CARDIOVASCULAR DISEASE IN AMERICAN INDIANS
(PHASE III)

OPERATIONS MANUAL - VOLUME ONE

GENERAL DESCRIPTION AND SURVEILLANCE PROCEDURES

THE NATIONAL HEART, LUNG AND BLOOD INSTITUTE
OF THE NATIONAL INSTITUTES OF HEALTH
THE STRONG HEART STUDY

Cardiovascular Disease in American Indians (Phase III)

Operations Manual

Volume One

GENERAL DESCRIPTION AND SURVEILLANCE PROCEDURES

September 15, 1997

For copies, please contact

Strong Heart Study Coordinating Center

Center for American Indian Health Research

University of Oklahoma Health Sciences Center
College of Public Health

P.O. Box 26901
Oklahoma City, OK 73190
ACKNOWLEDGMENTS

The members of the Steering Committee of the Strong Heart Study would like to acknowledge that this manual and the extension of this study would not have been possible without the contributions and support of a large number of individuals and organizations. First, in the preparation of the manual, we would like to acknowledge contributions and in some cases interview forms or instruction sheets from the following studies: Framingham, CARDIA, ARIC (Atherosclerosis Risk in Communities), CHS (Cardiovascular Health Study), The Longitudinal Diabetes Study of the Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health and the Diabetic Renal Disease Study. The Steering Committee also wishes to express its appreciation to the thirteen Tribal Communities, whose approval and support have been so willingly offered and whose members are participants in the Strong Heart Study. We wish to thank the Indian Health Service for providing us with access to medical records and reports which have facilitated the planning and execution of the study. Finally, we wish to thank the staff of the Clinical and Genetic Branch, Epidemiology and Biometry Program, Division of Epidemiology and Clinical Applications Branch of the National Heart, Lung and Blood Institute for making this study possible.
MANUAL ONE

GENERAL DESCRIPTION AND SURVEILLANCE PROCEDURES

Table of Contents

1. General Description and Study Management

1.1 Background

1.1.1 General

1.1.2 Scientific Background

1.2 Research Objectives

1.3 Study Design

1.3.1 Surveillance

1.3.2 Clinical Examination

1.4 Study Questions

1.5 Study Management

1.5.1 Introduction

1.5.2 Confidentiality of Data

1.5.3 Communications

1.6 Data Management and Statistical Analysis

1.6.1 Data Forms and Guidelines for Completing Forms

1.6.2 Procedures for Data Entry and Verification of Completeness

1.6.3 Data Transmission

1.6.4 Data Backup

1.6.5 Quality Assurance Program

1.6.6 Statistical Analysis

Strong Heart Study III 9/26/97
1.7 Publication Policy ......................................................... 22

1.7.1 Submission of a Paper Proposal .................................. 22

1.8 Ancillary Studies Policy ................................................. 32

1.8.1 General Policy ......................................................... 32
1.8.2 Definition of an Ancillary Study .................................. 32
1.8.3 Requirements for Approval of an Ancillary Study .......... 32
1.8.4 Preparation of Request for Approval of an Ancillary Study ......................................................... 32
1.8.5 Review of Ancillary Study Proposals ......................... 32
1.8.6 Analysis and Publication of Results of Ancillary Studies .. 33
1.8.7 Agreement for Ancillary and Collaborative Investigation .. 34
1.8.8 Feedback of Results of Ancillary Studies to Participants .. 34

2. Overview of Strong Heart Study Phase III Mortality and Morbidity Surveillance

2.1 Objectives .................................................................. 35

2.2 Overview of Surveillance Procedure .............................. 35
  2.2.1 General Surveillance Methodology ......................... 35
  2.2.2 Specific Surveillance Approaches ......................... 38

2.3 Surveillance Staff ....................................................... 39

2.4 Surveillance Reporting ................................................ 39

2.5 General Guidelines for Processing Mortality and Morbidity Packets .... 42

3. Mortality Surveillance

3.1 Mortality Surveillance .................................................. 44
  3.1.1 Detailed Procedures for Mortality Surveillance .......... 44
  3.1.2 Review of Medical Charts of the Decedents ............ 47
  3.1.3 Informant Interview ............................................ 48
  3.1.4 Death Occurring Outside the Study Community ...... 48

Strong Heart Study III 9/26/97
3.2 Definitions of CVD Deaths .................................................................................. 49
  3.2.1 Definite Fatal Myocardial Infarction (MI) ................................................. 49
  3.2.2 Definite Sudden Death Due to Coronary Heart Disease (CHD) ...................... 50
  3.2.3 Definite Fatal CHD ..................................................................................... 50
  3.2.4 Possible Fatal CHD .................................................................................... 51
  3.2.5 Definite Fatal Stroke ................................................................................. 52
  3.2.6 Possible Fatal Stroke ............................................................................... 52
  3.2.7 Definite Fatal CHF .................................................................................... 52
  3.2.8 Possible Fatal CHF ................................................................................... 53
  3.2.9 Other Fatal CVD ....................................................................................... 53

3.3 Definitions of Abnormal ECG, Abnormal Enzymes and Prolonged Chest Pain ................................................................................. 54
  3.3.1 Abnormal ECG ......................................................................................... 54
  3.3.2 Abnormal Enzymes .................................................................................. 56
  3.3.3 Prolonged Cardiac Pain ........................................................................... 57

3.4 Mortality Survey Forms ...................................................................................... 57

4. Morbidity Surveillance

  4.1 Eligible Population ......................................................................................... 59

  4.2 Surveillance Events ......................................................................................... 59

  4.3 Diagnostic Criteria: Non-Fatal Myocardial Infarction ..................................... 59
     4.3.1 Definite Non-Fatal MI ............................................................................. 59
     4.3.2 Possible Non-Fatal MI ........................................................................... 59
     4.3.3 Definite Coronary Heart Disease (CHD) ................................................ 60
     4.3.4 Possible Coronary Heart Disease (CHD) ................................................ 60
     4.3.5 Other Non-Fatal CVD ............................................................................ 60
     4.3.6 ECG Tracings To Be Photocopied .......................................................... 60

  4.4 Diagnostic Criteria: Non-Fatal Stroke ............................................................ 63
     4.4.1 Definite Non-Fatal Stroke ...................................................................... 63
     4.4.2 Possible Non-Fatal Stroke ..................................................................... 63
     4.4.3 Unequivocal Laboratory Findings .......................................................... 64
4.5 Definite CHF ................................................................. 64
4.6 Abnormal ECG ............................................................. 65
4.7 Abnormal Enzyme ........................................................ 67
4.8 Prolonged Cardiac Pain .................................................. 68
4.9 Procedure for Identification of Incident and Recurrent Cases .............................................. 69
4.10 Morbidity Survey Forms ............................................... 71

5. Training and Quality Control of Mortality & Morbidity Surveillance

5.1 Training ................................................................. 72
5.2 Quality Control ........................................................ 72
  5.2.1 Ascertainment of Cause of Death ................................ 72
  5.2.2 Review of Non-Fatal CVD ........................................... 72

Related Readings ............................................................ 73

APPENDIX A

1 The Strong Heart Study III -- Principal and Co-Investigators .......................................... 1
2 The Strong Heart Study III -- Organizational Structure
   Steering Committee ....................................................... 3
3 Organizational Chart of the Strong Heart Study ............................................................... 4
4 The Strong Heart Study III -- Subcommittees ................................................................. 5
5 The Strong Heart Study III -- Other Key Personnel ......................................................... 6
6 The Strong Heart Study III -- Consultants ................................................................. 10
7 The Strong Heart Study III -- Confidentiality Pledge .................................................... 12
8 Study Communities and Codes ................................................................. 13
9 Codes for IHS Facilities by Area and Service Unit .................................................. 23
10 Non-IHS Hospitals and Codes ................................................................. 28
11 Personnel Codes ........................................................ 31
### APPENDIX B  Instructions for Mortality/Morbidity Surveillance Data Forms

<table>
<thead>
<tr>
<th>Page</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Instructions for Death Certificate Form</td>
</tr>
<tr>
<td>13</td>
<td>Informant Interview Form Instructions</td>
</tr>
</tbody>
</table>

### APPENDIX C  Mortality Surveillance Data Forms

<table>
<thead>
<tr>
<th>Page</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Death Certificate Form</td>
</tr>
<tr>
<td>15</td>
<td>Informant Interview Form and Instructions</td>
</tr>
<tr>
<td>16</td>
<td>Autopsy Report Form</td>
</tr>
<tr>
<td>17</td>
<td>Photocopy Checklist for Medical Records Review</td>
</tr>
<tr>
<td>18</td>
<td>Mortality Survey Final Decision Form II</td>
</tr>
<tr>
<td>19</td>
<td>Mortality Survey Packet Checklist</td>
</tr>
</tbody>
</table>

### APPENDIX D  Morbidity Surveillance Data Forms

<table>
<thead>
<tr>
<th>Page</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Master List of Hospitalization and Outpatient Visits</td>
</tr>
<tr>
<td>21</td>
<td>Morbidity Survey Medical Records Abstract and Checklist</td>
</tr>
<tr>
<td>22</td>
<td>Morbidity Survey Decision Form</td>
</tr>
<tr>
<td>23</td>
<td>Cardiovascular Test Procedures Abstract</td>
</tr>
</tbody>
</table>
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 (1). 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

Although age-adjusted mortality rates for cardiovascular disease are lower in American Indians than in the U.S. population as a whole, 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. Age-adjusted mortality rates for cerebrovascular disease were similar to U.S. rates for Oklahoma and Pima Indians and higher for Aberdeen Area Indians in 1981-83.

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. The relatively low rates of cardiovascular disease in American Indians as a group obscure both regional differences in heart disease and the high mortality rates from heart disease in younger Indians (those aged 25-44 years). The 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.

The Strong Heart Study was initiated in response to a recommendation by the Subcommittee on Cardiovascular and Cerebrovascular Disease of the Secretary of Health and Human Services Task Force on Black and Minority Health that concluded that information on CVD in American Indians was inadequate.
B. Description of Strong Heart Study Phases I and II

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 from October 1, 1988 to July 31, 1996 and 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 two components. 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 of resident tribal members (the cohort). During the 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. 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 Phase I included fasting and post-load glucose and fasting insulin, fasting lipids, apoproteins B and Al, 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 Phase II 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 and an echocardiogram 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 SHS has shown that the three groups of American Indians included in the study are not homogenous with respect to cardiovascular disease and its risk factors. Initial data analysis indicate that the prevalence of ECG diagnosed myocardial infarction varies: among non-diabetic participants, southwestern Oklahoma Indians have the highest (5.8%), followed by Sioux Indians in North and South Dakota (4.5%), and the Pima Indians in Arizona have the lowest (2.9%). For diabetic patients, Sioux Indians have highest rate (10.4%), Oklahoma Indians are slightly lower (9.2%), and the Pima Indians have the lowest rate (6.3%).

