THE STRONG HEART STUDY

Cardiovascular Disease in American Indians
(Phase IV)

Operations Manual

Volume One

GENERAL DESCRIPTION

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# VOLUME I

## GENERAL DESCRIPTION

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CHAPTER ONE

GENERAL DESCRIPTION AND STUDY MANAGEMENT

1.1 BACKGROUND

1.1.1 General

A review of existing data by the Subcommittee on Cardiovascular and Cerebrovascular Disease of the Secretary of Health and Human Service's Task Force on Black and Minority Health concluded that information on CVD in American Indians is inadequate and strongly recommended epidemiologic studies of this problem. The Strong Heart Study is designed to respond to this recommendation.

1.1.2 Scientific Background

A. Rationale for studying heart disease in American Indians

Cardiovascular disease has become the leading cause of death in American Indians. Cardiovascular morbidity and mortality rates may be increasing in some tribes, and the rates appear to differ greatly among various tribes. Cerebrovascular disease is the fourth leading cause of death for American Indians.

Several problems have made it difficult to determine the prevalence and severity of cardiovascular disease among American Indians. Small community size, relatively young age, cultural and anthropologic diversity, and the geographic dispersion of the American Indian population have made it difficult to include large numbers of Indians in research examinations and surveys of vital statistics. High rates of CVD in younger Indians suggest that the overall CVD rates will increase as the population ages and that CVD may be a more serious health problem among Indians in the future. Definitions of the term "Indian" are variable in published reports, and the denominators from which disease rates were calculated often were based on uncertain estimates of the population at risk. Definitions of disease and methods of its ascertainment have also varied among studies. In addition, health care services available to Indians differ considerably in different geographic areas and possibly contribute to differences in reported rates of cardiovascular disease morbidity and mortality.

B. Description of Strong Heart Study, Phases I, II, and III

The Strong Heart Study (SHS) is a study of cardiovascular disease among American Indian men and women supported by the National Heart Lung and Blood Institute since October 1, 1988 and is the largest study of American Indians ever undertaken. The SHS, which uses standardized methodology, is designed to estimate cardiovascular disease mortality and morbidity and the prevalence of known and suspected cardiovascular disease risk factors in
American Indians and to assess the significance of these risk factors in a longitudinal analysis. The study population consists of 13 tribes in three geographical areas: an area near Phoenix, Arizona, the Southwestern area of Oklahoma, and western and central North and South Dakota.

The SHS has included three strategies. The first is a survey to determine cardiovascular disease mortality rates from 1984 to 1994 among tribal members aged 35 - 74 years of age residing in the 3 study areas (the community mortality study).

The second is the clinical examination and morbidity and mortality surveillance of resident tribal members (the cohort). During the baseline (Phase I) examination, conducted between 1989 and 1991, 4549 tribal members, ages 45-74 years of age (62% of the total population ages 45-74 yrs.), were seen. The second examination (Phase II), between 1993 and 1995, re-examined 89% of all surviving members of the original cohort. The final examination (Phase III) between 1997 and 1999 re-examined 90% of all surviving participants. In the Phase I examination, medical history, family history of related illnesses, diet, alcohol and tobacco consumption, physical activity, degree of acculturation, and socioeconomic status were assessed in personal interviews. The physical examination included measurements of body fat, body circumferences, and blood pressure, an examination of the heart and lungs, an evaluation of peripheral vascular disease, and a 12-lead resting electrocardiogram. Laboratory measurements in the baseline exam included fasting and post-load glucose and fasting insulin, fasting lipids, apoproteins B and AI, apo E phenotype, fibrinogen, Lp(a), LDL size, Gm allotype, and glycated hemoglobin. Measures were also made of urinary creatinine and urinary albumin, and DNA from lymphocytes was isolated and stored. During the second examination, medical history was updated and a 24-hour dietary recall was performed on all individuals. Alcohol and tobacco consumption were reassessed. The physical examination included measures of body fat, body circumferences and blood pressure, an evaluation of peripheral vascular disease, and a 12-lead resting electrocardiogram. Measures of pulmonary function, an echocardiogram, and a gallbladder sonogram were added. Laboratory measurements included fasting and post-load glucose, and fasting insulin, fasting lipids, fibrinogen, PAI1, glycated hemoglobin, and urinary albumin and creatinine; red blood cell allotypes were also assessed. DNA from lymphocytes was again stored at -70°C.

The third examination included personal habits and medical history update, twenty-four hour dietary recall, and assessment of alcohol and tobacco consumption. The physical exam included measures of body fat, body circumferences and blood pressure, an evaluation of peripheral vascular disease, and a 12-lead resting electrocardiogram. Ultrasound assessment of carotid arteries and measurement of peripheral sensation were added; skin testing, and monitoring of pulmonary function were done in those with history of asthma. Laboratory measures included fasting and post-load glucose, and fasting insulin, fasting lipids, fibrinogen, PAI1, glycated hemoglobin, and urinary albumin and creatinine, hematocrit and Chemistry Profile (SMAC 12, including electrolytes, BUN, creatinine, total protein, SGPT, and SGOT).

The third strategy, added with Phase III, was an assessment of heritability of CVD and risk factors in families that included three or more siblings from the original cohort. 945 men
and women over 18 years of age in 32 families underwent a physical exam which included all aspects of the baseline exam from the cohort study plus carotid ultrasound and measures of peripheral sensation.

CVD incidence data from the SHS clearly show that CHD rates in American Indians now exceed rates in other US populations and that CHD may more often be fatal in American Indians that in other groups. Compared to reported CHD incidence rates in 45 to 64 year old African American and white women and men in the Atherosclerosis Risk in Communities (ARIC) Study, American Indian women have nearly two-fold higher rates and men have rates that are approximately 1.5 times higher. Surveillance data are substantiated by data from carotid ultrasound measures comparing overall prevalence of atherosclerosis in American Indians in the SHS compared to age-matched individuals in the ARIC Study. The prevalence of carotid atherosclerosis is higher in American Indians in the SHS than in whites and blacks in the ARIC Study.

A mortality review of the 13 communities in the three geographic areas from which the SHS cohort was derived shows CVD death rates approximately 30% higher than those of the general populations of these areas, i.e., Arizona, Oklahoma and North/South Dakota. Thus, there appears to be a rising tide of CVD among American Indian communities that is reaching epidemic proportions. This phenomenon may be a preview of what will happen to CVD rates in other US populations with increasing prevalence of diabetes.

C. Rationale for Phase IV of the Strong Heart Study

The Strong Heart Study is the largest multicenter study of CVD in American Indians and is one of the best resources for standardized data on many other diseases related to CVD in this population. Analyses of the community mortality data from 1984-1988 indicated differences between centers in types of CVD and in several other causes of death compared to non-Indians in the three geographic areas.

The continued surveillance of the cohort becomes more valuable as they age. Participants now range in age from 57-86 years. The availability of data from the baseline and two follow-up examinations will allow the evaluation of the effects of a large number of risk factors on the incidence of CVD and the progression of prevalent disease in this population. Since all the SHS communities have high rates of diabetes and glucose intolerance, continued surveillance will provide a unique resource to evaluate risk factors for and mechanisms of CVD in diabetic individuals. Since there are now many elderly individuals in this population, the risk factors for cerebrovascular disease can also be more fully examined. Finally, lifestyles are changing rapidly in all three areas and, in addition, there have been marked recent improvements in the economic situation in some of the communities because of the initiation of gaming and monies gained from land settlements. This provides the opportunity to examine effects of those changes on incidence of disease and mortality.
Since it is well established that many risk factors for CVD and the tendency toward atherosclerosis and atherosclerotic events are familial, the Strong Heart Study now provides a very valuable resource for evaluating genetic determinants of CVD. DNA is available from individuals from the cohort from Phases I, II, and III. Since family sizes are large (median live births = 5; range 0-18), and since there were siblings from many families examined in all three centers, we have the opportunity to map genes that influence cardiovascular risk factors in this population. It is most valuable, however, to collect data on risk factors and target organ damage and DNA on large kindreds. This population provides a particularly promising opportunity for such a study, since the average family size is large and the communities are very stable. Thus, many people remain on the reservation or within the Indian communities all of their lives. Even if they move, many of their relatives remain who know the location of these individuals. The close ties that Strong Heart Study investigators have with community members allow us to communicate the importance of the information that can be gathered from large families.

**Family Studies -**

Studies over the past 50 years have identified numerous risk factors for CVD, including increased serum lipid levels, male gender, cigarette smoking, sedentary lifestyle, a diet high in fat and cholesterol, various diseases such as hypertension, diabetes, and obesity, and a positive family history of CVD. The Strong Heart Study is the only large-scale study of CVD risk factors in American Indians. Until now, however, analyses of the contribution of genetic factors to CVD risk have not been included in the Strong Heart Study.

There is ample evidence that the development of CVD is genetically mediated, although the genes identified so far have been for the most part relatively rare mutations with extreme effects (the APO E polymorphism is a notable exception). A long-term goal of the Strong Heart Family Study is to detect and map new polymorphic genes that influence variation in risk factors for CVD and other related disorders in American Indians. The family study will take the first steps toward achieving that goal.

We will establish a resource of extended families beginning with sibships who already are Strong Heart Study participants. Using new statistical and molecular genetic methods for human gene mapping, we will conduct a genome-wide search for genes that influence CVD risk. Among the measures to be analyzed are risk factors such as plasma concentrations of lipoproteins, and apolipoproteins, insulin and glucose, measures of obesity, measures associated with hemostasis, and target organ features such as carotid artery wall thickness and stiffness. Such quantitative variables have the advantage that they provide more information for genetic analysis and are less subject to error than are dichotomous traits defined by imposing a (sometimes arbitrary) threshold on a continuous distribution. Genes that influence these disease risk factors have the potential to account for a high proportion of the variation in disease risk among individuals and thus to be of substantial public health importance.

We expect our results to lead to estimates of the magnitude of the genetic effects on CVD risk factors in American Indians, and to generate testable hypotheses that will form the focus of
further genetic studies of CVD risk in American Indians. The detection and mapping of genes that influence CVD risk as well as selected measures of preclinical CVD will set the stage for the larger task of isolating these genes. Future research will determine how they exert their effects on disease susceptibility in American Indians, and how gene action is influenced by environmental factors. This research will enable identification of individuals who, on the basis of their genotypes, will most benefit from specific therapies or lifestyle changes.

SHS demonstrated in Phase III that it was able to recruit and retain large kindreds from which physiologic measurements were made and blood samples taken for direct genotyping. This effort will continue in Phase IV to recruit and examine 90 more families and perform linkage analysis on a total sample of 3600 individuals.

Phase IV of the Strong Heart Study will perform the following:

1. Continued mortality and morbidity surveillance of the Phase I examination cohort.
2. A continuation of the effort to examine family participants (first degree relatives and grandchildren) of members of the Strong Heart Study. Thirty families with at least 30 members will be identified at random from each of the three centers from among Strong Heart Study participants where two or more siblings were examined at baseline. The examination on these individuals will include all components of the Phase III family examination and DNA samples isolated for genotyping. Heritabilities of selected risk factors will be estimated, and risk factors will be screened for linkage to genetic markers distributed throughout the genome.
3. The 945 members of the original 32 families examined during Phase III will be reexamined, repeating components expected to change (as in the Phase II exam) and including both carotid and cardiac ultrasound.

