and authors of the abstract/paper
d. Date on which the Coordinating Center notifies the first author the results of NHLBI's review

3. Semi-annual status reports on Data and Materials Distribution Agreements that contain at minimum the following:
   a. Date of request
   b. Title of project
   c. Names of investigator and Institution
   d. For materials, the amount requested, including type and number of samples
   e. Date of Executive Committee approval (for materials) or Publication Committee approval (for data)
   f. Date materials are delivered to investigator(s), including amount of material and number of samples delivered and a return date of DNA/specimen if applicable.
4. Quarterly financial reports, as required by NIH.
5. A final report, due September 30, 2013, documenting and summarizing the results of the entire contract work, including salient results, recommendations and conclusions based on both the general experience and the individual viewpoint of the Coordinating Center.

END OF CARDIA COORDINATING CENTER'S STATEMENT OF WORK

Attachment 1.b.: STATEMENT OF WORK - FIELD CENTERS

III. BACKGROUND

The Coronary Artery Risk Development in Young Adults (CARDIA) Study started as a study of the distribution and evolution of risk factors for cardiovascular disease during young adulthood in black and white men and women. At Year 25 participants will be 43-55 years old, when risk factors and subclinical abnormalities become more prevalent and clinical events begin to emerge. CARDIA offers the opportunity to address aspects of the development and progression of subclinical vascular, ventricular, and pulmonary function abnormalities that cannot be addressed in older cohorts.

The study, which began recruitment in 1985, has completed 7 examinations over 20 years in a cohort of 5,115 men and women aged 18-30 years in four communities. Participants were initially sampled from the total population, selected census tracts or, in the case of one Center, the membership of a large health plan. The original cohort had approximately equal representation by blacks and whites, men and women, those aged 18-24 and 25-30, and those with no more than a high school education and more than a high school education. The baseline examination (Year 0) was conducted over a 14-month period during 1985-86. The examination consisted of questionnaires on sociodemographic characteristics, health behaviors, and psychological factors; an exercise treadmill test; resting electrocardiography; a diet history assessment; anthropometry; pulmonary function testing; and resting blood pressure. Fasting blood measurements included total cholesterol and its subfractions, insulin, glucose, liver enzymes and other serum chemistry measurements, and hematology.

Six additional examinations have been completed every 2-5 years, including a Year 20 examination completed in 2006. Repeat measurements on traditional risk factors, including plasma lipids, blood pressure, anthropometry, smoking behavior, physical activity, and pulmonary function testing (except Years 7 and 15) have used the same methods at each examination to assess age and secular trends in these factors during young adulthood. In selected years, additional measurements have been made, including a treadmill exercise test at baseline and Year 7; diet history at baseline, Year 7, and Year 20; cardiovascular reactivity measurements in Year 2; echocardiography and ambulatory blood pressure monitoring (in a subset) at Year 5; skin reflectance and assessment of the experience of discrimination and other psychosocial measures and urine sodium and creatinine in Year 7; echocardiography (in a subset) in Year 10, glucose tolerance testing, and microalbuminuria in Year 10 and Year 20; coronary CT scan in Year 15 and Year 20; and carotid intima media thickness in Year 20.

Retention of the surviving cohort was 90, 86, 81, 79, 74, and 72 percent at each of the respective follow-up examinations. Cohort members are contacted every six months to obtain information on vital status and current residence. Every other six-month contact also includes speaking with the participant to ascertain information on current smoking status, major illness or injury, and hospitalizations.

CARDIA ECHOCARDIOGRAPHY READING CENTER

A. Scientific Objectives

This renewal will fund continued follow-up and examination of the CARDIA study to address the following five objectives:

11. Assess the impact of timing and varying levels of risk factors throughout young adulthood on the development of subclinical ventricular, vascular, and pulmonary function abnormalities in mid-life

    CARDIA will study the impact of traditional and novel risk factors acquired throughout young adulthood on the development of subclinical abnormalities in mid-life. Predictors of changes in left ventricular structure and function (measured by echocardiography) will be examined. Several subclinical vascular abnormalities will be identified, including early cerebral vascular abnormalities (manifested by cognitive decline and white matter disease), lower extremity arterial perfusion (measured by ankle-brachial index), arterial stiffness (measured by pulse wave velocity), and microalbuminuria. Changes in pulmonary function from young adulthood to mid-life will also be characterized.