Preliminary analyses of our data indicate that the prevalence of cardiovascular disease (CVD) risk factors also differs from center to center. Diabetes is high in all groups, but highest among the Pimas in
Arizona (over 65% prevalence). Mean levels of cholesterol in Sioux and Oklahoma Indians are comparable to those for the U.S. (all races) but considerably lower among the Pimas. The prevalence of smoking is high in the Sioux (approximately 50%), low in the Pimas and intermediate in Oklahoma Indians. Hypertension is less prevalent than in the U.S. in all groups, but the prevalence is higher among the Pima and Oklahoma Indians than among the Sioux. A high prevalence of sedentary lifestyle exists in all three groups. Prevalence of obesity is high in all three groups and highest in the Pimas. Genetic admixture was determined by interview: over 90% of Pimas are full blood Indian, less than half of the Sioux are full blood, and seventy-three percent of Oklahoma Indians are full blood.

C. Rationale for Phase III of the Strong Heart Study

The Strong Heart Study is the largest multi-center 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 rates 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. By the time of the Phase III examination, participants will range in age from 53 - 82 years. Data on prevalent CHD showed differences in rates between centers, and the availability of baseline data from the Phase I and II 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. In addition, it will be possible to evaluate changes in risk factors as the cohort ages. 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 risk factors and prevalence of disease.

In Phases I and II, the end-points of interest have been fatal and non-fatal cardiovascular events, and there have been no direct assessments of atherosclerosis. Ultrasound measurements of the carotid arteries will provide the opportunity to assess the relationships of arterial intimal thickness and discrete atherosclerosis to the risk factors previously measured. In addition, the availability of echocardiographic data from Phase II in these same individuals will provide an extremely interesting comparison of cardiac structure and function to the degree of atherosclerosis and arterial dysfunction. This comparison should provide insight into the mechanisms of diabetes-associated CVD. It will be especially important to further investigate the factors that may explain the lower prevalence of coronary heart disease among Arizona participants who in fact have the highest prevalence of diabetes (>65%). Compared to OK and SD/ND, AZ has both lower CHD prevalence and CVD mortality. Of interest is that the reduction in prevalent CHD in AZ compared to the other centers is greater than the reduction in confirmed CVD mortality. The data on cardiac function and carotid atherosclerosis will help to investigate whether AZ participants actually have less atherosclerosis, whether it is manifest in different parts of the vascular tree, or whether traditional
measures such as T-wave abnormalities do not reflect the same disease processes in this population.

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 both Phases I and II. 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 would be most valuable, however, to collect data on risk factors and target organ damage and DNA on large kindreds. This cohort 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 will allow us to communicate the importance of the information that can be gathered from large families. Thus, the SHS will be able to recruit and retain large kindreds from which physiologic measurements can be made and blood samples can be taken for direct genotyping.

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

1. A continuous mortality and morbidity surveillance of the Phase I examination cohort.

2. A second reexamination of the Phase I cohort with an abbreviated personal interview, measurements of carotid intimal thickness, discrete atherosclerosis and arterial function using ultrasound and tonometry, additional laboratory tests, measurement of asthma and carbon monoxide levels in breath, and a repeat of the basic risk factor assessments done in the Phase I and Phase II examinations.

3. An initial study to examine family participants (first degree relatives and grandchildren) of members of the Strong Heart Study. Ten 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 in Phase I. The examination on these individuals will include all components of the Phase III examination plus selected components from the Phase I and II examinations, 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.

Rationales for New Components of Phase III of the Strong Heart Study

1. 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 0.1 mm 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 the relationship between these measures and several CVD risk factors and the presence of diabetes and its complications.

2. **Computerized Electrocardiography**

The digital acquisition of ECGs, which facilitated ECG handling in Phases I and II, will be used in Phase III to improve characterization of cardiac status in Strong Heart Study participants. Computerized measurements of digital ECGs that have already been recorded and archived or that will be recorded in Phase III, will be used to assess QRS voltage and duration measures of left ventricular (LV) hypertrophy and myocardial infarction and to assess ST/T measures of repolarization indicative of LV hypertrophy or ischemia. In addition, the validity of an approach to computerized performance of Minnesota coding will be tested to determine whether this standard method of diagnostic classification can be made less expensive and time-consuming.

3. **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 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 proposed pilot family study will take the first steps toward achieving that goal.

We will establish a resource of extended families beginning with sib-ships 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 by positional cloning. 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.

4. **Pulmonary Function**

The daily lability of peak expiratory flow (PEF) is an index of airway hyper-reactivity, the hallmark of asthma. The prevalence and mortality rates of asthma have increased during the last 20 years in developed countries. The actual prevalence of asthma is unknown in the American Indian population. The prevalence of self-reported asthma from the SHS Phase II medical questionnaire was 6% (preliminary data from 3029 exams). The prevalence of asthma symptoms (attacks of wheezing with dyspnea or wheezing during colds) was 17%. The procedures employed during the Phase II exam may have under diagnosed asthma, since spirometry is often normal in persons who have asthma but who are without symptoms at the time of testing. An objective measurement of asthma in a sub-sample of SHS participants would be very helpful in estimating the true asthma prevalence. Airway hyper-reactivity, or excessive airway lability are cardinal features of asthma. The "gold standard" test for airway reactivity is the histamine or methacholine inhalation challenge test. Although this test has been adapted for use in large population surveys, it requires 30-45 minutes and the presence of a physician in the same building. An acceptable alternative is ambulatory monitoring of lung function, where the participant blows into a hand-held spirometer several times each day for two weeks. If the participant has asthma, their early morning PEF (or FEV1) is at least 20% lower when compared with the values from later in the day. New hand-held, battery powered electronic spirometers can store the results, eliminating the need for a written diary. This will provide a feasible way to further explore the prevalence and impact of asthma in the SHS populations.

Cigarette smoking is a very powerful risk factor for CVD. Mis-classification of smoking status can, therefore, reduce the power of many analyses of associations of risk factors with CVD outcomes. It is well known that a percentage of participants in medical research studies misrepresent their smoking status. Moreover, many SHS participants report sporadic smoking or are exposed to smokers at home or at the workplace; thus an objective measure would help to classify their degree of smoking. There are several biochemical methods available to verify smoking status, including blood, urine or salivary samples analyzed for thiocyanate or cotinine levels, and breath carbon monoxide (CO) levels. The primary advantages of breath CO include non-invasiveness, speed (30 seconds) and a very low cost per sample. In addition, it can also detect exposure to CO in environmental tobacco smoke. Such devices have been beneficial in motivating smokers to stop smoking and to promote a smoke-free environment. Limitations include the
relatively short 4-hour half-life of carbon monoxide in the blood and breath, and the occasional high reading in non-smokers exposed to faulty gas heaters in enclosed homes during cold months. However, follow-up of such high levels of CO will be beneficial in detecting the presence of faulty heaters so that corrective action can be taken to prevent lethal CO exposure. The instruments to measure CO in exhaled air cost less than $1,000. The multi-center Lung Health Study of smoking cessation successfully used the hand-held, battery-powered Vitalograph "BreathCO" to validate smoking status. A similar protocol will be employed to measure expired CO levels in SHS participants in Phase III.

5. **Laboratory Tests**

The Strong Heart Study investigators, in their planning, have been careful not to repeat laboratory measurements unless they were of interest and it would be reasonable or feasible to assess changes in them over time. Thus, in Examination II, the glucose tolerance test, insulin, fasting lipids, albuminuria, and fibrinogen were repeated; however, apoprotein measurements, apo E phenotype, Lp(a), and Gm allotypes were not. For Examination III the same reasoning was applied. In order to assess progression of glucose intolerance and abnormalities in hemostasis, fasting and post-load glucose, fasting insulin, urinary albumin/creatinine, and fibrinogen and PAII1 will be included. Red blood cell allotypes, Gm allotypes, apo E phenotypes, Lp(a), apo B and A1 will not be re-measured because they would not be expected to change or have measurable changes. HbA1c will not be re-measured because of its high correlation with plasma glucose in our diabetic population. LDL size will be repeated because of the interesting question of how it changes along with triglycerides, insulin and other components of the insulin resistance syndrome. On the other hand, a Chemistry Profile (SMAC 12 including electrolytes, BUN, creatinine, total protein, SGPT, SGOT), which has never been determined on this cohort, will now be included. These basic chemistries will yield data which are generally not available among Indian populations in a standardized way and will assist in the interpretation of a number of CVD risk factors.

Studies have documented that increased hematocrit, plasma viscosity or whole blood viscosity are associated with hypertension and diabetes and predict subsequent cardiovascular events. One possible mechanism of these associations is by the increased shear stress imposed on the arterial intima by more viscosity blood flowing past it. To assess the relevance of these associations to the arterial hypertrophy, dysfunction and atherosclerosis to be detected in SHS Phase III in a cost-effective way, hematocrits will be measured as well as total plasma protein (in the chemistry profile). These two variables are the principal determinants of whole blood viscosity (WBV) and predicted WBV at a shear rate of 208 per sec accurately compared to direct WBV measurements.