**Rationales for Major Components of Phase IV of the Strong Heart Study**

1. **Carotid Ultrasound and Pressure Waveform Analysis**

   Recent progress makes available non-invasive methods to evaluate arterial structure and function. Ultrasound measurement of carotid wall thickness (combined intimal and medial thickness) has been validated using gross and histopathologic reference standards and has been found to be highly reproducible. Ultrasonography permits the detection of discrete atheromata within the extracranial carotid arteries. The presence of carotid atherosclerosis is strongly correlated with coronary atherosclerosis and constituted an independent risk factor for the development of subsequent myocardial infarction in the Kuopio Heart Disease Risk Factor Study. For each 0.1mm increase in common carotid artery intimal-medial thickness, the risk of myocardial infarction increased by 11%. Thus the inclusion of this measure will give precise measures of structure and detect atheromatous plaque and early atherosclerosis. Additional recording of the arterial pressure waveforms will allow assessment of arterial compliance and...
permit assessment of the relation of diabetes and other CVD risk factors, prevalent CVD, and symptomatic atherosclerosis to arterial dysfunction. The combination of these data with the previously collected echocardiographic data and the ongoing surveillance of mortality and CVD morbidity will allow a comprehensive assessment of cardiovascular structure and function in the Strong Heart Study participants and afford an opportunity to evaluate its relationship between these measures and several CVD risk factors and the presence of diabetes and its complications.

2. Measures of LV Structure and Function by Echocardiography

Echocardiographic structural and functional abnormalities are very prevalent in diabetic American Indians and appear to be strong predictors of CVD events. A particular dramatic finding in the SHS is that LV mass on SHS Exam II echocardiograms obtained between August 1993 and December 1995 predicted higher CVD mortality through the end of 1997 (2.6 vs. 0.8%, odds ratio = 3.4 [1.8-6.3], p<.001). In regression analysis that considered other predictors of mortality, cardiovascular death was most strongly predicted by higher LV mass/height^2.7 (p=0.0001), older age (p=0.0009), higher urine albumin/creatinine ratio (p=0.05) and lower BMI (p=0.003). When analyses were restricted to participants with DM at the second SHS examination, all-cause mortality, cardiovascular death, and non-fatal cardiovascular events were all more common in those with LV hypertrophy.

Measures of LV function derived by echocardiography also strongly predict adverse outcomes in patients with DM. When stress-corrected LV midwall shortening was considered as a predictor of cardiovascular death, SHS participants with low LV myocardial function had a substantially increased rate of CVD death (5.2 vs. 1.0%, p<0.001, OR = 5.3 [2.6-10.9]). In logistic regression was a strong predictor of shortening was a strong predictor of CVD death (p=0.0002) along with older age (p=0.0001) and higher albumin/creatinine (p=0.006). These analyses confirm that echocardiographic measures of LV mass and myocardial function strongly predict CVD death in diabetic American Indians despite a relatively short follow-up period, demonstrating the robustness of these variables as predictors of CVD events. In one of the first analyses of prognostic implications of abnormal LV diastolic filling in a population-based sample, we showed that an elevated ratio of early diastolic/atrial phase LV filling (E/A ratio) (>1.5) was a stronger predictor (p=0.0003) of cardiovascular death than age (p=0.0072), DM (p=0.001), or systolic BP, (p=0.04) and that reduced E/A (<0.6) also predicted CVD death. The high prevalence of LV hypertrophy (32%), myocardial dysfunction (15%), and abnormal LV filling (24%) detected by echocardiography in SHS participants may contribute to the high CVD death rate in diabetic American Indians.

3. Laboratory Tests

In Phase IV, based on the death rate observed so far, there should be more than 1000 deaths in the cohort, approximately one-third of which are expected to be from cardiovascular disease. Therefore, in the interest of economy, certain measurements are planned using a case-
cohort design. Analyses will be done on stored samples from the baseline (Phase I) examination. These will include measures of:

A. Thyroid Stimulating Hormone (TSH)

Over the years, several studies have identified hypothyroidism as a stimulus to dyslipidemia and, potentially through that mechanism, coronary atherosclerosis. Since these studies have depended on use of coronary arteriography, an invasive technique with a measurable complication rate, little is known of the relation of thyroid metabolism to atherosclerosis in population-based samples. In addition, it is well known that skeletal muscle relaxation is slowed in the setting of hypothyroidism, but whether this phenomenon occurs in arterial and cardiac muscle is unknown. Preliminary data from SHS reveals that 553/4475 subjects in Phase I were receiving thyroid replacement therapy. This yields a prevalence of treated hypothyroidism of 3.4% vs. a pooled prevalence of 0.5-2% in nationally published studies.

B. Endothelin and VCAM-1

The coronary arteries have an active role in the pathogenesis of atherosclerosis and coronary heart disease; they are not simply the passive repositories of injury caused by oxidative stress, dyslipidemia, thrombosis and sheer injury. Both genetic and environmental factors affect the vessel’s susceptibility to injury and its response in terms of tone and vascular wall proliferation.

Since SHS began, a great deal has been learned about the molecular processes leading to vascular wall injury and its responses to damage. These responses are regulated by the production and release of a variety of substances including prostacyclins, nitric oxide, cellular adhesion molecules, vasoactive growth factors and G-protein-coupled receptor agonists including endothelin. There is accumulating in vitro evidence that these factors are essential elements in the acute and long term responses to injury and development of atherosclerotic cardiovascular disease (ASCVD). In addition, vascular responses mediated by nitric oxide are abnormal in established pathological states such as essential hypertension, stroke, atherosclerotic coronary heart disease and heart failure. There is no agreement on a clear relationship or cascade between these factors and the vessel wall. However, it is hypothesized that risk factors for atherosclerosis such as dyslipidemia, hypertension, diabetes and oxidative stress impair nitric oxide bioactivities. Reduced nitric oxide activity may, in turn, adversely affect coronary vasodilation and antithrombotic activities. Reduced synthesis (or intravascular residence time) of nitric oxide also appears to increase inflammation by stimulating the expression of vascular adhesion molecules (e.g., vascular cell adhesion molecule-1 or VACM-1) for monocytes, and the growth of vascular smooth muscle through the production of local growth factors. Vascular wall injury also causes production and release of endothelin, a G-protein-coupled-receptor agonist. Endothelin elicits cell growth through production of both autocrine and paracrine factors.
In Phase IV of SHS, we will measure endothelin and VCAM-1 in stored Phase I plasma samples. While these factors appear to be elevated in established vascular injury, it is not clear what role they play in pre-clinical or pre-morbid states of ASCVD. Specifically, we will test the hypothesis that VCAM and endothelin are elevated in the blood of individuals who were initially free of clinically apparent ASCVD, but subsequently developed “definite” or “probable” CHD. Our data may allow us to infer that those elevated blood levels of VCAM and endothelin are pre-clinical risk factors for CHD. The practical importance of this may relate to earlier, focused interventions designed to reduce vascular wall injury. These interventions may include ACE inhibitors, estrogen, lipid lowering agents, physical activity, improved diabetic and blood pressure control, and the development and use of new agents such as endothelin or VCAM selective antagonists.

For the case-cohort studies, the control group will be a large random sample of the Phase I examination cohort. Selecting controls in this way will allow them to serve as controls for each of the case groups studied.
1.2 RESEARCH OBJECTIVES

The Strong Heart Study-IV (SHS, Cardiovascular Disease in American Indians Phase IV) is to continue the mortality and morbidity surveillance on the original cohort, to continue the study of the inheritance of risk factors in families, and to re-examine the members of the original families initiated in Phase III.

The study will address the following specific aims:

Specific Aim #1. Expand the available data and power for genetic analyses of CVD and its risk factors by extending the pilot family study.

a. Identify and recruit 30 families with approximately 30 members each, ages 15 years and older in each of 3 geographic areas (Arizona, Oklahoma, South/North Dakota).

b. Estimate heritabilities, covariate and household effects, and genetic and environmental correlates for a large set of CVD risk factor phenotypes as well as echocardiographic and carotid atherosclerosis measures by quantitative genetic analysis.

c. Generate a 10 centimorgan map that includes genotyping or 386 short tandem repeats in each of the 2700 newly recruited individuals.

d. Screen the phenotypes for linkage using a variance component approach in full pedigrees and do finer scale mapping in regions of interest.

e. Assess changes in risk factors and carotid atherosclerosis by reexamining the original 900 family members.

Specific Aims #2. Continue Morbidity & Mortality surveillance of the original cohort (45-74 years at baseline) in order to explore the role of the many biomarkers and measures of cardiovascular function made in the baseline and two follow up exams.

a. Determine CVD mortality and morbidity rates and all cause death rates.

b. Compare rates and risk factors for differing manifestations of CVD – coronary, cerebral, and peripheral.

c. Relate quantitative measures of systemic atherosclerosis, cardiac hypertrophy, and cardiovascular dysfunction (ECHO, carotid and tonometry) to CVD incidence.

d. Determine the relations of some additional biomarkers (TSH, endothelin, and VCAM-1) with CVD using stored baseline blood samples in a nested case control design.
### STUDY DESIGN

#### Timeline

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<td>Phases I-III &amp; Surveillance data analyses (5 yrs, 06/01/00 - 05/31/05)</td>
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<td>Train ultrasound staff (9 mos, 06/01/00 - 02/28/01)</td>
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<td>Develop protocol, manual, forms (9 mos, 06/01/00 - 02/28/01)</td>
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<td>Purchase supplies (9 mos, 06/01/00 - 02/28/01)</td>
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<td>Identify candidate families (9 mos, 06/01/00 - 02/28/01)</td>
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1.3.1 Surveillance

In Phase IV of the SHS, surveillance will include annual ascertainment of deaths and non-fatal CVD events in the Phase I cohort.

For the mortality surveillance, death certificates will be reviewed and independently classified for all deaths, regardless of the cause. Annual contacts with participants and annual reviews of IHS listings of relevant ICD-9 codes will be used to identify non-fatal events that have occurred since the date of last contact with the participant. Included in the morbidity surveillance will be annual ascertainment of the occurrence of hospitalized non-fatal myocardial infarction and stroke.

Individuals will be designated at each center to be specifically responsible for mortality and morbidity surveillance activities. Surveillance contacts will be accomplished using a variety of approaches specific to the SHS populations. These approaches include home visits, monitoring of IHS facility records, telephone calls and mail contacts. All reports of primary endpoints and selected secondary events of interest obtained through surveillance procedures will be validated from medical records. (See Volume Two – Morbidity and Mortality Surveillance)

1.3.2 Clinical Examination

Components of the Clinical Examination. These are described on page III-2 of this manual. The clinical examination will include a personal interview and a physical examination of family members from the 90 newly recruited families, as well as family members seen in Phase III. For the latter, only information that is likely to have changed since the last exam will be collected. All of the procedures will be the same as in Phases I - III. Procedures are described in brief below, with details presented in the manual Volume III.

i. Personal Interview

The following questionnaires will be administered:
1) Demographic information: income, residence, marital status, number of household members and employment will be determined. Tribal enrollment, degree of Indian blood, marital status, education/income, use of native language, smoking and alcohol use, medical conditions, and reproductive history will be ascertained.
2) Health habits: Smoking and alcohol intake will be assessed.
3) Medical history, including Rose questionnaire for angina pectoris and intermittent claudication will be assessed.
4) Dietary survey: The Block Food Frequency Questionnaire (FFQ) will be used.
5) Quality of life and psychosocial parameters: The Quality of Life instrument (Rand MOS SF-12) will be used in Phase IV rather than the longer SF-36 that was used
in Phases II and III. Other psychosocial instruments will include a cultural assessment, CES-D to assess depression, Locus of Control, Social Support, and Anger & Hostility (Anger & Hostility will be optional).

ii. Physical Examination

The physical examination includes the following procedures that were used previously:

1) Anthropometric measurements will be made with participants in loose clothing with shoes and heavy objects removed from pockets:
   i) Weight -- The scale will be balanced on a level and firm surface prior to weighing a participant. The participant will stand in the middle of the scale platform, head erect and looking straight ahead. Results will be rounded to the nearest kg.
   ii) Height -- The participant will stand erect on the floor with his back against the vertical mounted ruler, heels together and looking straight ahead. The right angle will be brought down snugly but not tightly on the top of the head so that height can be accurately measured.
   iii) Waist and hip circumferences -- For the waist, anthropometric tape will be applied at the level of the navel with the patient supine and breathing quietly. Results will be rounded to the nearest cm. For the hip, the participant will stand erect but relaxed with weight distributed equally over both feet. The measure will be made at the level of maximum protrusion of the hips with the tape kept horizontal.
   iv) Body fat measurement -- Using an RJL bioelectric impedance meter, resistance and reactance are recorded. Percent body fat will be estimated by the RJL formula based on total body water.
   v) Arm circumference -- The participant will sit on a table so his right arm hangs freely with the right hand resting on the right knee. The tape measure will be placed horizontally at the midpoint between the acromium and olecranon. Results will be rounded to the nearest cm. The measure will be used to select the proper size blood pressure cuff.