12. Examine young adult antecedents and consequences of obesity and the longitudinal relationships and interactions among adiposity, insulin resistance, and inflammation

    CARDIA will study the genetic, biological, behavioral, and psychosocial factors that predict obesity, as well as the impact of obesity on the development of subclinical and early clinical abnormalities. The differential associations between visceral, subcutaneous, and intermuscular fat on insulin resistance and inflammation will also be examined.

13. Identify determinants and trajectories of subclinical disease development in women during menopause transition compared to men of similar age

    CARDIA will study subclinical disease development in the context of menopause transition. Changes in menstrual patterns over time will be evaluated for associations with increasing risk factor incidence and subclinical disease. The determinants and trajectories of subclinical disease development in women during menopause transition will be compared to men of similar age, as will comparisons between pre- and post-menopausal women of similar age.

14. Further assess the basis for racial differences in subclinical disease development

    CARDIA will assess the basis for differences between blacks and whites in the development of subclinical ventricular, vascular, and pulmonary function abnormalities. Racial differences in predictors and their varying consequences on the development of subclinical abnormalities will be explored.

15. Provide a platform for in-depth ancillary studies in cardiovascular and other areas

CARDIA will continue to replenish and further enrich its rich repository of data and specimens to allow additional in-depth ancillary studies on how changes that occur in young adulthood contribute to the development of cardiovascular and other abnormalities in mid-life, and how these changes differ by race, sex, and other factors.

The final protocol (including any additional scientific objectives and measurements) will be developed by the CARDIA investigators in collaboration with the NHLBI Project Office, and will be reviewed and approved by NHLBI in consultation with the existing CARDIA Observational Studies Monitoring Board (OSMB).

The study will support in-depth ancillary studies that are funded outside of the current contract. These studies will be operationally integrated into the main study, and the data will be shared across both types of studies, per current CARDIA and NIH data-sharing policies. The study's data will be provided to interested investigators through a defined process that encourages maximum data utilization but that protects participant confidentiality.

The study will also continue to serve as a training ground for junior investigators, who will work with senior investigators and be provided with guidance on conducting research.

B. Study Operations

All surviving and willing members of the CARDIA cohort will be followed up and included in the Year 25 Exam during 2010-2011 (approximately 12 months in duration). It is estimated that approximately 3600 participants will be examined. Participants will be contacted every 6 months to ascertain vital status and change in address; every other 6-month contact includes speaking with the participant to characterize new clinical events and other changes in health status.

A timeline for the study is provided in Table 1. A list of exam components is provided in Table 2.

Collaborating centers will include the four current Field Centers, a Coordinating Center, and an Echocardiography Reading Center. The Coordinating Center will establish Reading Centers for Electrocardiogram (ECG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Pulmonary Function , and laboratories. Principal Investigators from each of these 6 collaborating centers plus any relevant large subcontracts as determined by the NHLBI Project Office, and the NHLBI Project Officer form the CARDIA Steering Committee. The chairman of the Steering Committee serves through a subcontract with the Coordinating Center.

Data analysis, publications, and cohort follow-up for morbidity and mortality will occur throughout the contract period. The total contract period is 5 years.

Table 1. Timeline for CARDIA Year 25 Exam

Activity	Time period
Protocol development	October 1, 2008 – March 15, 2010 (16 months)
OMB clearance package preparation	June 1, 2009 – October 1, 2009 (4 months)
Protocol review by NHLBI And CARDIA OSMB	March 15, 2010 – April 1, 2010 (3 weeks)
Staff training	April 15, 2010 – May 1, 2010 (2 weeks)
Pilot testing	May 3, 2010 – May 10, 2010 (1 week)
Year 25 Exam	June 1, 2010 – May 31, 2011 (12 months)
Follow-up of cohort for morbidity and mortality	October 1, 2008 – September 30, 2013 (60 months)
Close-out	October 1, 2012 – September 30, 2013 (12 months)

Note: It is possible that the OMB Clinical Exemption under which the study currently operates will remain in effect during the renewal but this is not guaranteed.

Note: Timeline is accurate to within 2 months.

C. Examination Components

Data to be collected are approximated by the following list of components, which may be modified during protocol development. Unless there is a strong rationale, procedures should be similar to those used for previous data collections in CARDIA. The final protocol as approved by the NHLBI in consultation with the OSMB shall constitute the final content and schedule of the data to be collected.