By the time of the Phase III examination, based on the death rate observed so far, there should be more than 800 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 homocysteine to allow the assessment of this potential risk factor in the Indian population; an assessment of lipoparticle AI:A1-AII, a recent measurement of HDL distribution, which may provide additional information on the relationship between HDL function and coronary disease; a measure of proinsulin which will allow the assessment of pro-insulin's role in CVD and the development of diabetes. 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-III (SHS, Cardiovascular Disease in American Indians Phase III) is to continue the mortality and morbidity surveillance on the original cohort, to follow and re-examine the original cohort of American Indian men and women in three geographic areas, and to initiate a study of the inheritance of risk factors in families. The study will address the following specific aims:

1. To determine mortality rates for CVD and other causes in the original SHS cohort using a standardized methodology.
2. To determine rates of CVD and CVD risk factors in these Indian groups by longitudinal surveillance and a second follow-up examination of the Phase I cohort (ages 53 - 82 years at the Phase III examination).
3. To compare risk factors and their changes over time in the three geographic areas and relate them to different rates of CVD among the three areas.
4. To identify and compare risk factors for CVD among diabetic and non-diabetic participants.
5. To obtain quantitative measures of systemic atherosclerosis and arterial dysfunction using ultrasound studies of the carotid artery and to relate these measures to prevalent CVD and CVD risk factors and to previous echocardiographic measures of cardiac structure and function.
6. To determine whether echocardiographic measures of cardiac structure and function predict incident CVD events and death.
7. To compare the risks of differing manifestations of vascular disease (e.g. CHD, PVD, carotid atherosclerosis, cardiac wall motion abnormalities) among American Indians in the three areas and to determine the risk factor profile associated with each measure of disease.
8. To identify at random in each of the three geographic areas, 10 families with two or more siblings who participated in the original Phase I examination and with approximately 30 adult members aged 18 years and older, in each family; on each family member to perform an examination to measure CVD risk factors; and to conduct preliminary linkage analyses to assess the inheritance of CVD risk factors.
1.3 STUDY DESIGN

Time Line:

\[
\begin{array}{cccccc}
8/1/96 & 8/1/97 & 8/1/98 & 8/1/99 & 8/1/2000 \\
[ & [ & [ & [ & [ & ] \\
\end{array}
\]

> mortality & morbidity surveillance until 5/31/99

> continue to analyze SHS-II data

> development of protocol, manual, data forms and pre-testing

4/97

> training and pilot study

5/97 12/97

> family examination

1/98 8/99

> Phase III examination

> data analysis

1.3.1. Surveillance

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

For the cohort 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.
1.3.2. Clinical Examination

a. Components of the Phase III Clinical Examination for SHS Cohort. These are described on page II-2 of this manual.

The Phase III clinical examination will include a personal interview and a physical examination. 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 Phase I and Phase II. Procedures are described in brief below, with details presented in the manual Volume II.

i. Personal Interview

The following questionnaires will be administered:
1) Demographic information
2) Health habits
3) Medical history
4) Dietary survey
5) Quality of Life

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
   ii) Height
   iii) Waist and hip circumferences
   iv) Body fat measurement
   v) Arm circumference

2) Examination of the following:
   i) Pedal pulses
   ii) Ankle edema

3) Blood pressure measurements

4) Twelve-lead resting ECG measurement

5) Glucose Tolerance Test (GTT)

6) Fasting blood samples for measurements of total triglyceride (TG) and cholesterol, LDL and HDL cholesterol, plasma fibrinogen, and PAI-1, and DNA isolation, glucose, creatinine, insulin, and SMA-12 will be obtained.
7) Urine will be collected at the beginning of the physical examination for measurement of albumin and creatinine.

8) Peripheral sensation will be measured in the right foot by mono-filaments.

9) **The following procedures will be added:**
   i) **Echocardiography of the carotid artery** (see Manual Volume VI, Special Studies for details).
   
   ii) **Carbon monoxide in exhaled air** will be measured to validate smoking status.

   iii) **Ambulatory pulmonary function (PF) monitoring**

b. Components of the Examination for Family Members

The family members will have all the information collected that is described above for the Phase III exam of the cohort, except for the ambulatory PF monitoring. Each center will pilot the family member exam in at least 10 persons and appropriate revisions in the procedure will be made and standardized for use in all three centers for 300 family members age 18 or over at each center. 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. As much of the information as possible that was collected on the original participants will be collected on the family members. The interview will include the following:

i. Phase I Information: This includes: tribal enrollment, degree of Indian blood, marital status, education/income, use of native language, smoking and alcohol use, medical conditions, reproductive history, and current physical activity.

ii. Phase II Information includes: history of attending boarding school, respiratory/snoring, cultural factors, risk factor knowledge, quality of life.
1.4 STUDY QUESTIONS

The morbidity and mortality surveillance of the original cohort and the new approaches in Phase III, will provide information that can be used to address multiple questions related to furthering our understanding of the etiologies of CVD and the impact of diabetes on risk. These questions include:

1. How have the absolute rates and proportional mortality ratios for CVD and other causes of mortality changed over 10 years (1989-1998) in American Indians in the three centers?
2. What changes in CVD risk factor levels have occurred over time in these study populations, and what are the most important determinants of these changes?
3. What are the relationships between CVD risk factors, clinically manifested CVD, and measures of atherosclerosis (intimal medial thickness and discrete atheromas) within and among centers?
4. Do these relationships differ in individuals with diabetes?
5. What are the explanations for the differences in CHD morbidity and mortality between Indians in the three geographic areas?
6. What are the relationships between cardiac disease as measured by echocardiography and systemic atherosclerosis as estimated from carotid ultrasound studies? Do the relationships between these differ in individuals with diabetes?
7. Do the relationships of CVD risk factors to carotid wall thickness and morphology in American Indians differ from those in previously reported aged-matched cohorts?
8. Does renal dysfunction as measured by albuminuria predict the risk of CVD? How does it relate to abnormalities in the carotid wall?
9. What is the impact of the rapid change in economic status induced by gaming activities in some of the communities on CVD risk factors and quality of life?
10. Can the current family history data collected in Phase I and Phase II of the Strong Heart Study be used to identify groups of related individuals (family members) in the initial cohort?
11. Can families of large size with multiple siblings be successfully recruited, starting with sibships who are current Strong Heart cohort members?
12. There are many interesting questions concerning genetic effects on CVD risk factors in American Indians. The proposed family studies will lay the groundwork for addressing some of these questions:
   a. Are there genes that have large effects in explaining the low plasma cholesterol levels in American Indians? Can their chromosomal locations be determined?
   b. Is blood pressure in American Indians influenced by genes whose effects are individually detectable and whose chromosomal locations can be determined?
   c. Are there detectable genes that influence diabetes susceptibility in American Indians? Can these genes be mapped to specific chromosomal regions?
   d. Are the amount and distribution of body fat in American Indians influenced by genes with large effects? Can we determine their chromosomal locations?
   e. Carotid wall intimal-medial thickness (IMT) has been shown to have high heritability in a Hispanic population. Is IMT in American Indians influenced by one or a few genes whose chromosomal locations can be determined?
   f. Little is known for any population about the genetic mediation of phenotypes related to
clotting (for example, fibrinogen and PAI-1). Are there genes that have substantial effects on these phenotypes in American Indians, and can they be mapped to specific chromosomal regions?
g. Is there evidence for heterogeneity among tribes with respect to the genes that influence CVD risk factors?

1.5 STUDY MANAGEMENT

1.5.1 Introduction

The Strong Heart Study Phase III 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. The operations of the study are directed by the Strong Heart Study Phase III Steering Committee, which includes members from each center and the NHLBI Project Manager (see Appendix 2 for the members of Steering Committee). An organizational chart of the Strong Heart Study Phase III is given in Appendix 3. 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 Medical Center under the direction of Dr. Richard Devereux serves as both the ECG Reading Center and the Carotid ultrasound reading center. Peak flow pulmonary function testing results are analyzed at the Coordinating Center under the direction of Dr. Paul Enright. Analysis of the family study genetic component is directed by Dr. Jean MacCluer at the Southwestern Medical Center. SHS-III 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 prepares and distributes a quarterly newsletter to facilitate communication among Study staff. In general, each edition includes: (1) reports from the Program Office, the Coordinating
Center, the Core Laboratory, the ECG Reading Center, Carotid Ultrasound Reading Center, Pulmonary Function Testing Center, and the Steering Committee, (2) a description of the facilities and staff of one field center or central agency, (3) general information on data management and (4) a calendar of 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 will be the major electronic mail facilities to be used by all field centers, the Coordinating Center, Core Laboratory, ECG and Ultrasound Reading Center, Genetic Study Center, and the Program Office. This electronic mail network will allow rapid and efficient communication among centers for messages such as announcements, meeting agendas, abstracts for clearance and acknowledgments of receipt of data.

3. Field Center Visits:

The Program Office and Staff from the Coordinating Center, ECG and Ultrasound 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 Data Forms and Guidelines for Completing Forms

Uniform data entry forms for all information to be collected will be 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 who return for the third phase examination, 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>AZxxxxx</td>
<td>360001 - 36zzzz</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>Oxxxxx</td>
<td>260001 - 26zzzz</td>
</tr>
<tr>
<td>South and North Dakota (1)</td>
<td>Dkxxxx</td>
<td>160001 - 16zzzz</td>
</tr>
</tbody>
</table>

Where xx: family number.
yyy: 001 - 999 for each family member.
zzz: a unique number for each family member who participates in the examination and interview.

(1) The numbering system for the Dakota center is not sequential for the first four families.
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 8. Hospitals where the subject 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 9 and 10, 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 11. 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 will 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 key punch 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-III Operations Manual Volume VII - Data Entry*

1.6.3 Data Transmission -- See *SHS-III Operations Manual Volume VII - Data Entry*

The lab data, ECG data, and ultrasound data will be electronically transmitted to the Coordinating Center, and will be converted to SAS data-sets. 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 PROGRAM

1. Data Collection

Every data form will be checked for completeness by the field staff before entering into computer. Ambiguous or erroneous items will be clarified and corrected. All forms will then be double-entered for the first two months of the study. The Coordinating Center will check the error rates of data entry. If the error rate is less than 0.5% between the two entries, only 10% of the data forms are required to double entry for the following month. The Coordinating Center will continuously monitoring data entry errors for the three field centers. If the error rate raises above 0.5%, all the data will required double entry for the month until the error rate drops below 0.5%. The data entry program will provide a second quality control check. Range and logic checks will be built into the data entry program. The program will refuse to accept such data until the errors are corrected. Computer printouts of data received will be sent to each field center. 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**

   Biannual quality control site visits will be made to each of the three centers. 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, impedance meter, 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 monitoring of the impedance meter will include checking the battery charge daily before the instrument is used, following the manufacturer’s instructions. 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 measurement 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 ankle blood pressure using a Doppler will be made by two observers simultaneously. Duplicate measures of anthropometry (height, weight, waist/hip ratio, and electrical impedance measurements) will be performed by a second observer on a 10% 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 units
   - vi) Waist circumferences: 1 cm
   - vii) Hip circumferences: 2 cm
Duplicate data for blood pressure, height, and weight 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 and by Doppler 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. Duplicate blood pressures taken by Doppler will be performed quarterly by the supervisor.