2) Examination of the following:
   i) Pedal pulses -- The presence of posterior tibial (palpating inferior to the medial malleolus of each foot) and dorsalis pedal (palpating superior) pulses will be determined.
   ii) Ankle edema -- With foot coverings removed, participant will be examined in the supine position. Gentle but firm pressure will be applied along the mid-tibia, anteriorly down to the ankle in each leg. The degree of edema (0-4) will be recorded.
3) Blood pressure measurements:
   i) With the participant sitting with right arm on table, the cuff will be connected to a standard manometer and the pulse obliteration pressure will be established and recorded. After five minutes, the cuff will be reconnected and inflated to +30 mm above the obliteration pressure and held constant for 5 seconds. The cuff will be slowly deflated (2 mm/sec) while reading pressures for 1st and 5th phases. Before measurements 2 and 3 are taken, the participant will raise the arm for five seconds. After another 25 seconds with arm on the table, the measurement will be repeated a second and third time. The average of the last two measurements will be used for analysis.
   ii) Using a Doppler, with the participant supine, right brachial and both ankle systolic pressures will be measured two times.

4) Twelve-lead resting ECG measurement -- Using a Marquette Mac-PC or Mac1200-based system, a 12-lead EKG will be obtained in a standard manner. EKGs will be electronically transmitted to Cornell University and confirmed interpretations will be transmitted back to field location to be filed in the participant’s medical record. Tracings will be Minnesota coded.

5) Fasting blood samples will be obtained for measurements of total triglyceride (TG) and cholesterol, LDL and HDL cholesterol, plasma fibrinogen, PAI-1, DNA isolation, glucose, creatinine, insulin, and CBC. The complete blood count (CBC) will be measured at the local IHS laboratory.

6) Urine will be collected at the beginning of the physical examination for measurements of albumin and creatinine.

7) The following cardiovascular procedures will be performed:
   i) Ultrasound examination of the carotid artery (see Manual Volume V, Special Studies for details).
   ii) Echocardiography (see Manual Volume V, Special Studies for details).
   iii) Radial Artery Tonometry (see Manual Volume V, Special Studies for details).

The clinical examination will last approximately three hours. The participant will arrive at the clinic fasting in the morning. After registration, a study staff member will explain the study and procedures to the participant, answer questions, if any, and administer the consent form. The participant will then be instructed to go to the laboratory for blood drawing and to obtain the urine specimen. The participant is then offered a light snack. The nurse clinician and other staff will then conduct the personal interview, obtain anthropometric measurements, blood pressure, impedance measurement for body fat composition, and ECG measurements. Project staff who have been trained and certified will perform echocardiography, ultrasound exams of the carotid artery.
artery, and radial artery tonometry. After all the procedures are completed, the participant will receive payment or sign a payment form, will be provided appropriate health educational material to reduce his/her cardiovascular risk, and will be thanked for his/her participation.

If possible, all of the components will be completed in one visit. If an individual leaves before the examination is completed, every effort will be made to complete all components of the examination before the study is completed. The personal interview and consent may be completed up to two weeks prior to the physical examination, if such arrangements are more convenient.

Each center will pilot the exam in at least 10 persons and appropriate revisions in the procedure will be made and standardized for use in all three centers for 900 family members age 15 or over at each center. If no major revisions are made in the procedure, data from the pilot participants will be included in the analysis. For pregnant women, the examination will be conducted no earlier than six weeks after delivery. Lactating women will be included in the study if six weeks or more postpartum.
1.4 STUDY QUESTIONS

The wealth of data from this and the previous three phases of SHS will provide answers to many important questions concerning CVD which will impact the health care of American Indians. Since the SHS now contains the largest number of diabetic individuals in a longitudinal study of CVD in the US, the results will also benefit many other populations throughout the US and the world who have high rates of diabetes.

The genotyping of the extended families coupled with the availability of risk factors provides a unique database of CVD risk factors in a population with insulin resistance and high rates of obesity and diabetes to ask:

a. Are there genes that have large effects in explaining the low plasma cholesterol in American Indians, and can their chromosomal locations be determined?

b. Are there detectable genes that influence diabetes susceptibility in American Indians? Can these genes be mapped to specific chromosomal regions?

c. Are the amount and distribution of body fat in American Indians influenced by genes with large effects, and are their chromosomal locations near those of genes for diabetes?

d. Are there genes that have significant effects on renal disease as assessed by albuminuria that can be mapped to specific regions?

e. Are LDL size and other measures of the dyslipidemia associated with the insulin resistance syndrome influenced by a gene or genes with large effects and can these genes be mapped to specific chromosomal regions?

The availability of comprehensive ECHO and carotid measures provides a unique opportunity to ask:

a. Are intima-media wall thickness (IMT) and atherosclerotic plaque influenced by one or a few genes whose chromosomal locations can be determined?

b. Are measures of ventricular mass, function, and other echocardiographic parameters influenced by one or a few genes whose chromosomal locations can be determined?

The continued surveillance of the cohort with very high completion rates and systematic assessment of endpoints will allow us to ask:

a. How do incidence rates for various manifestations of CVD change with age and diabetes in this population?

b. What are the major risk factors for stroke in this population and do they differ by gender and diabetic status?

c. Is the strong predictive value of renal disease attributable to its relations to general vascular impairment?

d. Are high TSH, endothelin, or VCAM-1 levels independent predictors of CVD?
The unique availability of ECHO, carotid and tonometry data on individuals allows us to ask:

a. Which echocardiographic measures of cardiac function are significant predictors of CVD and how do these predictors interact with other established risk factors?

b. Is arterial stiffness as measured by tonometry a predictor of CVD events?

c. What aspects of carotid wall thickness and morphology are predictive of CVD in this population, and how do they relate to established CVD risk factors?
1.5 STUDY MANAGEMENT

1.5.1 Introduction

The Strong Heart Study Phase IV is funded by the National Heart, Lung, and Blood Institute, and directed by the Clinical and Genetic Epidemiology Branch, Epidemiology and Biometry Program, Division of Epidemiology and Clinical Applications. The Principal and Co-investigators are listed in Appendix 1 below. An organizational chart of the Strong Heart Study Phase IV is given in Appendix 2. The operations of the study are directed by the Strong Heart Study Phase IV Steering Committee, which includes members from each center and the NHLBI Project Manager (see Appendix 3 for the members of Steering Committee). In addition to being a field center, the Oklahoma Center assumes the responsibility of the Coordinating Center and the Arizona Center acts as the Core Laboratory. The Cornell University Reading Center under the direction of Dr. Richard Devereux serves as both the ECG Reading Center and the Carotid ultrasound reading center. Analysis of the family study genetic component is directed by Dr. Jean MacCluer at the Southwest Foundation for Biomedical Research. SHS-IV Sub-Committee members are listed in Appendix 4. Other key personnel at each center and consultants of the Study are listed in Appendix 5 and 6, respectively.

1.5.2 Confidentiality of Data

All personnel with access to data collected for the study at each center are required to sign a confidentiality pledge which states that they understand the sensitive and confidential nature of the data and that divulgence of any information will result in disciplinary action. The pledge will be co-signed by the principal investigator. A sample of the confidentiality pledge is given in Appendix 7.

Completed data forms will be placed in locked file cabinets in offices assigned to the study at each study center. Only authorized staff members have the key to the office and access to the data forms.

Data on computers at the Coordinating Center will be safeguarded by a password, which is known only to authorized personnel.

1.5.3 Communications

1. Newsletter:

The Coordinating Center periodically prepares and distributes a newsletter to facilitate communication among Study staff and with the SHS participants. In general, each edition includes: (1) reports from the Program Office, the Steering Committee, the Coordinating Center, the Core Laboratory, the Cornell Reading Center (ECG, Carotid Ultrasound, and Echocardiogram), and the Southwest Foundation for Biomedical Research (Genetic Study Center), (2) a description of the facilities and staff of a field center or central agency, (3) general
information on data management, (4) information about new ancillary studies, and (5) upcoming events. The newsletter also provides reports on issues such as recruitment and participant follow-up rates, the development and use of new equipment, and preliminary study results and abstracts.

2. Electronic Mail:

E-mail through Internet and FAX continue to be the major electronic mail facilities used by all field centers, the Coordinating Center, Core Laboratory, Cornell Reading Center, Genetic Study Center, and the Program Office. This electronic mail network allows rapid and efficient communication among centers for messages such as announcements, meeting agendas, abstracts for clearance, and acknowledgments of receipt of data.

3. Web Site http://strongheart.ouhsc.edu/

A list of scientific publication from the Strong Heart Study is available and linked to abstracts. This Phase IV Manual and the study Newsletters will also be available on the web site in Phase IV.

4. Field Center Visits:

The Program Office and staff from the Coordinating Center, Cornell Reading Center, Core Laboratory, and Genetic Study Center conduct periodic monitoring visits to field centers as needed to: (1) maintain channels of communication with field center investigators and staff, (2) monitor participant recruitment and surveillance procedures, (3) monitor adherence to the protocol, and (4) provide technical support for activities such as data management and quality control.
1.6    DATA MANAGEMENT AND STATISTICAL ANALYSIS

1.6.1    Development and Production of Study Manual and Data Collection Forms

The Coordinating Center worked closely with the Steering Committee in the development and production of the study manual and data collection forms. A Forms Committee reviewed all forms and made recommendations for revisions, deletions, and additions of forms. The Psychosocial Committee held frequent conference calls and devised a set of psychosocial forms comprised of forms used previously in SHS and elsewhere. The Manual was revised by Steering Committee members and the Field Coordinators. Revisions were circulated by email attachments, and further input and improvements were provided during the training sessions held in Oklahoma City (January 29 – February 2, 2001). After pilot testing the data forms in February 2000, the entire manual was reviewed page by page and modifications were incorporated.

a.    Sources of data

Data forms for the SHS are generated from a variety of sources.

i.    From the three field centers: Clinical examination forms (personal interview, medical history, physical examination, quality of life and other psychosocial forms, machine reading of ECG, and local clinic lab assays of blood chemistry and CBC), Death Certificate Form, and Morbidity Survey Medical Chart Review Form.
ii.   From the Core laboratory at Medstar Research Institute: Lipids, fasting glucose, insulin, plasma creatinine, glycated hemoglobin, urinary albumin and creatinine.
iii.  From Cornell University, cardiologist's ECG reports, computerized Minnesota ECG codes, blood pressure tonometry waveform data, echocardiography, and carotid ultrasound data.
v.    From Dr. Maurice Sievers: Mortality study final decision package (Mortality Study Chart Review Form, Final Decision Form, and Informant Interview Form).
vi.   From Mortality and Morbidity Review Committees (Mortality or Morbidity Study Chart Review Form, Mortality or Morbidity Final Decision Form, and Mortality Informant Interview Form).
vii.  From Dr. Jean MacCluer: DNA data.
viii. From Block Dietary Data Systems: Analyses of the Food Frequency Questionnaire.

b.    Database development

In SHS-IV, the Coordinating Center continues to use a distributed data entry system. In Phase IV the Coordinating Center is using Microsoft (MS) ACCESS to develop the data entry programs (as before) and MS Windows 2000 Terminal Services to support real-time data entry (as opposed to batch transmission as used in Phase III) via
high-speed Internet connections with state of the art field center computers. Separate files have been created for each data form; these files and the data files are stored solely on the server(s) at the Coordinating Center. Maintenance of the data programs and files occurs on the server(s) at the Coordinating Center; the field centers transmit the exam data to the Coordinating Center for data cleanup and permanent storage.