Table 2. List of Year 25 Exam components

- Consent
- Demographic information
- Anthropometry
- Blood pressure
- Smoking history
- Medical history, including medications
- Cognitive assessment,
- Questionnaires, including perimenopause, behavioral factors related to weight gain and weight loss, and physical activity
- Fasting phlebotomy for whole blood, serum, plasma, and DNA collection
- 2-hour oral glucose tolerance test
- Spot urine collection for albumin and creatinine
- Pulmonary function
- Ankle-brachial index
- Peripheral pulse wave velocity
- Electrocardiogram
- 2-D echocardiography
- CT of the abdomen and mid-thigh for fatty liver and body composition
- Brain MRI (in a subset)

D. Laboratory Measures

The following specific types or classes of measurements will be made. The final protocol for lab measurements will be determined by the Steering Committee. The Laboratory Committee will coordinate proposals and incorporation of new assays over time, based on scientific priorities and costs.

1. Established clinical measures of metabolism, renal function, and lipid metabolism, including glucose, insulin, HbA1c, 2-hour oral glucose tolerance test, creatinine, cystatin C, and a lipoprotein panel.
2. Biomarkers that are putative risk factors for cardiovascular and pulmonary disease measured from blood samples, including but not necessarily limited to measures related with adiposity and markers of immune and inflammatory response.
3. Urine creatinine and albumin.
4. Other measures that will further understanding of the development of atherosclerosis and other forms of cardiovascular disease, and other related conditions.
5. Collection and storage of DNA, serum, plasma, and urine.

E. Event Ascertainment

Follow-up will be performed for morbidity (acute myocardial infarction, angina, stroke, heart failure, atrial fibrillation; peripheral vascular disease; chronic obstructive pulmonary disease); mortality; and any cardiovascular disease interventions received. In addition, all hospitalizations will be identified and data collected on discharge diagnoses. All participants, including those who have refused participation and unequivocally expressed the desire not to be re-contacted, will be followed through the Social Security Death Index and other commercial databases as appropriate.

Table 3. Types of data to be collected for event ascertainment

Dates of deaths and hospitalizations
Interview data from participants
Hospital discharge diagnosis and ICD codes
Data collected from hospital inpatient and outpatient records

New to this renewal will be the addition of centralized data abstractor(s) from the Coordinating Center. The CARDIA protocol and Manual of Operations for event ascertainment shall be refined to include standardized procedures and forms for data abstraction by the abstractor(s).

Events will be classified in a standard manner and consistent with current CARDIA practice, as developed by the Morbidity and Mortality Committee. Refinements to the protocol and Manual of Operations for event ascertainment should to the extent possible be comparable to other NHLBI-sponsored large cohort studies such as the Multi-Ethnic Study of Atherosclerosis (MESA).

F. Mentoring Junior Investigators

Each Field Center will provide formal and/or informal training opportunities for junior or inexperienced investigators (assistant professors, fellows, and students). This includes but is not limited to the junior investigator working on data analyses and publications and serving on study subcommittees. Sites are encouraged to apply for supplements from existing NIH programs or include CARDIA experiences in existing training programs.

IV. GENERAL REQUIREMENTS AND TASKS

Note: Throughout this statement of work, the terms "Contractor" and "Field Center" are used interchangeably.

Throughout the period of performance, the Contractor shall provide appropriate personnel with expertise in cardiovascular epidemiology, clinical and subclinical cardiovascular disease,

echocardiography, neurovascular imaging, body composition, obesity, pulmonology, genetics, laboratory measurements, statistics, longitudinal studies, clinic operations, clinical events follow-up, and management to:

A. Participate in and designate staff to lead the study and participate in committees, such as the Steering Committee, Morbidity and Mortality Committee, Laboratory Committee, Imaging Committee, Quality Control Committee, Publications Committee, Pulmonary Function Committee, Clinic Coordination and Retention Committee, and other subcommittees, as appropriate.
B. Recruit and re-examine the local established CARDIA cohort for CARDIA Year 25 Exam.
C. Conduct surveillance of the cohort for clinical events.
D. Provide junior investigators with experience and responsibilities for specific scientific and study management areas and data analysis and publication.
E. Participate actively in data analysis, presentation, and publication.
F. Prepare and submit technical and financial reports as specified herein.

V. SPECIFIC REQUIREMENTS AND TASKS, IN PHASES

Note: Throughout this statement of work, the terms "Contractor" and "Field Center" are used interchangeably to facilitate description of the tasks to be performed.