2) Laboratory tests

Duplicate blood and urine specimens will be collected on approximately 10% of the participants and 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 errors 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 will be observed monthly by the study coordinator. Problems and errors are identified using a checklist and corrected immediately.

4) Dietary interviews

The dietary consultant, Ms. Ellie Zephier, will conduct field observation during the first three months after the initial training session. Field observation will include evaluation of 1) Introduction and confidentiality statement, 2) mannerism and eye contact, 3) flow of the-interview, 4) use of neutral probes, 5) proper use of food models, 6) proper use of the edit system, and 7) review of dietary logs.

The dietary consultant will also review dietary recalls completed the day of observation and provide immediate feedback at the time of the field visit. Questions and concerns will also be discussed during these visits as needed.

Once a month, one interview per dietary interviewer will be taped and reviewed by the dietary consultant for interview quality. After receiving permission from the participant and/or proxy, the interview will be recorded and reviewed by the study coordinator. The dietary consultant will provide written feedback to each interviewer on how to improve interview techniques.
5) Quality control for surveillance data

In the mortality and morbidity surveys, records of every non-injury death and 10% of all morbid events will be sent to a second member of the mortality or morbidity Review Committees. Each physician independently will determine the classification of a cause of death or CVD event, and the Coordinating Center then will compare the results from both physicians. The adjudication process is described in the surveillance section of this manual.

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. Re-certification will occur every six months to ensure accurate and consistent performance.

1.6.6. Statistical Analysis

Major statistical analyses of Phase III data include: 1) determination of mortality rates by cause of death in the SHS Phase I cohort (cohort mortality), 2) estimation of incidence of CVD and other diseases of interest, e.g., diabetes, PVD, and renal disease, in the SHS Phase I cohort, and 3) identification of risk factors that are related to cohort mortality and incidence of CVD and other diseases of interest.

Death rates due to CVD calculated on the basis of death certificates alone will be compared with those based on the confirmation of the Mortality and Morbidity Committee. The center-specific all-cause and CVD mortality rates will be compared to those obtained from the U.S. population, the respective states, and other ethnic groups. Using the mortality data from all three phases of the SHS, we will be able to examine the trends of CVD and all-cause mortality over a 10-year period (1989-1999) in the three Indian populations.

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 the phase III examination, 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 U.S. and in other ethnic populations, and to those obtained in the community mortality survey of the same population. Lifetable analysis techniques will be used to estimate median remaining lifetime.

Data on disease status obtained from the morbidity surveillance and the clinical examination will be used to estimate incidence rates of CVD, diabetes, PVD, renal disease, etc. If the date of diagnosis is unknown, we can estimate a seven-year (baseline is Phase I) cumulative incidence or a three-year (baseline is Phase II) 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.

Statistical analyses to be used to identify risk factors related to mortality and to morbidity include, in the uni-variate analysis, comparisons of cumulative incidence, incidence density, mortality rates, and disease-free time and survival time distributions between "exposure" subgroups. The survival time will be calculated from Phase I examination to the time of death or last-follow-up and the disease-free time will be from 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.

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 in Rothman. The distributions of survival time and disease-free time in different "exposure" subgroups can be compared by using the logrank or K-sample tests. The association between categorical risk factors and disease status can be further analyzed by adjusting for possible confounding factors using the Cochran-Mantel-Haenszel test. Trends will be analyzed and summary odds ratios calculated. Continuous risk factors will be categorized and analyzed accordingly in addition to being treated as continuous data.

After the uni-variate and bivariate analyses, selected variables will be included in the Cox's proportional hazards model or logistic regression model depending on whether or not the date of diagnosis is known. The relative importance of individual risk factors will be determined by step-wise procedures. If the changes in a risk factor were not consequences of the event of interest, a Cox model with time-dependent co-variates may be adopted. Recurring events such as hospital-based MI and stroke can also be modeled with Cox's continuous time model using a counting process formulation.

Changes in the means of the risk factors will be assessed graphically and either qualitatively or quantitatively. The patterns of changes across the three phases will also be characterized. For simple comparisons of the means between genders, centers, and other "exposure" groups, the Hotelling T square and multi-variate analysis of variance will be used. The data will be transformed if warranted to stabilize the variance. Adjusted means can be computed using multivariate analysis of covariance.

The longitudinal observations will allow us to assess and model the association of disease outcome with risk factors or the association of a risk factor with other risk factors by utilizing the marginal models. By using the marginal models, we will be able to distinguish changes over time within subjects (aging effects) from differences among individuals in their baseline levels (cohort effects). In the model, age at baseline and change in age from baseline can be included as co-variates. The coefficient for age at baseline is sensitive to cohort effects but that for change in age is not. It is of interest also to examine if, and in what way, these two age coefficients are different.

Another advantage of the longitudinal design is the allowance of addressing questions such as what are the important determinants that are associated with the changes in CVD risk factors (e.g. cholesterol level) over time. Statistically, one can address this question by regressing the cholesterol level on time, the determinant variable and the interaction between the two variables. This marginal model approach was suggested in the recent monograph on analysis of longitudinal data by Diggle et al.
The distribution of the response variable is not required to be Gaussian in a marginal model. The marginal mean is modeled as in cross-sectional studies. The parameters are estimated by a generalized estimating equation, a multi-variate extension of quasi-likelihood. Since the number of subjects is larger than the number of observations per subject, the inference is robust to mis-specification of the covariance structure between observations in the same subject. For continuous dependent variables, the covariance structures will be estimated using the auto-regressive models and one where the co-variances are estimated from the data. For binary response variables, the variance is determined by the mean. Odds ratios and confidence intervals will be estimated for various risk factors. A SAS macro using SAS IML is available to estimate the regression coefficients in marginal models. Further, we may be able to address both the regression objective and the within-subject correlation simultaneously by using the transition (Markov) models, and discuss the correlation among responses for an individual by using random effects models.

1.7 PUBLICATION POLICY

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

Dr. Elisa T. Lee (Chair)
Mr. Richard R. Fabsitz
Dr. Barbara V. Howard
Dr. Thomas K. Welty

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

1.7.1 Submission of a Paper Proposal

I. Proposal

A formal paper proposal must be submitted to the Chair of the P&P Committee at least one week prior to the monthly P&P meeting. 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 (include the phrase "Strong Heart Study" whenever possible)
2. Primary author’s name and affiliation
3. Suggested co-authors
4. A detailed outline which includes:
   a) Introduction (Rationale)
   b) Methods
   c) General analysis plan
   d) Lay summary for the tribes
5. Analysis responsibility (authors or Coordinating Center, CC)

It is assumed that all proposals are submitted with the knowledge of the field center 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, deferral, or disapproval (with reasons)
2. Upon approval, the paper is given an SHS Paper Number
3. The paper may then be given a priority score if analyses are to be done by the Coordinating Center

The decision will be forwarded to the author who submitted the proposal. If the proposal is approved and CC is responsible for the analysis, the author must then submit a "Request for Data Analysis" form (see below) to CC as soon as possible. CC will then assign a statistician to work with the author. The statistician is the CC representative to the writing group.

The P&P Committee will periodically report its decisions to the SHS Steering Committee, and SC may nominate additional co-authors for any papers that have been approved by the P&P Committee.

III. Analysis

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 time table 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 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. The author should then complete a first draft within 4 months and submit it to the P&P Committee for comment (to be returned by the Chair within 1 month).

4. After P&P approval of the first draft, the author then has 3 months to submit the penultimate draft to the P&P Committee for final review (to be returned by the Chair within 1 month).

5. Review by the P&P Committee may result in suggestions which are essentially editorial in nature, in which case the paper is approved and the Chair conveys these suggestions to the author. If the P&P Committee considers the paper to require substantive changes, approval is deferred until the paper is revised in light of the Committee’s critique and reviewed further by the Committee.

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

7. After P&P approval, the penultimate draft must be submitted by the author to NHLBI (through Mr. Fabsitz) for review (to be returned to the author within 1 month of submission).

Simultaneously, the principal investigators should send the penultimate draft to their respective IHS Area IRB and to their tribes for review and approval.

8. After NHLBI approval, the author should submit the final manuscript to a journal, and a copy of the cover letter and the final manuscript should be sent to the P&P Chair.

9. The author should inform the P&P Chair regarding outcome of the journal review process and send a reprint of the published article to the Chair. At least one copy (reprint) of all published papers must be sent to NHLBI (R. Fabsitz). **NOTE:** Papers that are likely to result in press coverage or substantial press/media interest require **notice in advance** to the NHLBI so that the staff and public information office can be prepared.

10. The P&P Chair will maintain a list of published SHS papers and papers in various stages of preparation.

11. 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.

12. 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. Summary of Abstract Approval Process
1. An author submits an abstract proposal (see abbreviated proposal form below) to the P&P Committee Chair.

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

3. Abstracts should also be submitted to NHLBI, IHS Area IRBs, and Tribes for approval.

4. Approximately 2 weeks prior to a poster or slide presentation, the author should submit the material for review and comment by one P.I. and two other Steering Committee members, preferably outside of the writing group.

5. Copies of all published abstracts should be sent to the P&P Chair, along with complete citation data, for inclusion in a list of published SHS abstracts.

VI. Examples of Paper and Abstract Proposal Forms

The following two pages display the desired format for paper and abstract proposals submitted to the P&P Committee. These forms will be transmitted electronically to SHS authors by e-mail so that e-mail 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 e-mail, or more traditional means if desired.
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:

Outline of Paper:

a) Introduction (Rationale)
b) Methods
c) General analysis plan
d) Lay summary for the tribes

Analysis Responsibility: (authors or Coordinating Center)

Note: 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.