The laboratory data and data from special studies are transmitted to the Coordinating Center electronically over the Internet or by sending data-containing media such as diskettes. The Coordinating Center stores the raw data sent from the specific study centers and converts them into SAS data files for analysis.

c. **Procedures for data entry and verification of completeness**

Each field center reviews every data form for completeness and accuracy before entering it into the field computer. Details of the data entry process and data management can be found in Volume 7 of this SHS IV Operations Manual. The completeness of data entry for each form is checked again by the Coordinating Center. Any incomplete items (missing, questionable, unclear) are recorded, and the corresponding field center is contacted to find out the reason. When these items are completed by the individual center and received by the Coordinating Center, the information is updated in the Coordinating Center’s database. To ensure the data quality, the field centers are required to double enter all of the forms in the first 2 months. If the disagreement rate is less than 0.5% in these two months, the double entry ratio drops to 10% of the data or at least one double entry per transmission. The Coordinating Center checks the disagreement rate for double entry on a monthly basis. If the disagreement is greater than 0.5% in that transmission, that center is asked to re-enter (as second entry) the data of all the forms in that transmission.

The data received from the Core Laboratory via the Internet as ASCII files are directly converted into SAS datasets. Before these data are merged into the permanent data files, various quality and consistency checks are performed.

Uniform data entry forms for all information to be collected have been designed by the Coordinating Center for use by each Study Center. Each study subject will have a unique identification number (ID number). Please see the Strong Heart Study Phase I Manual page 12a for the detailed procedure to assign the study ID number. For those original cohort members who participate in Phase IV, the original ID number assigned in the Strong Heart Study Phase One will still be used. The ID number will be stamped on every page of all forms at each center. For laboratory specimens, printed labels supplied by the Core Lab will be used.

<table>
<thead>
<tr>
<th>Center</th>
<th>Family ID</th>
<th>SHS ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>AZxxyy</td>
<td>360001 - 36zzzz</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>Okxxyy</td>
<td>260001 - 26zzzz</td>
</tr>
<tr>
<td>South and North Dakota</td>
<td>Dkxxyy</td>
<td>160001 - 16zzzz</td>
</tr>
</tbody>
</table>
Where xx: family number.
    yyy: 001 - 999 for each family member.
    zzzz: a unique number for each family member who participates in the examination and interview.

Standard IHS community codes will be used to identify the community where the participant resides. A list of community codes for the three centers is given in Appendix A-1 of Volume 2. Hospitals where a Phase I cohort member died or was treated for CVD are also coded. Standard IHS facility codes will be used to identify IHS hospitals and clinics. Codes for other non-IHS hospitals will be assigned by each center. The hospital/clinic codes are given in Appendix A-2 and A-3 of Volume 2, respectively. In addition, every member of the Study is assigned a Personnel Code which will be used to identify the person who filled out a specific data form. The Personnel Codes for the three centers are listed in Appendix A-4 of Volume 2. Additional Codes will be added sequentially as new employees begin to work on the project.

All data forms must be filled out legibly and completely. Each and every form must be reviewed and checked for completeness and legibility before it is entered into the computer.

1. All forms should be filled out in black pen. Print all information in block capital letters, with one letter only in each box, so that data entry errors can be minimized. For example, one should differentiate: 7 from 1, U from V, 4 from 6, P from D, M from N, C from O, and T from J.

2. For names and addresses, start from the leftmost box and leave the unused boxes blank. Include periods for initials.

3. For numerical values, fill in the boxes in a right justified manner and leave the unused boxes blank.

4. For dates, two digits are allowed for the month and day, and four digits for the year. If the number has only one digit, use zero in front of the number.

5. When recording dates, use the following rule for missing dates:

   If date is unknown/missing: 01/01/1001
   If only year is known: 06/30/year (assign mid-year as the date)
   If only year and month are known: month/15/year (assign mid-month as the date)

6. To correct an error, draw a single line through the mistake and write the correct value above.
7. Fractions should be rounded up to the nearest whole number if the fraction is 0.5 or more, otherwise, drop the fraction, e.g. \(2.25 = 2\); \(2.75 = 3\); \(3.5 = 4\).

8. If an interval is given, record the midpoint of the interval if it is a whole number. If the midpoint includes the fraction 0.5, use the rounding rules previously given.

9. Unless otherwise instructed, no item on any of the forms should ever be left blank. Codes to be used in the event of missing or incomplete data are given under the heading of each specific item. If there is not a code for the "unknown" category, draw two parallel lines horizontally through the box or boxes to indicate that the interviewer or abstractor did not ignore the question. For example, if the time of death is unknown, draw two lines across the boxes.

1.6.2 Procedures for data entry and verification of completeness -- See SHS-IV Operations Manual Volume VII - Data Entry

1.6.3 Data Transmission

The lab data, ECG data, and ultrasound data will be electronically transmitted to the Coordinating Center, and will be converted to SAS datasets. However, before these data are merged into the permanent data files, they are checked against the values given by the laboratory on paper to ensure the conversion is correctly done.

1.6.4 Data Backup

Several backup procedures are suggested to ensure the safety of the SHS data files in both field centers and the Coordinating Center.

a. Daily backup: Two sets of cartridges are rotated to backup the data every day from Monday through Thursday (one for Monday and Wednesday and the other for Tuesday and Thursday).

b. Weekly Backup: Similar to daily backup, two sets of cartridges are rotated, each for every other week. Backup of the week's data set is done every Friday.

c. Optical disk backup: Additional permanent files are stored in the optical disk for long term storage.

d. Storage of backup data: Cartridges and optical disks are stored in locked file cabinets in different offices and one set of them will be stored in a different building.
1.6.5. Quality Assurance (QC) Program

The quality control (QC) program was improved in Phase II with close monitoring of the quality of all measurements and interview data. At the beginning of SHS-III, a Quality Control Subcommittee was formed to oversee the QC program of the Study. The members of this Subcommittee include the NHLBI Project Manager, a representative from the Coordinating Center, one principal investigator, and the three Field Center Coordinators. The Quality Control Committee meets periodically via conference calls during the examination period to assess the results of quality control activities. The QC Committee reviews the QC data and summary statistics provided by the Coordinating Center and reports to the Steering Committee with recommendations. Recommendations are made to the appropriate centers when problems are identified. Follow-up procedures are established and monitored for all the QC activities. After each site visit, reports are reviewed. If indicated, field staff are retrained, re-certified, and re-monitored by the QC personnel. For lab data, aberrant pairs are investigated and corrective actions are taken both in the core lab and in the field sites. The quality control program includes: a) data collection, b) site visits, c) routine maintenance and monitoring of instrument performance, d) duplicate measures for physical examinations, laboratory tests, observations of personal interviews, QC for cardiology tests, and QC for surveillance (each of these components is described below). Each clinical center has a quality control officer who is responsible for all aspects of quality control at that center. The Coordinating Center closely monitors the recruitment and progress of the Study. According to the target numbers to be recruited by each center during the whole study examination period, the CC develops a timetable to indicate the projected goal for each month. The field centers report the number of participants actually examined to the CC, and the CC then compiles these numbers on a monthly basis. Cumulative achievement for each field center is then calculated by comparing the actual number examined to the projected number for the corresponding month. In addition to recruitment, the CC also monitors whether each field center had completed their quotas for double entry of data, QC physical examinations, and QC blinded blood samples. The CC submits progress reports to the SHS Steering Committee as a tool to monitor the progress of the study. If the percentage of projected recruitment in a certain field center falls below 80%, the PI and the field coordinator are informed, so that the efforts can be focused on recruitment in the following months. Field center coordinators are responsible for reviewing all QC data as they become available and following up on any problems that are detected. The QC committee monitors the efficacy of retraining and problem solving.

1. Data Collection

Every data form will be checked for completeness at the field center. Ambiguous or erroneous items will be clarified and corrected. The data entry programs, which will be generated by the Coordinating Center, will provide an additional quality control check by building in range and logic checks. The program will refuse to accept such data until the errors are corrected. During the first two months of examination, all forms will be double entered. After this initial period, 10% of the examinations will be randomly selected for double entry.
The Coordinating Center will track the data entry error rates. If the data entry error rate of any field center is greater than 0.5%, that center will have to double enter all the examination data of that month. Computer printouts of inconsistent data items will be sent back to each field center for clarification or correction. Summary statistics such as mean, median, range, maximum and minimum for continuous variables and frequency distributions for categorical variables will be calculated monthly for each center, and data not meeting consistency checks will be flagged. Summary statistics will be generated quarterly to identify any peculiar or unreasonable values. Further verifications will be made and errors corrected.

2. **Quality Control Site Visits**

Two quality control site visits will be made to each of the three centers in the first year and one in each year thereafter. The site visit teams will include representatives from the program office at NHLBI and investigators and staff members from each of the centers. Procedures used in the clinical examination will be carefully observed for adherence to protocol. Equipment will be inspected and problems noted. The site visitors then will meet with all the clinic staff to inform them of any observed discrepancies. In addition, a written evaluation including corrections or improvements needed will be sent to each center.

3. **Quality Control -- Equipment**

Other quality control measures will include maintenance of the scale, sphygmomanometer, Doppler, and ECG machine. The scale will be zeroed daily and calibrated with a known weight (50 lbs) every month or whenever the scale is moved. The standard sphygmomanometer will be inspected once a month. These inspections will include checking of the zero level, mercury leakage, manometer column for dirt or mercury oxide deposit, and the condition of all tubing and fittings. Other quality control measures for the blood pressure measurements will include simultaneous Y-tube observation of each technician and frequent staff meetings to provide feedback.

4. **Quality Control -- Examination**

1) **Anthropometry and blood pressure**

Duplicate measures of brachial artery blood pressure (systolic and diastolic) simultaneously using a double head stethoscope with two observers will be taken. Duplicate measures of anthropometry (height, weight, waist, hip, and electrical impedance measurements) will be performed by a second observer on a 5% random sample of participants. These data will be sent to the Coordinating Center for monthly analysis. Results of the analysis will be provided to the field centers and the Steering Committee on a quarterly basis. Differences between duplicate measures exceeding the following values will be considered unacceptable:

i.) **Systolic Blood Pressure**: 4 mmHg, using Y-shaped stethoscope for two simultaneous observations.
ii.) Diastolic Blood Pressure: 4 mmHg, using Y-shaped stethoscope for two simultaneous observations.

iii.) Height: 1 cm

iv.) Weight: 1 Kg

v.) Resistance: 15 ohms

vi.) Waist circumference: 2 cm

vii.) Hip circumference: 2 cm

Duplicate data for blood pressure, height, weight, impedance, hip, and waist circumferences will be compiled by the Coordinating Center and reported to the clinics and Steering Committee quarterly; in addition, distributions of measurements and digit preference for each staff member will be compiled and repeated quarterly.

Anthropometric measurements and blood pressure by standard sphygmomanometer will be observed and evaluated quarterly by the clinic supervisor. This person will also assure that each of the other operators of the impedance meter is re-certified quarterly by having him/her perform an impedance measure on the same participant as the supervisor. In addition, a simultaneous Y tube observation of each observer by the blood pressure supervisor will be made. All results will be analyzed by the Coordinating Center on a quarterly basis.