E. During the entire contract period, the Contractor shall:

3. Designate key personnel to lead and manage the study who have the appropriate qualifications.
    a. A principal investigator with the following:
        i. Training and experience in cardiovascular epidemiology
        ii. Demonstrated excellence as a manager and collaborator
        iii. Experience successfully recruiting participants into an epidemiology study
    b. Co-investigator(s)* knowledgeable in scientific areas relevant to the study and skilled in study design and data analysis
    (*Include the designation of one co-investigator who is qualified to temporarily serve in the place of the principal investigator as needed.)

    Note: The NHLBI Project Office must approve key personnel.

4. Provide other staff as follows:
    a. Investigators
    b. Data analysts
    c. Clinic operations staff, including a manager/coordinator, recruiters, technicians and interviewers

d. Surveillance, follow-up contacts investigations staff
e. Data management staff

5. Participate in and designate staff to participate in the Steering Committee and other committees, as appropriate. Subcommittees include, but are not limited to:
   a. Genetics Committee
   b. Clinic Coordination and Retention Committee
   c. Quality Control Committee
   d. Laboratory Committee
   e. Imaging Committee
   f. Morbidity and Mortality Committee
   g. Publications and Presentations Committee
   h. Pulmonary Function Committee

   Note: The final composition of subcommittees will be determined during protocol development.

6. Conduct surveillance of the cohort for clinical events, collecting information as specified in the Manual of Operations.

   a. Information to be collected includes: occurrence of cardiovascular events, other significant illnesses and hospitalizations, including information from participants, hospital records, and death certificates, and according to a standard protocol developed by the Morbidity and Mortality Committee and approved by the Steering Committee.
   b. As part of the Morbidity and Mortality Committee, participate in classification of type and severity of cardiovascular events.
   c. Perform biennial Social Security Death Index searches on participants lost to follow-up.
   d. Perform and/or coordinate other searches using commercial databases to find participants who are lost to follow-up.

7. Analyze and publish data from the study.
   a. Perform data analysis, write and present abstracts, and write and publish manuscripts based on CARDIA data.
   b. Submit at least three (3) manuscripts for publication in each year of the contract with an investigator from the site as the first author.
   c. Submit abstracts and manuscripts proposed for presentation or publication to the Publications and Presentations Committee, per study policy, and through the CARDIA Coordinating Center to NHLBI for review prior to submitting to scientific meetings or journals.
   d. Provide publications and presentations emanating from the Field Center in a timely manner, for a data base to be managed by the Coordinating Center.

8. Provide junior investigators with experience and responsibilities for specific scientific and study management areas and data analysis and publication. Contribute to new scientific developments within the study and work collaboratively with all centers to support young investigators in training.
    a. In collaboration with the other centers, or within the Coordinating Center, propose new ideas for analyses, testing, and scientific directions.
    b. Propose new collaborations to achieve the goal of advancing new scientific objectives.
    c. Support training of and providing experience for young investigators.
        i. Both at the Field Center and at collaboration centers, provide assistance to develop new research projects
        ii. Encourage young investigators to apply for programs to bring support for training.
        iii. Provide informal training experiences.
        iv. Provide guidance in accessing the data set, proposing manuscripts, analyzing data, interpreting findings, preparing manuscripts, identifying next steps for research, and proposing ancillary studies.

9. Prepare and submit technical and financial reports, including the following:
    a. Semi-annual progress reports that describe main operational activities during the period, problems encountered and how they were resolved, an accounting of personnel, including levels of effort and changes during the period, and scientific productivity.
    b. Periodic financial reports, as required by NIH, specific to your institution.

F. During the period October 1, 2008 through May 10, 2010, the Contractor shall:

1. Participate in the study protocol development of the Year 25 Exam and pilot testing for all examination components.
2. Assist the Coordinating Center as necessary in identifying and establishing reading centers for imaging, pulmonary function testing, and laboratories.
3. Identifying and establishing agreements with local imaging centers to use their scanners and technicians for the acquisition of Year 25 imaging scans/
4. Develop an informed consent prototype with common language for all Field Centers.
5. Based on draft protocols developed and approved by the Steering Committee, plan and participate in central training sessions for clinic staff.
6. Perform pilot testing for the examination after training is complete, consisting of performing the all of the components of the Year 25 Exam according to the draft

Manual of Operations, in at least 9 volunteers per Field Center who are not study participants. The pilot tests also are to include shipping blood samples to the appropriate laboratories and transmission of images to the appropriate reading centers. Results will be reviewed by the Steering Committee.

7. Redesign and implement changes in protocol, as recommended by the Operations Committee and approved by the Steering Committee, based on pilot testing results.
8. Assist the Coordinating Center in making final modifications to the Manual of Operations based on the pilot test results at the direction of the Steering Committee.
9. Develop local recruitment procedures, while cooperating in common efforts and sharing ideas as coordinated by the Clinic Coordination and Retention Committee.
10. Obtain approval from the Institutional Review Board to conduct the study.