Submitted by: (Corresponding author, with address for correspondence)

Date:
STRONG HEART STUDY

ABSTRACT PROPOSAL

Title of Abstract: (include the phrase "Strong Heart Study" whenever possible)

Name of Primary Author:

Author Affiliation:

Co-Authors:

Outline of Abstract:

a) Brief rationale
b) General analysis plan

Analysis Responsibility: (authors or Coordinating Center)

Submitted by: (Corresponding author, with address for correspondence)

Date:
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: ____________________________________________

_____________________________________________________

_____________________________________________________

_____________________________________________________

_____________________________________________________

_____________________________________________________

_____________________________________________________

_____________________________________________________

_____________________________________________________

_____________________________________________________

***********************************************

COORDINATING CENTER USE ONLY:

STRONG HEART STUDY PAPER NUMBER: __________________________

ANALYSIS NUMBER: __________________________

DATA ANALYST: __________________________

DATE REQUEST RECEIVED: __________________________

DATE RESULTS SENT OUT: __________________________
**STRONG HEART STUDY**

**SCHEDULE OF DEADLINES FOR REQUESTED DATA ANALYSIS**

<table>
<thead>
<tr>
<th>Paper #</th>
<th>Received by Coordinating Center:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Date Due</th>
<th>Date Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outline &amp; Analytic plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First draft</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second draft</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third draft</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final draft</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Date published**

__________________________

**NOTE TO FIRST AUTHOR:** Please sign, date, make a copy for your files and return original to the Coordinating Center.

__________________________

Signature

__________________________

Date

*Strong Heart Study III 9/26/97*
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: _______________
1.8. ANCILLARY STUDIES POLICY

1.8.1 General Policy

To enhance the value of 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 in 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 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 is responsible for obtaining IRB approval from the 3 areas and the national IHS IRBs. In all cases IRB approval is needed if the proposed studies were not mentioned in the original protocol that received IRB approval.

1.8.6 Analysis and Publication of Results of Ancillary Studies

The 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 a confidentiality statement (Appendix 7). In addition the investigator will need to sign a statement that indicates his/her willingness to submit draft manuscripts for approval by the Steering Committee, NHLBI, IHS and the tribes. Manuscripts resulting from ancillary studies will require approval by the Steering Committee and by NHLBI, IHS and the tribes prior to submission for publication or presentation. 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 title and listed as a key word whenever possible. Manuscripts will also contain an appendix listing all Strong Heart Study Principal Investigators as well as other individuals deemed appropriate.
1.8.7 Agreement for Ancillary and Collaborative Investigation

The following agreement must be signed by ancillary and collaborative investigators:

I agree to read and follow the SHS protocol with regard to analysis of Strong Heart Study data I request. I will comply with the SHS policies regarding maintaining data security and will sign a confidentiality statement. I have attached a research protocol describing how I will use these data to better understand cardiovascular and pulmonary diseases in American Indians and how to benefit the health of American Indians.

I agree to submitting a draft report of the results of this analysis for review and approval of the SHS Steering Committee, NHLBI, IHS and the participating tribes. If approval for publication is not granted, I agree not to publish these results.

I understand the SHS Steering Committee will assist me in revising my report in such a way that will make it acceptable for publication. I agree to include one of the SHS Steering Committee members as a co-investigator and a co-author.

Signed:_________________________ Date:_________________________

1.8.8 Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to participants and/or their physicians if medically useful. Such reporting should follow standard Strong Heart protocol for notification of participants. A copy of any resultant article should be sent to the Program Office and the participating tribes.
CHAPTER TWO

OVERVIEW OF STRONG HEART STUDY PHASE III
MORTALITY AND MORBIDITY SURVEILLANCE

2.1 OBJECTIVES

All surviving participants from the SHS Phase I examination are eligible for morbidity and mortality follow-up in Phase III. The primary objectives of surveillance of the exam cohort are to capture events that can be related to possible risk factors for CVD and to provide annual mortality and morbidity rates in these populations. Table 2.1 summarizes the non-fatal endpoints ascertained in the SHS by various mechanisms. All deaths in cohort members will be identified and the cause of death determined by review of medical records information. Events will be ascertained annually, thus providing on-going and up-to-date information about the cohort, independent of the Phase III examination. Surveillance activities in Phase III will continue until May 31, 1999.

It is important in designing and implementing the surveillance protocol that the intensity of ascertainment is the same at all three centers, otherwise, there is likely to be bias in both the frequency and nature of events ascertained, and what may appear to be center differences would, in fact, be artifactual.

2.2 OVERVIEW OF SURVEILLANCE PROCEDURE

2.2.1 General Surveillance Methodology

The general approach to surveillance at each center is to divide the total number of participants into twelfths from a listing of surviving Phase I participants, ordered by calendar time from least to most recent exam date. This would result in an approximately equal distribution of participants across the calendar year, and the Phase III follow-up would begin with those seen earliest in Phase II.

Using this monthly division, the persons listed for that month would be followed up (methods described below) to determine their vital status and if living, whether any of the study events of interest had occurred since last contact. The monthly listing provided by the Coordinating Center includes all known identifying information for the individual, their Phase I and II exam dates, and the dates of any morbid events already ascertained (providing an event history that is useful when doing the follow-up). A sample of the tracking form is given in Figure 2.1. When a new event (either fatal or non-fatal) is identified, procedures for obtaining the necessary information for physician review are implemented. Using this approach, each member of the cohort is contacted (either directly or indirectly) once a year, and the physicians' review of events are done on an on-going basis.
Figure 2.1  Example of Tracking Form

<table>
<thead>
<tr>
<th>SHS ID: 10xxxx</th>
<th>DOB: 4/27/40</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAME: Smith, James</td>
<td>DOD:</td>
</tr>
<tr>
<td>SSN: 000-00-0000</td>
<td>SHS-II Exam: 09/20/93</td>
</tr>
<tr>
<td>Address: PO Box 5, Rapid City, SD 57577</td>
<td>SHS-III Exam:</td>
</tr>
<tr>
<td>Home Phone: (605) 555-5555</td>
<td>IHS Rec #: 000000</td>
</tr>
<tr>
<td>Work Phone: (605) 555-5556</td>
<td></td>
</tr>
</tbody>
</table>

EVENTS ABSTRACTED: None

<table>
<thead>
<tr>
<th>Contact Date</th>
<th>Method of Contact</th>
<th>Result</th>
<th>INIT</th>
<th>MI/Stroke Other CVD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTES:
<table>
<thead>
<tr>
<th>Endpoints/Events</th>
<th>Type of Rate</th>
<th>Source of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Clinical Endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>I</td>
<td>S, E II &amp; III</td>
</tr>
<tr>
<td>Stroke</td>
<td>I</td>
<td>S, E II &amp; III</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>I</td>
<td>S, E II &amp; III</td>
</tr>
<tr>
<td>ECG evidence of new MI</td>
<td>I</td>
<td>E II &amp; III</td>
</tr>
<tr>
<td>Coronary bypass surgery/angioplasty</td>
<td>I</td>
<td>S, E* II &amp; III</td>
</tr>
<tr>
<td><strong>Secondary Events of Interest/Pre-clinical Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>P</td>
<td>E II</td>
</tr>
<tr>
<td>Angina</td>
<td>I</td>
<td>E II &amp; III</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>I</td>
<td>E II &amp; III</td>
</tr>
<tr>
<td>Cardiac catheterization, positive</td>
<td>I</td>
<td>S, E* III</td>
</tr>
<tr>
<td>Positive treadmill test</td>
<td>I</td>
<td>S, E* III</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (LVH)</td>
<td>P</td>
<td>E II</td>
</tr>
<tr>
<td>Global evaluation of LV function</td>
<td>P</td>
<td>E II</td>
</tr>
<tr>
<td>Cardiac wall motion abnormalities</td>
<td>P</td>
<td>E II</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
<td>P</td>
<td>E II</td>
</tr>
<tr>
<td>(Ratio FEV1/FVC or FEV1/SVC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease (ESRD)</td>
<td>I</td>
<td>E* II &amp; III</td>
</tr>
</tbody>
</table>

$E = \text{Incidence}$  \quad $E = \text{Examination, Phase II or Phase III}$  \quad $E^* = \text{By interview, with medical record confirmation}$

For each event, there is a designation as to whether it is an incident or prevalent event and the source(s) through which it will be initially ascertained. Because baseline data for the primary endpoints are available from Phase I, new events ascertained in Phase II will be incident events, and all of the primary endpoints, with the exception of ECG evidence of new myocardial infarction, can be identified both through surveillance contacts and during the Phase II examination. The majority of secondary events of interest shown in the table were not specifically ascertained in Phase I, and thus, persons identified with these conditions in Phase II will be prevalent cases. In addition, most of the secondary events will be ascertained only through systematic, uniform examination of participants in Phase II.

Once the Phase III exams begin in 1998, the exam serves as the annual contact for the participant. Otherwise, the participant is contacted again after the Phase III exam to have their annual contact completed. All participants will be contacted within the last six months of morbidity and mortality surveillance that ends 5/31/99. The primary advantages of this surveillance approach are: 1) each individual is contacted annually and vital status is automatically ascertained when determining morbidity status, 2) annual (or biannual) data on the frequency of events can be provided to NIH for monitoring purposes, 3) the flow of work is more evenly distributed, and 4) the intensity of surveillance is the same at each center.
2.2.2 Specific Surveillance Approaches

Table 2.2 presents the percentage of each SHS center’s population who have a telephone and who have a P.O. address.

**Table 2.2 Frequency of Home Telephones and P.O. Mailing Addresses by SHS Center**  
*(SHS Phase II, 8/96)*

<table>
<thead>
<tr>
<th>Type of Contact</th>
<th>AZ</th>
<th>OK</th>
<th>SD/ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home Telephone</td>
<td>N</td>
<td>640</td>
<td>964</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>55%</td>
<td>77%</td>
</tr>
<tr>
<td>Mailing Address is PO Box</td>
<td>N</td>
<td>654</td>
<td>427</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>56%</td>
<td>34%</td>
</tr>
</tbody>
</table>

It is clear that the ability to contact individuals by typical follow-up measures varies by center. The percent of participants who get their care exclusively through IHS and thus, for whom monitoring of IHS user listings would be nearly complete, also varies by center. IHS computerized user listings are a useful source for each center, however, they will be augmented with other methods, especially in Oklahoma. Thus, the following approaches, to be carried out in the order listed, are used for monthly surveillance contacts.

For each name on the monthly list, check:

1. IHS computerized user listings (both inpatient and outpatient) for the occurrence of SHS events of interest
2. For participants who do not regularly receive care at IHS facilities:
   a. check with physicians who have previously provided information to the SHS for that participant
   b. send a follow-up questionnaire by mail to the participant, with a telephone call to non-respondents within 4 weeks of mailing (telephone could be used first).
   c. make a home visit to obtain surveillance information if there is no telephone and contact questionnaire is not returned.
3. After 3 months of repeated attempts to contact an individual have passed without success, contact efforts should be terminated for that contact year, and the morbidity information for that person will be collected at the time of the Phase III examination.