2) Laboratory tests

Duplicate blood and urine specimens will be collected on approximately 10% of the participants in the first 3 months of Phase IV and then on approximately 5% of the participants thereafter. These duplicates will be sent to the Core Laboratory in a blind fashion. Results obtained for each test will be analyzed monthly by the Coordinating Center for accuracy and consistency. The percent of pairs with differences within 5% and 10% will be computed. Correlation coefficients and technical error rates will be calculated. Poor correlation or unreasonably high technical error will be reported to the Laboratory and the Steering Committee.

3) Personal interview

Personal interviews by new staff will be observed monthly by the study coordinator until the staff member meets the standards of the study. Then new staff will be observed on a quarterly basis along with experienced interviewers. Problems and errors are identified using a checklist and corrected immediately.

4) Food Frequency Questionnaire (FFQ)

Block FFQ is self-administered; participants will receive guidance in how to fill out the questionnaire. The developer, Block Dietary Data Systems, has provided a specification manual that describes each question. Ellie Zephier, SHS Nutrition Investigator, will use this manual to train the field staff in how to instruct participants. Those participants who have difficulty will be assisted by trained staff.
5) Quality control for surveillance data

Surveillance activities at each center are monitored on a monthly basis by the Coordinating Center. Contact rates, numbers of potential events, rate of medical record abstraction and forwarding of packets for review are evaluated each month according to pre-set, expected completion rates. Final decisions on possible CVD deaths and morbid events are made by members of the Mortality Review and Morbidity Review Committees. These surveillance Committees also evaluate the quality of chart reviews and advise clinic staff when changes are needed. The Mortality Review Committee is composed of a primary physician reviewer who reviews all deaths (Dr. Maurice Sievers) and a group of six physicians who serve as secondary reviewers for all potential CVD deaths. Each physician independently determines the classification of the cause of death, and the Coordinating Center then compares the results from both physicians. Two neurologists from the Mayo Clinic are secondary reviewers and adjudicators for all cases of potential stroke. A detailed description of the steps in the process of identifying deaths and confirming the underlying cause is given in Volume 2. Monthly reports are reviewed by the Steering Committee in order to monitor the progress of surveillance and event reviews. An example of a monthly surveillance report is included in Volume 2.

6) Certification of technicians

Each center will recruit the most qualified personnel. Clinical staff will be centrally trained and certified before the examination begins and newly hired personnel will be trained at each clinic. The study coordinators will monitor the technicians quarterly to ensure accurate and consistent performance.

7) Confidentiality and security of data

All personnel with access to the collected data are required to sign a confidentiality pledge (see Appendix 7 below). Completed data forms are placed in locked file cabinets at every center and are accessible by authorized staff members only. At the Coordinating Center, the data are stored on computers that are used exclusively by the Strong Heart Study and are safeguarded by passwords that are known only to authorized personnel. The data are stored on hard disk and four copies of floppy/optical diskettes. Two of the Zip disks/optical diskettes are stored in two different locations other than the Coordinating Center office.

8) Monitoring of study progress

The Coordinating Center will work closely with the field centers to monitor recruitment and progress of the examinations. At the beginning of the study, a projected monthly number of participants to be recruited will be generated, and the Coordinating Center will monitor the progress of each field center according to these projected numbers and provide monthly progress
reports to the Steering Committee. If the percentage of projected recruitment in a certain field center falls below 80%, the PI and the field coordinator will be informed, so that the efforts can be focused on recruitment. This program proved to be an efficient tool for monitoring the progress of SHS-III and will be continued, and refined if necessary, in Phase IV of SHS. The Coordinating Center will also monitor the number of double entries, QC physical exams, and QC blinded blood samples and report to the Steering Committee monthly.

1.6.6. Statistical Analysis

a. Major statistical analyses of the SHS Phase IV data will include:

1) Epidemiological analyses:

i. determination of mortality and morbidity rates for CVD and all causes of death in the SHS cohort.

ii. estimation of the incidence of CVD and other diseases of interest in the SHS cohort.

iii. identification of risk factors that are related to cohort mortality and incidence of CVD and other diseases of interest.

iv. determination and comparison of the associations of identified risk factors for CVD, diabetes, coronary heart disease (CHD), peripheral vascular disease (PVD), and other diseases of interest and associations among the risk factors.

v. identification of markers from comprehensive echocardiography and carotid data and their association to the incidence of CVD, carotid atherosclerosis, stroke, left ventricular mass, and cardiac wall motion abnormalities, and to other risk factors.

vi. determination of changes, pattern of changes, and age effects of risk factors for CVD, diabetes, CHD, PVD, and other diseases of interest.

2) Familial aggregation analyses:

i. familial aggregation analysis of CVD, diabetes, CHD, PVD, carotid atherosclerosis, stroke and other diseases of interest to compare and estimate the correlation of the disease outcomes within different family relationships, such as parents and siblings, and to compare the odds of disease for individuals with a diseased relative with the odds of disease for individuals without a diseased relative.
ii. estimation of the effects of age, household, and environment as well as their interactions with genetic factors on identified risk factors of CVD, diabetes, and other diseases of interest, and comparison of the results with other ethnic populations.

iii. in collaboration with investigators of the SW Foundation, study the genetic and environmental etiologies of quantitative phenotypes, such as cholesterol level, body fat and blood pressure, and complex traits such as CVD and diabetes, locating and characterizing the underlying putative genes and comparing the results with other ethnic populations.

b. Methods for epidemiological analyses:

1) Mortality rates:

From the cohort mortality surveillance data, we will be able to estimate mortality rates for CVD and other causes of death. We will calculate age-, sex-, center-, and cause-specific mortality rates by using person-years which will be computed from the time of Phase I examination to the date of death or last-follow-up, whichever comes first. The total number of person-years will be the denominator and the number of deaths the numerator. The mortality rates will be expressed per 100 or 1000 person-years. These rates will then be compared to those obtained in the US and in other ethnic populations, and to those obtained in the community mortality survey of the same population. Life-table analysis techniques (1) will be used to estimate median remaining lifetime.

2) Incidence rates:

Data on disease status obtained from the cohort morbidity surveillance will be used to estimate incidence rates of CVD, diabetes, PVD, renal disease, etc. If the date of diagnosis is unknown, we can estimate an 11-year (baseline is Phase I) cumulative incidence or a 7-year (for Phase II baselines) cumulative incidence. The number of disease-free participants at baseline will be the denominator, and the number of new cases identified during the follow-up period will be the numerator. If the exact date of first event is available, we will compute the incidence rate (or incidence density) by using person-years. Incidence rates so obtained will be compared to those from other studies.

3) Association study and modeling related observations:

Statistical analyses related to mortality and to morbidity include comparisons of cumulative incidence, incidence density, mortality rates, disease-free time, and survival time distributions between “exposure” subgroups. The survival time will be calculated from the Phase I examination to the time of death or last-follow-up, and the disease-free time will be from the Phase I examination to the date of diagnosis or last-follow-up. The
distributions of survival time and disease-free time will be estimated by the Kaplan-Meier method (1). The cumulative incidence between “exposure” subgroups will be compared using the chi-square test, and the incidence rates (density) and mortality rates between “exposure” subgroups will be compared by using methods by Rothman (2). The distributions of survival time and disease-free time in different “exposure” subgroups can be compared by using the logrank or K-sample tests (1) or Cox proportional hazards model (1) or some parametric (1) (e.g. Weibull, lognormal, gamma and log-logistic) models with covariates. In order to handle longitudinal observations from Phase I to IV, the distributions of survival time and disease-free time will be modeled further as non-proportional hazards models such as the Cox model with time-dependent covariates (1), stratified model (1), multiplicative hazards model (3) and piecewise exponential model.

The association of risk factors to disease can be analyzed by using conditional or unconditional logistic regression models or the classical Cochran-Mantel-Haenszel test (4) to adjust for possible confounding factors. The data used in analyses will be accumulated from successive risk factors data observed in the SHS Phase I-III exams and disease status data observed in Phase II-IV. To adjust the effects that may be caused by related observations in the study, namely, the repeated measurements from different SHS phases for each participant, the association of disease outcome with risk factors or the association of a risk factor with the other risk factors will be assessed and modeled by utilizing the marginal models (5), generalized linear or nonlinear mixed models (6,7,8) (which include the usual models like linear or nonlinear mixed, logistic regression with or without random effects, random coefficients, repeated measurements models, etc. as special cases) under different assumptions of covariance structure of related observations. The effects of related observations on estimating and testing the parameters in these models have been adjusted by their covariance. By using these models, we will be able to assess and model the association while taking care of the problem of the related observations and the changes in disease risk factors over time and age effects. For instance, we may use a generalized linear mixed model for CVD status on covariates (such as age, sex, center, blood pressure, lipoproteins, etc.) and assume that measures (e.g., lipoproteins) for a person observed from different examinations are correlated.

c. Methods for family data analyses:

Familial aggregation analyses. By applying the marginal model, generalized linear model, or nonlinear mixed model to the family data, we will be able to assess the effects of age and different family relationships on different risk factors and then on CVD and other diseases of interest, to compare with the respective results from the SHS Phase I-III, and to compare among different age groups. For example, we may use a generalized linear mixed model to estimate and compare CVD prevalence rates among different age groups or between siblings whose parents have CVD and siblings whose parents do not have CVD in the Family Study, assuming CVD risks among members in a family are correlated. It is possible that only a few observations will be available in certain
subgroups in the family data, and therefore analyses based on the few observations may be unreliable. Thus, in addition to using the marginal models and generalized linear and nonlinear mixed models for analysis of the family data, the multivariate composite estimation method (9), various Bayes models, and empirical Bayes procedures will be used. These methods will be used in estimating and modeling risk factors and associations of risk factor to diseases in order to reduce the variance of the estimators by using additional information from other related groups.

The marginal models, generalized linear or nonlinear mixed models, and variance components models (10,11,12) will be adopted to estimate the effects of heritability, covariates, and environment, as well as their interactions, on quantitative risk factors or qualitative diseases status under different family relationships. For instance, we may use a logistic regression model for a disease status on covariates (such as age, sex, center, tribe, household, degree of Indian heritage, education, income, smoking status, alcohol consumption, physical activity, dietary covariates, family history of this disease or other related diseases) and different family relationships (e.g., husband-wife, parents-offspring, sib pairs, etc.), or a linear mixed model for a quantitative risk factor on the covariates and different family relationships. Some preliminary results from the SHS Phase III family studies have shown applications of the variance components models in heritability assessments of CVD-related phenotypes (e.g., total cholesterol, LDL, and HDL) and diabetes-related phenotypes (e.g., fasting insulin, hemoglobin, please see SW Foundation’s application).

d. Literature Cited for Statistical Analysis

1.7 PUBLICATION POLICY

The SHS Steering Committee appointed the following members to form a Publications and Presentations Committee (P&P Committee):

Dr. Elisa Lee (Chair)
Dr. Lyle Best
Mr. Richard Fabsitz
Dr. Barbara Howard
Dr. Jean MacCluer
Dr. Mary Roman

The P&P Committee shall review and approve/disapprove all paper and thesis proposals. When the P&P Committee does not reach a consensus on a proposal, or when issues concerning a proposal (or other publication matters) are particularly problematic, the matter will be referred to the SHS Steering Committee (SC). The P&P Committee will present the issues and any of its recommendations to the SC, which shall have final authority for approval or disapproval of the paper or thesis proposal (or other publication matters).

The P&P Committee shall meet or discuss by telephone, monthly, or as needed, proposals submitted for a paper or a thesis (and any other publication matters).

1.7.1 Submission of a Paper Proposal

1. Proposal

A formal paper proposal (see Appendix 8 below - this form can be downloaded – see SHS website: http://strongheart.ouhsc.edu) must be submitted to the Chair of the P&P Committee (Elisa T. Lee, PhD at elisa-lee@ouhsc.edu) at least one week prior to the P&P meeting. Upon review for completeness (including preliminary review of the analysis plan by a statistician), the proposal will be added to the agenda of the next P&P Committee meeting for action. The Chair is responsible for distributing copies of the proposal to the members of the Committee.