G. During the period June 1, 2010 through May 31, 2011,

8. Work cooperatively with other study centers, including other Field Centers, Coordinating Center, Reading Centers, Laboratories, and the NHLBI Project Office staff in all relevant aspects of study development and execution.

9. Recruit and re-examine the local established CARDIA cohort for the Year 25 Exam.

k. Obtain informed consent from each participant.

l. Perform clinic examinations.

m. Obtain other measurements, as determined by the Steering Committee and Project Office.

n. Provide samples to the proper laboratories for assays or long-term storage.

o. Provide for refrigerated centrifugation, temporary storage at low temperature, laboratory procedures for sample preparation, and shipping with dry ice for blood and urine specimens, as appropriate.

p. Perform data entry and initial verification and correction of the entered data using software provided by the Coordinating Center.

q. In collaboration with the Coordinating Center, provide clinically relevant results of each examination and an indication of any abnormalities of clinical significance to the participant, and, with consent, to his/her physician. Provide recommendations for follow-up of abnormalities as appropriate.

r. Oversee local quality assurance and quality control activities, according to established study procedures, as recommended by the Quality Control Committee to assure high quality data collection.

s. Enter and edit the results from study interviews, examinations and quality assurance activities, including blind duplicates, into a computer, using software designed in cooperation with the Coordinating Center, and transmit the data to the Coordinating Center on a regular basis, as specified in the study protocol.

i. Transmit quality control data to the Coordinating Center according to specifications of the study protocol.

ii. Perform repeat measurements and send repeat lab samples for quality control, per the protocol. For planning purposes, estimate 5% repeat measurements and samples.

iii.

H. During the entire contract period, prepare and submit technical and financial reports to be delivered to NHLBI.

1. Semi-annual progress reports that include descriptive information about the activities undertaken during the reporting period and those planned for future reporting periods. The Contractor shall report on:

a. Administrative matters

b. General progress in each major Field Center activity, including but not limited to follow-up contacts of participants

c. Problems encountered and how they were resolved

d. An accounting of personnel, including levels of effort and changes during the period

e. Modifications to any subcontracts, if applicable

f. Scientific productivity (note: during the period June 1, 2010 through September 30, 2013, also provide progress on abstracts and papers generated that pertains to each of the Year 25 scientific objectives)

2. Quarterly Staffing Report: Table containing a list of all current staff (name, position, administrative group, level of effort, and change in effort) and an explanation of any staffing changes.

3. Financial reports, as required by NIH.

4. A final report, due September 30, 2013, documenting and summarizing the results of the entire contract work, including salient results, recommendations and conclusions based on both the general experience and the individual viewpoint of the Field Center.

END OF CARDIA FIELD CENTERS' STATEMENT OF WORK

Attachment 2. Description of Ancillary Studies

Investigators may propose ancillary studies to be conducted in one or more study Centers. A substudy is an investigation which, although not part of the core exam protocol, will yield additional information related to study objectives. An ancillary study is a study not funded by contract funds. They may include all or a subgroup of the cohort at a given center, and may involve additional interviews or examinations of study participants as well as analysis of blood or tissue samples, tapes, or images collected previously. Participation in ancillary studies requires NHLBI Project Office approval and will be contingent upon successful and up-to-date fulfillment and completion of the main study contract requirements and deliverables, including participant recruitment and follow-up, report development, and analysis and publication activities.

Ancillary studies are subject to the same policies, reviews and approvals as the core protocol. Ancillary study data, collected under a grant mechanism or other funding mechanism, will become part of the public use data set; these data will be incorporated into the study data set after an appropriate period of time (generally 12 months after completion of data collection). In addition, ancillary study data are required to become part of the limited access data set in accordance with the NHLBI Limited Access Policy (http://www.nhlbi.nih.gov/resources/deca/policy_new.htm). Investigators conducting ancillary studies are to be viewed as collaborating investigators of the primary study, with appropriate access to the full data set and to analytic resources of the study.

Ancillary studies will be evaluated by the Steering Committee. Highest priority will be given to studies which: 1) Do not interfere with the main CARDIA objectives, 2) Have the highest scientific merit, 3) Produce the smallest burden on CARDIA participants and the least demand on CARDIA resources, such as blood samples, and 4) Require the unique characteristics of the CARDIA cohort.