Other methods specific for each center may be developed in collaboration with the M&M coordinators, but these methods must be reviewed and approved by the Steering Committee prior to
implementation to ensure equal ascertainment across all three centers.

2.3 SURVEILLANCE STAFF

FIELD CENTERS: Each field center has an individual specifically responsible for mortality and morbidity follow-up of the cohort (the Mortality and Morbidity (M&M) Coordinator). The M&M Coordinator is responsible for the monthly surveillance contacts of cohort members, obtaining and forwarding the requisite medical records information for review for fatal and non-fatal events, and completing the monthly surveillance report and forwarding it to the Coordinating Center.

COORDINATING CENTER: The Coordinating Center has a specific individual designated as responsible for all aspects of M&M surveillance, including the distribution of packets for QC review, monitoring of progress at each center, and processing of data received.

2.4 SURVEILLANCE REPORTING

Monthly surveillance is done to account for all of the surviving SHS participants at least once each year. The purpose of the surveillance is to determine the vital status of each cohort member, and if still living, whether they have had any of the CVD events of interest to the study. An example of the monthly reporting form is given in Figure 2.2.

Monthly reports should be provided as a cumulative total since the start of surveillance for that contact year. The contact rate (# contacted ÷ target number) and the abstraction rate (# abstracted ÷ (# potential events - # ineligible)) will be used to track the field staff's surveillance completion rate. The following are explanations of each of the entries in the report.

TARGET NUMBER: The number of persons for whom M&M information should be determined. This number is equivalent to approximately 1/12th of the total surviving cohort at each center.

NUMBER CONTACTED: This is the number of target persons who have been accounted for. To account for someone means to determine whether or not they are alive or dead, and if alive, whether or not they MAY HAVE had an event of interest since the date of last contact (usually the Phase II exam date). If you have NO information on someone, then they have NOT been accounted for yet and are pending contact.

CONTACT METHODS CAN INCLUDE:

1) IHS computerized user listings. (For the first year of surveillance, visits within the past 3 years are sought. If none are found and the person is KNOWN to have no other sources of care, and you are sure that the listings are complete, then you may stop and consider this person as having had no events of interest. If these criteria cannot be met, you need to pursue other methods of follow-up.)

2) Telephone call with short questionnaire.

3) Letter, with short questionnaire.
4) Home visit to complete short questionnaire.
5) Chart review
<table>
<thead>
<tr>
<th>Site</th>
<th>Cumulative as of:</th>
<th>Target#</th>
<th>Contacted</th>
<th>Participants With Potential Events</th>
<th>Total # of Potential Events</th>
<th>Events Abstracted</th>
<th>Ineligible Events</th>
<th>Packets Forwarded For Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>OK</td>
<td>04/30/97</td>
<td>617</td>
<td>573</td>
<td>27  57</td>
<td>27  101</td>
<td>16  71</td>
<td>0  11</td>
<td>16  45</td>
</tr>
<tr>
<td>OK</td>
<td>05/30/97</td>
<td>717</td>
<td>672</td>
<td>28  63</td>
<td>28  116</td>
<td>18  86</td>
<td>0  14</td>
<td>18  53</td>
</tr>
<tr>
<td>OK</td>
<td>06/30/97</td>
<td>843</td>
<td>785</td>
<td>30  84</td>
<td>30  141</td>
<td>20  102</td>
<td>0  15</td>
<td>20  67</td>
</tr>
<tr>
<td>OK</td>
<td>08/01/97</td>
<td>943</td>
<td>875</td>
<td>30  93</td>
<td>30  163</td>
<td>21  129</td>
<td>0  18</td>
<td>21  77</td>
</tr>
<tr>
<td>OK</td>
<td>08/31/97</td>
<td>1140</td>
<td>1021</td>
<td>32  127</td>
<td>32  189</td>
<td>24  148</td>
<td>0  23</td>
<td>24  95</td>
</tr>
<tr>
<td>AZ</td>
<td>05/01/97</td>
<td>777</td>
<td>728</td>
<td>51  102</td>
<td>51  210</td>
<td>39  175</td>
<td>0  0</td>
<td>39  84</td>
</tr>
<tr>
<td>AZ</td>
<td>06/01/97</td>
<td>883</td>
<td>831</td>
<td>56  116</td>
<td>56  240</td>
<td>44  187</td>
<td>0  3</td>
<td>44  90</td>
</tr>
<tr>
<td>AZ</td>
<td>07/01/97</td>
<td>986</td>
<td>924</td>
<td>56  131</td>
<td>56  282</td>
<td>48  239</td>
<td>0  5</td>
<td>48  108</td>
</tr>
<tr>
<td>AZ</td>
<td>08/01/97</td>
<td>1086</td>
<td>1021</td>
<td>64  125</td>
<td>64  306</td>
<td>51  270</td>
<td>0  19</td>
<td>51  117</td>
</tr>
<tr>
<td>AZ</td>
<td>09/01/97</td>
<td>1191</td>
<td>1120</td>
<td>70  133</td>
<td>70  317</td>
<td>52  293</td>
<td>0  20</td>
<td>52  128</td>
</tr>
<tr>
<td>SD</td>
<td>04/30/97</td>
<td>798</td>
<td>798</td>
<td>47  59</td>
<td>47  110</td>
<td>16  76</td>
<td>0  0</td>
<td>16  39</td>
</tr>
<tr>
<td>SD</td>
<td>05/30/97</td>
<td>898</td>
<td>898</td>
<td>47  78</td>
<td>47  170</td>
<td>24  136</td>
<td>0  3</td>
<td>24  63</td>
</tr>
<tr>
<td>SD</td>
<td>06/30/97</td>
<td>998</td>
<td>998</td>
<td>47  84</td>
<td>47  182</td>
<td>29  172</td>
<td>0  7</td>
<td>29  77</td>
</tr>
<tr>
<td>SD</td>
<td>08/01/97</td>
<td>1111</td>
<td>1111</td>
<td>47  106</td>
<td>47  243</td>
<td>35  223</td>
<td>0  20</td>
<td>35  101</td>
</tr>
<tr>
<td>SD</td>
<td>09/02/97</td>
<td>1244</td>
<td>1244</td>
<td>49  116</td>
<td>49  267</td>
<td>40  247</td>
<td>0  20</td>
<td>40  112</td>
</tr>
<tr>
<td>SHS</td>
<td>04/30/97</td>
<td>2192</td>
<td>2099</td>
<td>125  218</td>
<td>125  421</td>
<td>71  322</td>
<td>0  11</td>
<td>71  168</td>
</tr>
<tr>
<td>SHS</td>
<td>05/30/97</td>
<td>2498</td>
<td>2401</td>
<td>131  257</td>
<td>131  526</td>
<td>86  409</td>
<td>0  20</td>
<td>86  206</td>
</tr>
<tr>
<td>SHS</td>
<td>06/30/97</td>
<td>2827</td>
<td>2707</td>
<td>133  299</td>
<td>133  605</td>
<td>97  513</td>
<td>0  27</td>
<td>97  252</td>
</tr>
<tr>
<td>SHS</td>
<td>07/30/97</td>
<td>3140</td>
<td>3007</td>
<td>141  324</td>
<td>141  712</td>
<td>107  622</td>
<td>0  57</td>
<td>107  295</td>
</tr>
<tr>
<td>SHS</td>
<td>08/30/97</td>
<td>3575</td>
<td>3385</td>
<td>151  376</td>
<td>151  773</td>
<td>116  688</td>
<td>0  63</td>
<td>116  335</td>
</tr>
</tbody>
</table>

09/04/97
# PARTICIPANTS WITH POTENTIAL EVENTS: This is the number of people for whom contact has been made and who MAY have a morbidity event of interest or who are reported to be deceased. Mortality and morbidity are reported separately. Included here can be persons who are known to have been hospitalized but for whom the reason for hospitalization is unknown.

# POTENTIAL EVENTS: This is the total number of possible CVD EVENTS (there may be multiple events per participant) and total number of reported deaths (this number will match the number of participant deaths). Included here can be events of hospitalization for which the reason is unknown prior to checking the record.

# ABSTRACTED: This is the total number of potential events for which abstracts have been completed.

# INELIGIBLE: This is the total number of potential events, which after medical records review, have been determined NOT to be SHS events.

FORWARDED PACKETS: These are the total numbers of mortality and morbidity packets which have been forwarded for panel review. This number will be used to track the review panels' work-loads and completion rates.

2.5 GENERAL GUIDELINES FOR PROCESSING MORTALITY AND MORBIDITY PACKETS

Mortality and morbidity packets are assembled by the M&M Coordinators in each field center according to the check lists provided in Appendix C in the Manual of this Volume. All mortality packets are forwarded to Dr. Maurice Sievers at the Arizona center. After review by Dr. Sievers, the original mortality packet, excluding Dr. Sievers's decision form, is forwarded to the next member of the Mortality Review Panel listed on the assignment sheet provided by the Coordinating Center. Thus, all deaths are reviewed by two members of the Mortality Review Committee, one of whom is always Dr. Sievers. Discrepancies are identified by the Coordinating Center. In these instances when both reviewers determine the death to be non-CVD but the assigned causes differ, Dr. Sievers's decision will be taken as the cause of death. Those cases in which one of the two reviewers assigns a CVD cause or when there is a discrepancy in type of CVD will be forwarded to Dr. James Howard for adjudication. Dr. Jim Howard will have the results of other two reviewers available to him so that the process in Phase III is consistent with that used in Phase I and II. Lists of reviewers for morbidity packets are provided to each center by the Coordinating Center for forwarding morbidity packets for review to members of the Morbidity Review Committee on a prescribed, alternating schedule. All suspected fatal and non-fatal stroke events are forwarded to Dr. David O. Wiebers at the Mayo Clinic for review by him and his staff after initial review by the first M&M physician. A complete listing of the members of each of the physician review panels is given in Appendix 4, M&M Review Committee of this manual.
When either a set of mortality or morbidity packets are forwarded by the field to the reviewers, the M&M Coordinator should do the following:

a. include inside the box a copy of the shipping list of the contents of the box
b. FAX or e-mail a copy of the shipping list to the recipient (so they know what’s coming) and a copy to the M&M contact person at the CC (so they know what’s been sent).

Material pertaining to M&M surveillance that is sent to the CC, should not be sent to Dr. Yeh, but rather to: "M&M Surveillance, attn. William Moore".