A formal paper proposal must include the following as a minimum:

1. Title (To maintain a cohesive body of literature, each publication using SHS data should include the phrase "Strong Heart Study" in its title and listed as a keyword whenever possible. Titles not meeting this guideline must be justified at the time of manuscript proposal submission.)
2. Primary author's name, contact information including fax and e-mail, and affiliation. Via distribution of P&P Committee minutes, the P&P Committee will periodically report its decisions to the SHS Steering Committee (SC), and SC may nominate additional co-authors for any papers that have been approved by the P&P Committee.

3. Suggested co-authors

4. Suggested key words

5. A detailed outline which includes:
   a) Introduction (rationale)
   b) Methods
   c) General analysis plan

6. Analysis responsibility (authors or Coordinating Center, CC)

7. References (the timeliness and originality of a proposal should be supported by the supplied references).

8. When submitting a proposal, authors are encouraged to send a copy of any journal articles that would support their choices for methods of statistical analysis. This will simplify the review process on the part of the statistician performing the preliminary review of the proposal.

9. Prior to submission, all proposals must be approved by an SHS P.I.

II. Review of Paper Proposal by the P&P Committee

   The P&P Committee shall review all formal proposals and make the following decisions:

   1. Approval (or approval with recommendation), deferral, or disapproval (with reasons).

   2. Upon approval, the paper is given an SHS Paper Approval Number.

   3. In the event a proposal does not receive full approval (approved with recommendations or disapproved), the P&P Committee will supply the author with a complete explanation and recommendations for re-submission, when applicable.

   4. The decision of the P&P Committee will be forwarded to the submitting author.

   5. Along with an approval memo from the Chair, the author of each approved manuscript proposal will receive an Author Agreement Form (an SHS author/investigator agreement must be signed by the author obtaining SHS data for a paper), Data Request Form, Data
Analysis Monitoring Form, and Data Analysis Request Form (Data Request/Analysis Forms are to be used by the author as needed). For maintaining better tracking, each form will be marked with the assigned SHS Paper Approval Number (see forms in Appendix 8 below). The author needs to complete, sign, and return the forms to the P&P Committee. CC (or the appropriate SHS PI) then provides required data to the authors. All primary authors must sign an agreement form before CC or the appropriate PI will provide the data.

6. The P&P Committee recommends that authors requesting data from the CC understand that a clear and concise rationale for data extraction is imperative. Representatives of the CC are well capable of streamlining the extraction of the database and analysis processes when supplied with this rationale.

7. If data analysis from the Coordinating Center (CC) is requested, the CC will assign a statistician to work with the primary author after the proposal is approved and all the required forms are returned to P&P Committee by the author. The paper may then be given a priority score if analyses are to be done by the CC. For those authors who choose to analyze their own data, CC representatives will be available for consultation. All statistical analyses in the penultimate draft that were performed outside of CC must be verified by CC before finalizing the paper.

8. Whenever an approved SHS paper proposal has no SHS PI as a co-author, the first draft of the paper must be sent to the P&P Committee Chair. The Chair will send the paper to 2 or more reviewers, and the comments of the reviewers will be communicated to the submitting author.

9. Prior to submission to a journal, the paper must be submitted by the author to NHLBI for review and to the IHS Area IRBs and the tribes for review and approval (see details in section IV below). Please note that as an integral part of the manuscript approval process, the IHS IRBs in the three centers require that all SHS manuscripts must contain the following disclaimer (verbatim): “The opinions expressed in this paper are those of the author(s) and do not necessarily reflect the views of the Indian Health Service.” A cover letter must be attached, requesting review and approval. The paper may not be submitted to a journal until the authors have received the NIH review (normally within one month of submission to NIH). The primary author is responsible for making sure that all Tribal/IHS approvals have been obtained prior to publication by contacting the responsible individual at each of the three field centers (see section IV below).

10. Minutes from the P&P Committee are circulated to the Steering Committee.

III. Analysis

If CC is responsible for the analysis, CC will assign a statistician to work with the author upon receiving the completed and signed "Request for Data Analysis Form" from the author.
The statistician is the CC representative to the writing group. Whenever the workload for CC is heavy, CC will work with the investigators in analyzing the data according to the priority scores assigned by the P&P Committee.

Guidelines for authors to use in dealing with CC are:

1. Communicate with the CC representative on the writing group and discuss the objectives of the paper, appropriate statistical methods to be used, format of presentation (tables and figures), etc.

2. Determine a timetable with the CC representative. Be sure that analysis requests are made clearly and in writing (using the "Request for Data Analysis" form) and in a way that will allow sufficient time to complete the analyses.

3. If CC falls behind, the investigator should inform the P&P Committee; if there is a problem, deadlines can be changed.

4. When the relevant statistical analyses have been performed outside of CC, the penultimate draft (next to final) must be submitted to CC so that all analyses utilized in the paper may be verified by CC prior to finalization of the manuscript.

IV. Summary of Paper Publication Process

1. An author submits a paper proposal in standard format (see form in Appendix 8 below) to the P&P Committee Chair. (Note: the phrase "Strong Heart Study" should be included in the title and listed as a keyword whenever possible).

2. The P&P Chair notifies the author of the committee decision.

3. Whenever an approved SHS paper proposal has no SHS PI as a co-author, the first draft of the paper must be sent to the P&P Committee Chair. The Chair will send the paper to 2 or more reviewers, and the comments of the reviewers will be communicated to the submitting author.

4. All statistical analyses in the penultimate draft that were performed outside of CC must be verified by CC before finalizing the paper.

5. Prior to submission to a journal, the paper must be submitted by the author to NHLBI for review (to be returned to the author within 1 month of submission) and to the IHS Area IRBs and the tribes with a lay summary and an attached cover letter requesting review and approval. These approvals are obtained through the following procedures:
a. The primary author will first send the paper to the co-authors for their input. **When the primary author feels the paper is ready for NIH review and IHS Institutional Review Board (IRB) and Tribal approval, he/she will send a copy of the manuscript (including a Tribal/lay summary) simultaneously to the following with the clear designation that the paper is being sent for such approval:**

1) Dakota Center: LaVonne Looking Elk  
Strong Heart Study - Dakota Center  
P.O. Box 9010  
Rapid City, SD 57709  
Phone: (605) 355-2377  
Fax: (605) 355-2502  
email: llooking@rapidcity.aberdeen.ihs.gov

2) Oklahoma Center: Lee Keesee  
Univ of Oklahoma Health Sciences Center  
CHB 112  
P.O. Box 26901  
Oklahoma City, OK 73190  
Phone: (405) 271-3090  
Fax: (405) 271-4390  
email: Lee-Keesee@ouhsc.edu

3) Arizona Center: Nanette Oram  
Aztec Building - Ste 250  
1616 E Indian School  
Phoenix, AZ 85016  
Phone: (602) 277-0488  
Fax: (602) 277-5979  
email: noram@medstarresearch.com  
with cc to: Marie Russell, MD  
Director, MedStar Phoenix Field Center  
email: mrussell@medstarresearch.com

4) NHLBI:  
NHLBI has instituted an electronic means for submission of manuscripts for NHLBI Review, and authors are instructed to use this system for NHLBI REVIEW. Comments will be returned to the email address provided by the author in the submission process. All manuscripts need to be submitted to the following email address for NHLBI Review: ebpdocs@nhlbi.nih.gov

**NOTE:** Please cc Dr. Richard Fabsitz, Project Officer-Strong Heart Study, (FabsitzR@nhlbi.nih.gov) when emailing your manuscript to the above NHLBI email address.
The three individuals listed in 1-3 above are then responsible for sending the manuscript for approval by Indian Health Service IRBs and the Tribes.

b. **The author must include a Tribal/lay summary** for all manuscripts, since such summaries are essential for obtaining Tribal and IHS IRB approval. The Tribal/lay summary should be no longer than one page of easily understandable text. One or two graphics illustrating major points could be included. Such summaries are critical to ensure tribal understanding of research results, and, hopefully, maintain tribal support for SHS research. **The intended journal should be mentioned for all papers in the cover letter/memo.**

c. The paper may not be submitted to a journal until the authors have received NIH review (see #4 above). Authors must check with Oklahoma, Arizona, and Dakota Centers (see contact info in #1-3 above) to ensure that IHS IRB and Tribal approvals have been obtained. This should be done at the time when the author receives reviewers’ comments from the journal and is in the process of making final revisions. The primary author is responsible for making sure that all approvals have been obtained prior to publication.

d. The manuscript must include the following disclaimer (verbatim) (usually in the Acknowledgments or in a footer on the first page): **“The opinions expressed in this paper are those of the author(s) and do not necessarily reflect the views of the Indian Health Service.”**

The intention of this procedure is to ensure that all principal investigators are aware of the status of publications and also to ensure that appropriate review by NIH and approval by IHS and the Tribes occur prior to publication.

6. After the article is published, the primary author must send at least one reprint of the published article to the NHLBI Project Officer

   Richard Fabsitz, PhD  
   Project Officer-Strong Heart Study  
   Two Rockledge Center-Rm 8178  
   6701 Rockledge Dr. MSC  
   Bethesda, MD 20892-7938  
   Phone: (301) 435-0458  
   Fax: (301) 480-1667 or 480-1455  
   email: FabsitzR@nhlbi.nih.gov

   and to each of the three persons designated in the field centers (as listed above in #1-3), who will then distribute the published articles to Tribes and Service Units in their center. The primary author should also send reprints of the published article to all co-authors.
7. **NOTE:** Papers that are likely to result in press coverage or substantial press/media interest require notice in advance to the NHLBI (contact Dr. Fabsitz) so that the staff and public information office can be prepared.

8. The P&P Chair will maintain a list of published SHS papers and papers in various stages of preparation (posted on the SHS website: [http://strongheart.ouhsc.edu](http://strongheart.ouhsc.edu)). In order to help update the status of their papers in the SHS publication list, authors are required to notify the P&P committee by sending the cover letter each time when submitting their papers to the NIH/IRBs and to a journal. Also they are required to notify the P&P when the papers are accepted by a journal for publication and when published. If using electronic transmission to submit papers, they need to copy Dr. Momotaz Begum ([momotaz-begum@ouhsc.edu](mailto:momotaz-begum@ouhsc.edu)).

9. To track the progress of approved paper proposals, the P&P Committee distributes a status survey of the approved papers by emailing a Paper Tracking Status Form every six months. The authors must fill out the respective space regarding the progress/current status of their paper(s) and return the form to the committee.

10. If the P&P Committee determines that progress on a manuscript is taking an unduly long time, the Chair will communicate with the author, asking for a plan of action for completing the paper or for the author(s) to release the topic for authorship by someone else.

11. In rare cases, the P&P Committee may need to make a recommendation to the Steering Committee regarding reassignment of a paper topic.

**NOTE:** It must be recognized that any step of this approval process may entail requested revisions and re-submissions by the authors.

V. Approval of Abstracts  *(Please note that a Lay Summary is now required by the IHS IRB of the Dakota Center)*

1. It is assumed that all SHS abstracts will have at least one SHS PI as a co-author. The PI co-author is responsible for ensuring that the abstract abides by SHS standards and guidelines. If none of the PIs is a co-author, the abstract must be approved by the PI who works most closely with the authors. The title of the abstract should include the phrase "Strong Heart Study" whenever possible.