Investigators must define the hypotheses to be investigated and the methodology to be used, and estimate the cost and burden on participants. Study data collection must not interfere with the conduct of the core examination. All studies with participant burden, confidentiality, direct clinical implications for participants, or safety issues must be approved by the Steering Committee, the CARDIA Monitoring Board, and the NHLBI Project Office before initiation.

DELIVERABLES

Item	Description	Quantity	Schedule	Delivery Information
1.	Echo Data for Comparability Study	1 Set	September 30, 2009	Coordinating Center
2.	Wording for the Echo component of the study's Year 25 Exam consent form	1	November 1, 2009	Steering Committee
3.	Summary of Comparability Study Findings	1	December 1, 2009	Steering Committee
4.	Training Materials for Field Centers	5	February 1, 2010	Field Centers and Coordinating Center
5.	Draft Field Center Manual of Operations	1	February 1, 2010	Send electronically to Coordinating Center for posting on web site
6.	Draft Reading Center Manual of Operations	1	February 1, 2010	Send electronically to Coordinating Center for posting on web site
7.	Develop clinical alert values for reporting echo results to participants	1	February 1, 2010	Steering Committee
8.	Final Field Center Manual of Operations	1	April 1, 2010	Send electronically to Coordinating Center for posting on web site
9.	Final Reading Center Manual of Operations	1	April 1, 2010	Send electronically to Coordinating Center for posting on web site
10.	Pilot Test Results and Recommendations	2	14 days after receipt	Coordinating Center and Steering Committee
11.	Electronic list of IDs for scans	1	7 days after receipt	Coordinating Center and Field Centers
12.	Reading Center Results Data	1 set	14 days after receipt of Field Center data	Coordinating Center

Item	Description	Quantity	Schedule	Delivery Information
13.	Quality Control Data	1 set	Monthly during exam	Coordinating Center
14.	Reading Center Status Report	1	Monthly	Steering Committee
15.	Site Visit Report	1	Within 3 weeks of each site visit	Project Office, Field Center that was visited and all other members of the site visit team
16.	Raw Data	1 set per participant	As requested by Project Office	Project Office
17.	Tracking Database	1	As directed by Project Office	Coordinating Center
18.	Draft manuscripts	1 per manuscript	At least 6 weeks prior to submission to scientific journal	CARDIA Publication and Presentation Committee and Project Office (through Coordinating Center)
19.	Draft abstracts	1 per abstract	At least 2 weeks prior to submission to scientific meeting	CARDIA Publication and Presentation Committee and Project Office (through Coordinating Center)
20.	Publications accepted by scientific journals	1 per publication	Within 2 weeks of publication	Coordinating Center
21.	Quarterly Staffing Reports	2	November 30, February 28, May 31, and August 31 of each year	Office of Acquisitions and Project Office
22.	Semi-annual Progress Reports	2	February 28 and August 31 of each year	Office of Acquisitions and Project Office
23.	Financial Reports	Per Contract Instructions	Monthly (invoice) OR Quarterly (letter of credit)	Office of Acquisitions
24.	Final Report	2	September 30, 2013	Office of Acquisitions and Project Office
25.	Echocardiograms	All originals and copies	September 30, 2010	As directed by Project Office

Section L. – Special Instructions for CARDIA Echocardiography Reading Center

Instructions to Offerors for what to include in the Proposal:

1. Include specific proposals for each element of the SOW or, as appropriate, specific plans for how these will be proposed either during protocol development or later. Include plans for collaborative development of elements with the CARDIA Coordinating and Field Centers, as appropriate.
2. Propose new scientific components that are within the scientific objectives of the study, taking cost into account. Include justifications for new proposals.
3. Principal Investigators require approval of the NHLBI Project Office. Include qualifications that address the criteria for the PI, as outlined in the Statements of Work.
4. Refer to the following general guidelines for FTE levels for the Echocardiography Reading Center:

Period	FTE Level
March 1, 2009 to November 30, 2009	1.45
December 1, 2009 to September 30, 2010	2.60
December 1, 2010 to September 30, 2011	2.60
December 1, 2011 to September 30, 2012	0.45
December 1, 2012 to September 30, 2013	0.45

5. Propose travel each year as follows:

   - Two people, for two trips each per year during the period of March 1, 2009 through September 30, 2013, for the CARDIA Steering Committee meetings at or near Bethesda, MD

   - One person, for four to six trips during the period of December 1, 2009 through September 30, 2011, for site visits to the CARDIA Field Centers