When preparing morbidity and mortality packets for forwarding to the physician reviewers, please observe the following guidelines:

a. Materials should be organized IN ORDER according to the photocopy check list for that event. Multiple events should be organized IN CHRONOLOGICAL ORDER from least to most recent.

b. A copy of the monthly tracking sheet (provided by the CC) for the individual for whom you are doing a packet should be included in the packet. This is because the tracking sheets include listings of all events previously reviewed and entered in the CC database and having this history is useful to the reviewers. This sheet is also intended to be useful to the field centers by providing a listing of what work has already been done for that participant.

c. All relevant information FOR A GIVEN EVENT should be collected before sending the packets off for review.

d. The CC will provide the reviewers with blank decision forms.

e. Reviewers should contact the M&M Coordinator at the field site from which the packet was sent if they need additional material or require clarification of something in the packet.

Specific instructions for reviewing and assigning causes of death and for documenting non-fatal CVD events are given in the next two sections of this manual.
CHAPTER THREE
MORTALITY SURVEILLANCE

3.1 MORTALITY SURVEILLANCE

The examination cohort will be monitored in an on-going fashion to identify deaths. The following sources will be monitored on a regular basis to identify additional deaths in the cohort as they occur: local newspapers and community notices, community and tribal members, and IHS, tribal and BIA records. Near the end of 1999, the final year of data acquisition in Phase III, the State Health Departments will be contacted to identify death certificates in the study communities for those deaths that may have been missed using other sources. A combined list from all three centers of "missing " participants will also be sent to the National Death Index.

3.1.1. Detailed Procedures for Mortality Surveillance

a. Cohort Mortality (date of Phase II exam through May 31, 1999)

Of the original 4,549 members of the Phase I cohort, 500 deaths occurred through the end of Phase II exam, and an additional 350-450 deaths are expected to occur before the Phase III examination. Thus, it is estimated that 3,600 to 3,700 surviving individuals will be eligible for Phase III. All members of the Phase I examination cohort, regardless of whether they participated in the Phase II exam, are eligible for ongoing cohort mortality surveillance. Each member of the cohort will be contacted annually during Phase III to determine their vital status. Based on the death rates experienced thus far in the cohort, it is anticipated that collection of mortality data will be required for approximately 30-35 deaths from each center each year.

When a death is identified in a SHS cohort member, the death certificate will be coded by the Study nosologist, Mr. Karl Wise. All deaths will be investigated, regardless of the cause indicated on the death certificate. In order to conduct an independent, standardized review of cohort deaths, the following types of information will be collected (processing forms are given in Appendix C of this Manual).

1) discharge summary of the terminal hospital admission and all other admissions within one year of death
2) emergency room report and related information
3) ambulance report and any clinical notes regarding those dead on arrival
4) autopsy report (if done)
5) pathology report (if done)
6) laboratory reports from the terminal visit (or those obtained closest to the date of death) for tests relevant to the possible causes of death, including X-ray, ECG, enzymes, liver function tests, cultures, etc. For non-CVD deaths, cause-specific tests will be used.
7) consultation reports regarding diagnoses pertinent to possible causes of death
8) medical examiner, coroner reports / police reports for unattended, out-of-hospital deaths, and special tests, such as toxicology studies.
9) informant interview (Appendix C) for possible CVD deaths when medical records data is not sufficient or for deaths listed as "unknown".

10) if not hospitalized in the year prior to death, copies of notes and test results from the last IHS outpatient visit (IHS records only).

The following information should be collected for specific types of non-CVD causes listed:

1) CANCER:
   a) pathology report on which the original diagnosis was based, or if not available
   b) any diagnostic reports that may help to determine the **primary** site of the tumor (i.e., X-ray, CT, MRI, ultrasound) or a later report with information on cell type and origin of the tumor.

2) INFECTIONS:
   a) culture results or, if not available or culture negative
   b) diagnostic serology
   c) TB or other skin test results, if relevant
   d) CBC and differential
   e) temperature record from nurses notes.

3) LIVER FAILURE OR OTHER GI CONDITION
   a) liver function tests (SGOT, Alkaline phosphatase, GGT, Bilirubin (direct and indirect), LDH, CPK, Ammonia levels)
   b) biopsy results
   c) reports of other diagnostic tests (e.g., CT, MRI, endoscopy).

4) MULTI-SYSTEM PROBLEMS -- obtain all consultant reports when the cause is not clear-cut (e.g., cancer, septic shock, gunshot wound).

5) INTENTIONAL OR UNINTENTIONAL INJURY -- Police and EMS reports, if available. Alcohol use information, including blood alcohol.

Potential CVD deaths in the examination cohort are documented and reviewed by the SHS Mortality Review Committee. In addition, the SHS Mortality Review Committee will review the material obtained for each non-CVD death among SHS Phase I participants according to the procedure described by Sievers, et al. Underlying and contributing causes of death will be coded. All causes of death will be coded from this review, but analyses will generally be restricted to a slightly modified list of the 15 leading causes of death (and their inclusive ICD-9 codes) used by Sievers, et al. These causes are: diseases of the heart, malignant neoplasms, cerebrovascular disease, unintentional injuries, and adverse effects, chronic obstructive pulmonary disease and allied conditions, pneumonia and influenza, diabetes mellitus, chronic liver diseases and cirrhosis, atherosclerosis, suicide, homicide and legal intervention, nephritis, nephrotic syndrome and nephrosis, septicemia, and HIV/AIDS. Each death will be coded by two members of the review committee,
and discrepancies in CVD diagnosis will be adjudicated by Dr. James Howard.

Eligible deaths outside of the study area, but within the State, are included in the review and confirmation procedure. For eligible out-of-state deaths, attempts will be made to obtain an abstract or summary from the hospital where they died, and an interview will be done with an informant concerning the circumstances of death. Local medical records for the decedent will also be reviewed.

b. Procedure

The identification and confirmation of CVD deaths will involve the following steps: (1) identification of all deaths occurring in the SHS-I examination cohort, (2) obtaining all death certificates, (3) coding of all death certificates by the central nosologist, (4) obtaining Coroner's/Medical Examiner's report, (5) review autopsy reports, (6) chart review, and (7) independent confirmation of cause of death by the Mortality Review Committee.

STEP 1: Identification of all deaths

All deaths in members of the Phase I cohort will be identified by each center from tribal records, IHS hospitals, BIA, State Department of Health and/or the National Death Index. The name, date of birth, date of death and place of death will be obtained for each eligible death. Persons who died out-of-state when visiting other states will be included.

STEP 2: Obtaining death certificates and reviewing charts

With the names of the decedents, dates of birth, dates of death, and places of death, copies of death certificates of all deaths will be obtained from the State Department of Health. The Death Certificate Form (Appendix 7) will be completed by the local data abstractor and transmitted to the Coordinating Center.

STEP 3: Coding of death certificates by central nosologist

The local center will stamp the back of the death certificate, add the ID number immediately above the stamp and send only the death certificate to the central nosologist,

Mr. Karl E. Wise
36 Fox Grape Lane
Southern Shores
Kitty Hawk, NC 27949

for coding of the cause of death. The corresponding Death Certificate Forms will simultaneously be sent to the Coordinating Center. Mr. Wise will, in a standardized approach using ICD 9th Revision, record the codes on the back of the death certificate and return it to the Coordinating Center. The nosologist's codes will be entered into the computer. A copy of the codes will be sent to the Study Center by the Coordinating Center.
STEP 4: Obtaining Coroner's/Medical Examiner's / Police Report

If it is indicated on the death certificate that an autopsy was performed, the autopsy report ans Coroner's/Medical Examiner's Report will be obtained by each study center. Police report should also be obtained for injury deaths, if available. Photocopy the autopsy report, complete the Photocopy Checklist, attach both to the death certificate, and send the entire package, including Final Decision Form, to Dr. Sievers for confirmation. Dr. Sievers will fill out the autopsy report form (Appendix C) based on the cause(s) listed on the report.

STEP 5:

Review medical chart to see if the decedent was hospitalized within one year prior to death and fill out Photocopy Checklist. All hospital admissions between exam and death must be reviewed.

STEP 6: Confirmation of Cause of Death

a. If the decedent was hospitalized within one year prior to death, the Photocopy Checklist will be completed. The Photocopy Checklist, Mortality Survey Packet Checklist, the death certificate, the autopsy report, the Coroner's/Medical Examiner's report, and police report, if available, and relevant medical records information are sent to Dr. Sievers for confirmation. (Mortality Survey Final Decision Form, Appendix C).

b. If the decedent died prior to arrival at the hospital, upon arrival, or in any other non-hospital location (e.g., home, nursing home), and if available information is not sufficient to determine whether the death was due to a cardiovascular problem, the attending physician or nursing home staff, and an informant will be identified from the death certificate or other sources and contacted for an interview. The Informant Interview Form (Appendix C), and the Photocopy Checklist will be completed. These two forms as well as the death certificate, autopsy report, and coroner's/medical examiner's report (if available) will be forwarded to Dr. Sievers. This process is done only for suspected CVD deaths for which there was no terminal hospital admission.

c. Dr. Sievers will return the completed, including Final Decision Form, injury-related non-CVD mortality packet to the Coordinating Center for data entry. The rest of the mortality packets will be forward to the next reviewer for independent classification of cause of death. Once their review is completed, their Final Decision Form and the mortality packet are forwarded to the Coordinating Center.

3.1.2 Review of Medical Charts of the Decedents

Unless the Coroner's / autopsy report is conclusive, medical records of the decedent will be
reviewed and pertinent data photocopied using the Photocopy Checklist. For deaths that occurred in hospitals other than IHS hospitals, additional efforts will be made to secure medical information. If the patient was hospitalized in more than one facility without intervening discharge, all available medical records will be reviewed. Discharge summaries, ECGs, X-ray reports, etc. will be photocopied and attached to the Checklist. If the patient died in a hospital as an in-patient, data accumulated in the period of hospitalization will be reviewed. If the patient died out-of-hospital or died upon arrival at the hospital, available information in the medical records for relevant hospitalizations and outpatient visits within one year prior to death will be reviewed.