2. Abstracts must be submitted for NHLBI review. NHLBI has instituted an electronic means for submission of abstracts for NHLBI Review, and authors are instructed to use this system for NHLBI REVIEW. Comments will be returned to the email address provided by the author in the submission process. All abstracts need to be submitted to the following email address for NHLBI Review:

   [ebpdocs@nhlbi.nih.gov](mailto:ebpdocs@nhlbi.nih.gov)
3. Abstracts must also be sent to the Dakota Center for approval by their IRB. (The Oklahoma and Arizona Centers do not have this requirement.) Please include a brief LAY SUMMARY of the work to be presented. Please specify that the abstract is being forwarded for Dakota Center IRB approval, include information about the meeting or other venue intended for the presentation, and send the abstract to:

   LaVonne Looking Elk  
   Strong Heart Study - Dakota Center  
   P.O. Box 9010  
   Rapid City, SD 57709  
   Phone: (605) 355-2377  
   Fax: (605) 355-2502  
   email: llooking@rapidcity.aberdeen.ihs.gov

4. Prior to presenting the paper, the presenting author should verify (if notice has not been received) that the NHLBI review and Dakota Center IRB approval have been received.

VI. Summary of Thesis Approval Process

1. A college student who wishes to use SHS data for a thesis must submit a thesis proposal to the P&P Committee Chair. (See thesis proposal form below in Appendix 8 - also, the form can be downloaded – see SHS website: http://strongheart.ouhsc.edu )

2. The Thesis Proposal must include the Prospectus for the Doctoral Thesis/Dissertation or an Outline for a Masters/Bachelor Thesis. If a prospectus is not required by the doctoral degree program, the student needs to submit a detailed outline.

3. A thesis proposal (see Appendix 8 below) must include: Title of Thesis, Name of Degree Candidate, Type of Degree, Candidate Affiliation including the contact information (full address, telephone, fax and email) and name of the Primary Mentor, including the same type of contact information.

4. Upon approval, the thesis is given an SHS Thesis Number, and the P&P Chair notifies the student of the committee decision. The student is provided with the Agreement Form, Data Request Form, and Data Analysis Monitoring Form to complete, sign, and return to the P&P Committee (see forms in Appendix 8 below). CC (or the appropriate SHS PI) then provides required data to the student.

5. As part of the agreement, the student agrees to write at least one paper based on the approved thesis proposal. At the time the student is ready to develop a paper for publication, the student must submit a separate paper proposal to the P&P Chair and follow all of the P&P paper approval procedures described above.
VII. Forms for Paper and Thesis Proposals

Appendix 8 below contains the desired formats for paper and thesis proposals submitted to the P&P Committee. Also, the forms can be downloaded from the Internet – see SHS website: [http://strongheart.ouhsc.edu](http://strongheart.ouhsc.edu). Additionally, upon receiving requests from the SHS authors, these forms will be transmitted electronically by email. For the electronic forms, email or word processing software may be easily implemented for form completion and submission. "Cut and Paste" or other electronic means may be used to download the proper form, to fill it in (electronically expanding the space as much as needed for each section), and to submit the form to the P&P Chair by email, or more traditional means if desired. An electronic file containing the SHS Publication Policy will also be included with the proposal form to make the prospective authors aware of the rules and procedures of the SHS P&P Committee.

The SHS P&P paper and thesis proposal forms (see Appendix 8 of this Volume) are:

1. Strong Heart Study Paper Proposal
2. Strong Heart Study Thesis Proposal Form
3. Agreement for Data Distribution/Paper/Thesis Proposals
4. Strong Heart Study Data Analysis Monitoring System
5. Strong Heart Study Request For Data
6. Strong Heart Study Request For Data Analysis
7. Sample of paper proposal approval Memo
8. Sample of thesis proposal approval Memo
9. Agreement for Ancillary Studies
10. Collaborative Agreement for Sharing SHS Data
1.8. ANCILLARY STUDIES POLICY

1.8.1 General Policy

To enhance the value of the Strong Heart Study and to ensure the continued interest of the investigators, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. Nevertheless, to protect the integrity of the Study, such ancillary studies must be reviewed and approved by the Steering Committee before their inception. In general, ancillary studies require outside (non-Strong Heart Study) funding.

1.8.2 Definition of an Ancillary Study

An ancillary study is one based on information from the Study participants in an investigation, which is not described in the Strong Heart Study protocol and involves data which are not collected as part of the routine Strong Heart Study data set. The core Strong Heart Study includes the use of blood and DNA stored for case-control studies selected by the Steering Committee; these are not considered ancillary studies.

1.8.3 Requirements for Approval of an Ancillary Study

Before an ancillary study can be approved, it must be shown that the ancillary study will have scientific merit but will not do any of the following:

(1) Interfere with the completion of the main objectives of the Strong Heart Study.
(2) Adversely affect participant cooperation or compliance in the Strong Heart Study.
(3) Create a serious diversion of study resources (personnel, equipment, or study samples), either locally or centrally.
(4) Jeopardize the public image of the Strong Heart Study.

1.8.4 Preparation of Request for Approval of an Ancillary Study

A written request for approval of an ancillary study should be submitted to the Steering Committee and should contain the following information:

(1) Description of objectives.
(2) Scientific merit of study.
(3) Methodology for data collection.
(4) Proposed statistical analyses.
(5) Names of definite or possible collaborators.
(6) Proposed funding sources.
(7) Discussion of impact on main Strong Heart Study.
1.8.5 Review of Ancillary Study Proposals

The Steering Committee, often in consultation with the Sample Committee, will review and will approve, reject or request modification of ancillary study proposals in a timely manner. At least one Strong Heart Study investigator must be included as a co-investigator in each proposal. Strong Heart Study investigators other than those submitting the proposal may request to become collaborators on a proposal, if they have a specific interest in the topic. The key criteria for approval of proposals are scientific merit and impact on the main Study. Formal IRB approval will be required, if such studies require interviews or additional procedures of the participants. The principal investigator of the ancillary study, working with the three field centers, is responsible for obtaining approval from the Indian communities, the grantee institution IRBs, and the three area IHS IRBs.

If the proposal will utilize laboratory specimens and data previously collected or routinely collected as part of SHS to answer research questions related to cardiovascular and pulmonary diseases, the IRBs will be informed of the changes in protocol with the annual IRB report. If the Steering Committee feels that the ancillary study will result in a major change in the protocol, the principal investigator will be required to seek IRB approval prior to conducting the study. Any ancillary study that is not related to cardiovascular or pulmonary diseases will require IRB approval.

1.8.6 Analysis and Publication of Results of Ancillary Studies

The principal investigator of the ancillary study, and if necessary the Steering Committee, will consult with the Coordinating Center during data analysis to ensure that all study data used in analysis of ancillary study results are consistent with data in the main study database. Ancillary study investigation personnel will be required to sign an Agreement for Ancillary Studies Form (see form in Appendix 8 below). This agreement stipulates that the ancillary study investigators agree to submit paper proposals for approval by the SHS P&P Committee and to submit draft manuscripts for approval by the NHLBI, the IHS IRBs, and the tribes (see section 1.7.1 IV above). Additionally, abstracts for presentations at meetings require approval by the NHLBI and the Dakota Center IHS IRB (see section 1.7.1 V above). The investigator who assumes lead responsibility for the ancillary study shall be listed as senior author. The phrase "The Strong Heart Study" should be included in the manuscript title and listed as a key word whenever possible. Manuscripts will also contain an acknowledgment section listing individuals deemed appropriate. Upon publication, reprints must be distributed as specified above in section 1.7.1 IV.

1.8.7 Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to participating tribes and to participants and/or their physicians, if medically useful. Such reporting should follow standard Strong Heart protocol for notification of participants.
RELATED READING


APPENDIX
APPENDIX 1

THE STRONG HEART – FAMILY STUDY
CARDIOVASCULAR DISEASE IN AMERICAN INDIANS, PHASE IV

Principal and Co-Investigators

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FAX: (301) 853-7591
Phoenix Office: (602) 277-0488
E-mail: Barbara.V.Howard@medstar.net

FAX: (301) 853-7554
E-mail: Helaine.E.Resnick@medstar.net

Dakotas Center
Lyle Best, M.D.
Principal Investigator
Strong Heart Study-Dakota Center
PO Box 9010
Rapid City, SD 57709
Express Service, change last two lines to:
3200 Canyon Lake Drive
Rapid City, SD 57702
Office: (605) 355-2401
FAX: (605) 355-2502

Home Address/Info:
R.R. 1, Box 88
Rolette, ND 58366
(Address good for Express Service)
Home: (701) 246-3884
FAX: (701) 246-3698(notify by phone before sending fax)
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Adjudicator, Mortality Review
Medical Affairs
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MedStar Research Institute
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Ellie Zephier, R.D., M.P.H.
Principal Investigator
Strong Heart Dietary Study
Indian Health Service
115 4th Avenue, SE
309 Federal Building
Aberdeen, SD 57401
Office: (605) 226-7456
FAX: (605) 226-7688
E-mail: ellie.zephier@ihsabr.ihs.gov

Oklahoma Center and Coordinating Center

Elisa T. Lee, Ph.D.
Principal Investigator
Center for American Indian Health Research
University of Oklahoma Health Sciences Center
P. O. Box 26901, Rm. CHB100
Oklahoma City, OK 73190
Express Service, change last two lines to:
801 NE 13th St., Rm. CHB100
Oklahoma City, OK 73104
Office: (405) 271-3090
FAX: (405) 271-4390
E-mail: elisa-lee@ouhsc.edu

Everett R. Rhoades, M.D.
Native American Prevention Research Center
University of Oklahoma Health Sciences Center
P. O. Box 26901, Rm. ROB532
Oklahoma City, OK 73190
Express Service, change last two lines to:
800 NE 15th St., Rm. ROB532
Oklahoma City, OK 73104
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FAX: (405) 271-6285
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THE STRONG HEART – FAMILY STUDY
CARDIOVASCULAR DISEASE IN AMERICAN INDIANS, PHASE IV

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THE STRONG HEART – FAMILY STUDY
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APPENDIX 5

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CARDIOVASCULAR DISEASE IN AMERICAN INDIANS, PHASE IV

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APPENDIX 7

THE STRONG HEART STUDY IV

Cardiovascular Disease in American Indians

Confidentiality Pledge

I, ________________________________, understand that data obtained for subjects of research projects are confidential.

I will not reveal to unauthorized persons any patient’s name or any identifying information or any other information obtained from subjects of the project entitled, “Cardiovascular Disease in American Indians (The Strong Heart Study)”.

I will not allow any persons who are not authorized members of the Strong Heart Study staff to have access to any information collected from or about the subjects.

I will properly store the data forms, computer printouts and other documents in locked file cabinets or drawers to protect confidentiality.

I understand that breach of this confidentiality pledge is grounds for dismissal from employment on the Strong Heart Study.

I will return all data to the Principal Investigator when my employment terminates.

______________________________
Staff Member

______________________________
Principal Investigator

______________________________
Date

Strong Heart Study IV  06/01/2001    I- Appendix 7-1    SHS Confidentiality Pledge
STRONG HEART STUDY

PAPER PROPOSAL

Title of Paper: (include the phrase “Strong Heart Study” whenever possible)

Name of Primary Author:

Author Affiliation:

Suggested Co-Authors:

Suggested Key words:

Outline of Paper:

a) Introduction (Rationale)
b) Methods
c) General analysis plan

Analysis Responsibility: (authors or Coordinating Center)

Note: 1) If the authors perform the statistical analyses, they must agree to submit the penultimate (next to final) draft to the Coordinating Center for verification of all analyses utilized in the manuscript.

2) Authors must comply and respond regularly to the status survey on their approved paper proposals conducted by the SHS P&P Committee twice a year.

3) Papers lacking a PI as a co-author. Drafts of these papers will need to be sent to the P&P committee for review by at least two (2) reviewers (selected by the Chairperson). This review is the first step that must be completed prior to review of the penultimate draft by NHLBI/Tribes/IHS.

4) PLEASE NOTE: A Lay Summary is required when submitting the completed draft for NHLBI review and IHS IRB and tribal approvals. Also, the IHS IRBs require that all SHS manuscripts must contain the following disclaimer (verbatim): “The opinions expressed in this paper are those of the author(s) and do not necessarily reflect the views of the Indian Health Service.”

Submitted by: (Corresponding author, address, telephone, fax and e-mail for correspondence)

Date:
STRONG HEART STUDY

THESIS PROPOSAL FORM

Title of Thesis:

Name of Degree Candidate:

Type of Degree:

Candidate Affiliation:

Primary Mentor:  (With e-mail, telephone and fax numbers, and address for correspondence)

Descriptions of Thesis Plan:

1. Prospectus - for Doctoral Thesis/Dissertation (if prospectus is not required by your degree program submit a detailed outline).

2. Outline - for Masters/Bachelor Thesis

Submitted by:  (Corresponding candidate, with telephone and fax numbers and address for correspondence)

Date:
Agreement for Data Distribution/Paper/Thesis Proposal*

To: Strong Heart Study Coordinating Center

From: __________________________(Principal Investigator / First Author)

Institution/Address: __________________________________________

Name of the associated SHS PI / Mentor: __________________________

Title of Study, Paper, or Thesis: __________________________

Paper/Thesis Number (if known): __________________________

I agree to read and follow the SHS protocol with regard to distribution and analysis of Strong Heart Study data that I request or that I generate in my research/paper/thesis. I have attached a research protocol or a paper/thesis proposal describing how I will use these data to better understand cardiovascular disease and its related diseases in American Indians.

I agree to protect the confidentiality and privacy of the SHS participants and the security of the data. I am not to transfer or disclose any individually identifiable information about the SHS participants at any time. Violation of the confidentiality agreement is considered a breach of confidentiality and may leave requesting investigator liable to legal action on the part of Study participants and their families. I also agree that the SHS data provided to me by the SHS Coordinating Center or SHS investigators are to be used only for the research protocol or the paper/thesis approved by the SHS P&P Committee or the Steering Committee. I further agree not to distribute SHS data to anyone else.

For each paper I wish to write using any SHS data, I agree to comply with the SHS Publication Policy and to submit a paper proposal for review and approval of the SHS P&P Committee. Further approvals from the NHLBI, IHS, and the participating tribes will be needed prior to submission to any journal for publication. If approval from the SHS P&P Committee, the NHLBI, IHS, or the participating tribes is not granted, I agree not to publish these results.

I understand that the SHS P&P Committee or Steering Committee will assist me in revising my paper in such a way that will make it acceptable for publication. I agree to include at least one of the SHS investigators as a co-investigator and a co-author. I will send a reprint of my published article to the NHLBI Program office, and all other as detailed in the SHS P&P Publication Policy.

Signed: __________________________ Date: __________________________

* Each requesting investigator must complete this agreement separately.
**Strong Heart Study Data Analysis Monitoring System**

When authors/researchers request Strong Heart Study (SHS) data for any purpose, the Strong Heart Study Coordinating Center (SHS-CC) would like to know how you manage and analyze the data. By answering the following questions, the SHS-CC is better able to track SHS data utilization patterns and to provide needed information for quality control. Thank you for your cooperation.

1. Do you use any of the following statistical package(s) for data analyses? Check all applicable.

   ___ a. SAS
   ___ b. SPSS
   ___ c. BMDP
   ___ d. S+
   ___ e. Statistic
   ___ f. StatXact
   ___ g. Other, specify: __________________________________________

2. Other than the routine SHS derived variables, do you plan to derive any variables for your analysis purposes?

   ___ Yes.               ___ No.

3. If you plan to derive your own variable(s), will you consult with the SHS-CC?

   ___ Yes.               ___ No.

   If you derive certain variables for your analysis purpose, please attach a copy of the algorithm that you will use to define your variable(s) and the program to generate the variable(s)
4. Do you usually use any of the following procedures in your statistical analyses? Check all applicable.
   ___ a. Multiple regression
   ___ b. Logistic regression
   ___ c. Time-related variables analysis
   ___ d. Modeling
   ___ e. Simulation
   ___ f. Other, specify: ________________________________

5. What training does your statistician(s) have? Check all applicable.
   ___ b. Doctoral degree in other field but with quantitative training.
   ___ c. Master degree in statistics/biostatistics/math statistics.
   ___ d. Master degree in other field but with quantitative training.
   ___ e. Bachelor degree in statistics/biostatistics/math statistics.
   ___ f. Bachelor degree in other field but with quantitative training.
   ___ g. Other, specify: ________________________________

Feedback:

Please return to Strong Heart Study-Coordinating Center either by email or fax as soon as possible.
STRONG HEART STUDY
REQUEST FOR DATA

Title of project:

Investigator(s):

Purpose:
- Paper
- Abstract for professional conference
- Invited talk
- Pilot data for grant or contract submission
- Quality control or local monitoring
- Other

Date Needed: _______ / _______ / _______ (please allow 1-2 weeks from data request received)

Data for Study Period:
- Phase-I
- Phase-II
- Both

Center:
- Arizona
- Oklahoma
- South/North Dakota
- All 3 centers

Variables Needed:(List all the variables)

************************************************************************************
COORDINATING CENTER USE ONLY:

Date Received:

Date Data Delivered:
STRONG HEART STUDY

REQUEST FOR DATA ANALYSIS

Title of project:

Major hypotheses: 1)  
2)  
3)  
4)  
5)  

Purpose: Paper  
Abstract for professional conference  
Invited talk  
Pilot data for grant or contract submission  
Quality control or local monitoring  
Other

Investigator(s):

Expected date of completion: mm/dd/yy

Variables to used: (List all the variables)
Statistical methods to be used (check all that apply):

- Summary statistics and frequencies
- Simple correlation and partial correlation
- Regression analyses
- t-test, ANOVA, and multiple comparison
- Logistic regression
- Other
  (Specify)

Comments:
THE UNIVERSITY OF OKLAHOMA
HEALTH SCIENCES CENTER
CENTER FOR AMERICAN INDIAN HEALTH RESEARCH

FAX TRANSMITTAL

TO:                              FAX NO.:

FROM:   Elisa T. Lee, PhD       FAX NO.: (405) 271-4390
    SHS P&P Committee

DATE:  

SUBJECT:  Paper proposal entitled:

SHS P&P Committee decision:

_____ Approval with recommendations as listed below:

_____ Disapproval

Recommendations:

Assigned paper no.:

(Please fill out and return all the forms attached with this memo. Refer to the above number for all correspondence about this paper. When the penultimate draft is ready to circulate, a copy must be provided to the statistician(s) performing the analyses at the CC. Please inform us when this paper is approved by the NIH or accepted by a journal and if there is a change of the title. It is very important that you respond promptly during our ‘Paper Progress Survey’ done twice a year.)

College of Public Health, P.O. Box 26901, Oklahoma City, OK 73190, Phone: (405) 271-3090
FAX TRANSMITTAL

TO: 
FAX NO.: 

FROM: Elisa T. Lee, PhD  
SHS P&P Committee 
FAX NO.: (405) 271-4390

DATE: 

SUBJECT: Dissertation/Thesis proposal entitled:

SHS P&P Committee decision:

_____ Approval with recommendations as listed below:

_____ Disapproval

Recommendation:

Assigned thesis approval no.: T

Please fill out and return all forms attached with this memo to SHS P&P Committee. Please include the above thesis approval number in all correspondence with us about this thesis. Also, be advised that, you need to write a paper for publication based on the SHS data used for this thesis, and you must submit a paper proposal to the SHS P&P Committee prior to writing that paper.

NUMBER OF PAGES _____ (INCLUDING COVER SHEET)

College of Public Health, P.O. Box 26901, Oklahoma City, OK 73190, Phone: (405) 271-3090
Agreement for Ancillary Studies

To: Strong Heart Study Coordinating Center

From: ______________________________

Name of the Ancillary Study: ______________________________________________________

________________________________________________________________________________

I agree to read and follow the SHS protocol with regard to analysis of Strong Heart Study data that I request or that I generate in my ancillary study. I will comply with the SHS policies regarding maintaining data security and confidentiality. I have attached a research protocol describing how I will use these data to better understand cardiovascular disease and its related diseases in American Indians and how to benefit the health of American Indians.

I agree that the SHS data obtained by me in my ancillary study or provided to me by the SHS Coordinating Center or SHS investigators is to be used only for studies approved by the SHS Steering Committee. I further agree not to distribute SHS data to anyone else.

I agree to comply with the SHS Publication Policy and to submit any papers resulting from the ancillary study for review and approval of the SHS P&P Committee, NHLBI, IHS, and the participating tribes. If approval for publication is not granted, I agree not to publish these results.

I understand that the SHS Steering Committee will assist me in revising my report in such a way that will make it acceptable for publication (after achieving proper approvals). I agree to include at least one of the SHS investigators as a co-investigator and a co-author. I will send a reprint of my published article to the NHLBI Program office and all others as detailed in the Publication Policy.

Signed: ________________________________ Date: _____________
Collaborative Agreement for Sharing SHS Data*

To: Strong Heart Study Coordinating Center

From: _______________________(Principal Investigator)

Institution/Address: ____________________________

Name of the associated SHS PI: __________________________

Title of Collaborative Project: __________________________

I agree to read and follow the SHS protocol with regard to distribution and analysis of Strong Heart Study data that I request or that I generate in my collaborative project. I have attached a collaborative project protocol describing how I will use these data to better understand cardiovascular disease and its related diseases in American Indians.

I agree that the above-named SHS PI or his/her designee will be included as a member of the collaborative group in order to represent SHS and to participate actively and fully in development of all analysis plans for the collaborative project.

I agree to protect the confidentiality and privacy of the SHS participants and the security of the data. Violation of the confidentiality agreement is considered a breach of confidentiality and may leave the requesting investigator liable to legal action on the part of the SHS participants and their families. I will not transfer or disclose any individually identifiable information about the SHS participants at any time. I will not make any portion of the SHS database available to the public. I also agree that the SHS data provided to me by the SHS Coordinating Center or SHS investigators are to be used only for the above-named collaborative project, as approved by the SHS P&P Committee or the SHS Steering Committee. I further agree not to distribute SHS data to anyone else.

The SHS data provided for this collaborative project and any data derived through this collaboration will be accessed solely by me or individuals working on this project under my supervision. I agree to maintain confidentiality of the data through storage of data in locked file cabinets and secure computers. Upon completion of all analyses for this collaborative project, I agree to delete all copies of the SHS data and derived data from all computers and media in which the data have been stored. I further agree to destroy or return to the SHS Coordinating Center any non-eraseable media, such as CD-ROMs and hardcopies containing the SHS data and derived data.
For each paper I wish to write using any SHS data, I agree to comply with the SHS Publication Policy (see SHS Phase IV manual, vol. 1, sect. 1.7, available at http://strongheart.ouhsc.edu/) and to submit a paper proposal for review and approval of the SHS P&P Committee. Further approvals from the NHLBI, IHS, and the participating tribes will be needed prior to submission to any journal for publication. If approval from the SHS P&P Committee, the NHLBI, IHS, or the participating tribes is not granted, I agree not to publish these results. If my paper is published, I will send a reprint of the published article to the NHLBI Program office and all others as detailed in the SHS P&P Publication Policy, sect. 1.7.1, IV (see vol. 1 of SHS Phase IV manual at http://strongheart.ouhsc.edu/).

I agree to acknowledge the contributions of the SHS Investigators in any and all oral and written presentations and publications resulting from analysis of data. I will include the following disclaimer in my manuscript(s): “The opinions expressed in this paper are those of the author(s) and do not necessarily reflect the views of the Indian Health Service.”

Signed: _____________________________ Date: __________________________

*The principal investigator of the collaborative project must sign this agreement.