3.1.3 Informant Interview

Informant interviews are very helpful in deaths that occur outside the hospital, especially if no autopsy, coroner, or medical examiner reports are available. Using name and address information from the death certificate, an attempt will first be made to contact and interview the spouse or a first-degree relative (i.e., parent, son, daughter, or sibling) of the decedent, or someone else who witnessed the death including nursing home staff, if applicable. The following procedure will be followed:

1. Find the informant's telephone number and/or address.

2. If the telephone number is available, call him/her to request permission to interview and to set up an interview appointment. The interview may be conducted over the telephone, or if necessary, in person using the Informant Interview Form.

3. If phone contact is not possible, the local community health representative or public health nurse will be asked to assist in arranging the interview.

4. If the informant cannot be contacted by phone or in person, a form letter, a reply letter and a self-addressed and stamped envelope will be sent asking the informant for permission for an interview and convenient time for the interview. If the form letter is sent and no reply is received in three weeks, another such letter is sent by certified mail. If no reply is received within one month, no further effort to contact the individual is made.

When the death is witnessed by someone other than a member of the decedent's family, both a family member and the witness are interviewed. In such a case, the information from both interviews are recorded on separate Informant Interview Forms. Up to three (the three best) Informant Interview Forms may be completed for a given event.

3.1.4 Death Occurring Outside the Study Community

Eligible deaths outside of the study area, but within the State, will be included in the above review and confirmation procedure. For eligible out-of-state deaths, attempts will be made to obtain an abstract or summary from the hospitals where they died and to interview an informant. Their local medical charts will also be reviewed.
3.2 DEFINITIONS OF CVD DEATHS

The following will be the primary events of interest:

(1) Definite fatal myocardial infarction (MI)
(2) Definite sudden death due to coronary heart disease (CHD)
(3) Definite fatal CHD
(4) Possible fatal CHD
(5) Definite fatal Stroke
(6) Possible fatal stroke
(7) Definite fatal congestive heart failure (CHF)
(8) Possible fatal CHF
(9) Other fatal CVD

Criteria used for ascertaining the primary CVD deaths are the International Diagnostic criteria for acute myocardial infarction and acute stroke and criteria for fatal CHF of the Framingham study:

3.2.1 Definite fatal myocardial infarction (MI)

(la) Definite MI within 4 weeks of death by criteria:

1. Evolving diagnostic ECG

 AND/OR

2. Diagnostic ECG and abnormal enzymes

 AND/OR

3. Prolonged cardiac pain and abnormal enzymes.

 OR

(lb) Acute MI diagnosed by autopsy

 AND

(2) No known non-atherosclerotic or non-cardiac-atherosclerotic process that was probably lethal according to death certificate, autopsy report, hospital records, or physician records.
3.2.2 Definite sudden death due to coronary heart disease (CHD)

(1) Death witnessed as occurring within 1 hour after the onset of severe cardiac symptoms (cardiac pain - see below, shortness of breath, fainting) or within 1 hour after the subject was last seen without symptoms

AND

(2) No documentation of definite acute MI within, 4 weeks prior to death by criteria (see (1)a. in Section 3.2.1 for criteria for definite MI)

AND

(3) No known non-atherosclerotic or non-cardiac-atherosclerotic process that was probably lethal according to death certificate, autopsy report, hospital records, or physician report.

3.2.3 Definite fatal CHD

(1) Death certificate with consistent underlying or immediate cause(s) (ICD-9 codes 410-414)

AND

(2) No documentation by criteria of definite acute MI within 4 weeks prior to death

AND

(3) Criteria for sudden death not met

AND

(4) No known non-atherosclerotic or non-cardiac-atherosclerotic process or event that was probably lethal according to death certificate, autopsy report, hospital records, or physician records

AND

(5a) Previous history of MI according to relative, physician, or hospital records, or definite MI (see criteria above) or possible MI by criteria below:

(One or more of the following categories: * )

1) Equivocal enzymes and equivocal ECG (with or without pain)
2) Equivocal enzymes and diagnostic ECG (no pain)
3) Abnormal enzymes and other ECG (no pain)
4) Abnormal enzymes and equivocal ECG (no pain)
5) Abnormal enzymes alone (no pain, ECG absent or uncodeable)
6) Prolonged cardiac pain and equivocal enzymes (ECG absent or uncodeable)
7) Prolonged cardiac pain and equivocal ECG (enzymes incomplete)
8) Prolonged cardiac pain and diagnostic ECG (equivocal or incomplete enzymes)
9) Prolonged cardiac pain alone (ECG and enzymes incomplete)
10) Prolonged cardiac pain, "other" ECG, equivocal enzymes
11) Prolonged cardiac pain, "other" ECG, incomplete enzymes

OR

(5b) Autopsy reporting severe atherosclerotic-coronary artery disease or old MI without acute MI (50% proximal narrowing of two major vessels or 75% proximal narrowing of one more vessel if anatomic details given)

OR

(5c) Rapid death:

Death occurring greater than 1 and less than or equal to 24 hours after the onset of severe cardiac symptoms or after subject was last seen without symptoms.

* Definitions are given in Section 3.3.

3.2.4 Possible fatal CHD

(1) No documentation by criteria of definite acute MI within 4 weeks prior to death

AND

(2) No documentation by criteria of definite sudden death

AND

(3) No documentation by criteria of definite fatal CHD

AND

(4) Death certificate with consistent underlying or immediate cause (ICD-9 codes 410-414)

AND
(5) No known non-atherosclerotic or non-cardiac-atherosclerotic process that was probably lethal according to death certificate, autopsy report, hospital records, or physician records.

3.2.5 Definite Fatal Stroke

(1a) Cerebral infarction or hemorrhage diagnosed at autopsy

AND

(1b) No other disease process or event such as brain tumor, subdural hematoma, subarachnoid hemorrhage, metabolic disorder, or peripheral lesion that could cause localizing neurologic deficit or coma - according to death certificate, autopsy, hospital records, or physician records

OR

(2a) History of rapid onset (approximately 48 hours from onset to time of admission or maximum acute neurologic deficit) of localizing neurologic deficit and/or change in state of consciousness

AND

(2b) Documentation of localizing neurologic deficit by unequivocal physician or laboratory finding within 6 weeks of death with >24 hours duration of objective physician findings

AND

(2c) See list under (1b) above.

3.2.6 Possible Fatal Stroke

(1) Death certificate with consistent underlying or immediate cause (ICD-9 codes 431-437)

AND

(2) No evidence at autopsy examination of the brain, if performed, of any disease process other than cerebral infarction or hemorrhage that could cause localizing neurologic signs (see (1b) above).

3.2.7 Definite Fatal CHF

Two major or one major and 2 minor criteria must be present concurrently.
Major criteria

Paroxysmal nocturnal dyspnea or orthopnea
Neck vein distention
Rales
Cardiomegaly
Acute pulmonary edema
S₃ gallop
Increased venous pressure > 16 cm water
Circulation time ≥ 25 seconds
Hepatojugular reflux

Minor criteria

Ankle edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity reduced by one-third from predicted
Tachycardia (rate of heart ≥ 120/min)

Major or Minor criterion

Weight loss ≥ 4.5 kg in 5 days in response to treatment. No known non-cardiac process, such as renal failure, leading to massive fluid overload.

3.2.8 Possible Fatal CHF

Death certificate with consistent underlying or immediate cause, but neither autopsy evidence nor adequate pre-terminal documentation of the event.

3.2.9 Other Fatal CVD

1. Define other fatal CVD

   (1a) Autopsy evidence consistent with other CVD as cause of death

   OR

   (1b) Death certificate with consistent underlying or immediate cause

   AND
2. Possible other fatal CVD

Death certificate with consistent underlying or immediate cause, but does not satisfy any of the above criteria.

3.3 DEFINITION OF ABNORMAL ECG, ABNORMAL ENZYMES AND PROLONGED CHEST PAIN

3.3.1 Abnormal ECG

1. Evolving Diagnostic ECG

An evolving pattern on serial ECGs of a diagnostic ECG. (An evolving pattern of changes [appearance or disappearance within lead groups: anterior (V₁ – V₃); lateral (I, aV₅, V₆); or inferior (II, III, aV₆)] establishes the infarct as acute. Two or more ECG recordings during the hospitalization are needed for this classification.)

To Qualify as a Q wave, deflection should be at least 0.1 mV (1 mm.) in amplitude.

Possibilities:

a. No Q wave in one ECG record followed by a record with a diagnostic Q wave.

OR

b. An equivocal Q wave and no major ST segment depression in one ECG followed by a record with a diagnostic Q wave PLUS a major ST segment depression.

OR

c. An equivocal Q wave and no ST segment elevation in one ECG record followed by a record with a diagnostic Q wave PLUS ST segment elevation > 1 mm.

OR

d. An equivocal Q wave and no major T wave inversion in one ECG record followed by a record with a diagnostic Q wave PLUS a major T wave inversion.

OR
e. No Q wave and no ST Junction depression $\geq 0.5$ mm. and flat or down-sloping ST segment depression followed by a record with an equivocal Q wave PLUS ST Junction and flat or down-sloping ST depression of 0.5 mm.

OR

f. No Q wave and no ST elevation $> 1$ mm. followed by a record with an equivocal Q wave PLUS ST elevation $> 1$ mm.

OR

g. No Q wave and no T wave findings diagnostic of infarction followed by a record with an equivocal Q wave PLUS T wave findings diagnostic of infarction.

2. DIAGNOSTIC ECG WITH Q WAVE

a. Diagnostic Q and QS patterns.

3. DIAGNOSTIC ECG WITHOUT Q WAVE

a. ST segment elevation PLUS T wave depression indicative of infarction.
   (T wave depression cannot be used in the presence of ventricular conduction defects.)

4. EQUIVOCAL ECG WITH Q WAVE

a. ECG with Q and QS pattern possibly representing infarction.

5. EQUIVOCAL ECG WITHOUT Q WAVE

a. ST junction (J) and segment depression or T wave inversions or ST segment elevations possibly representing infarction.

6. OTHER

a. All other findings, including normal.

7. UNCODEABLE ECG

a. Missing Leads
b. Baseline drift (1 in 20) if it obscures ST-T segment.
c. Muscle tremor giving 2 mm. peak-to-peak oscillation.
d. Other technical errors making Q wave measurements impossible.
e. Major abnormal QRS conduction patterns (BBB, pacer, etc.)
3.3.2 Abnormal Enzymes

To be able to be used to evaluate an MI, enzymes must have been measured within 1-4 days of admission or onset of acute event, whichever is later.

1. Abnormal Cardiac Enzymes

   Enzymes are classed as "abnormal" if any appropriately-timed enzyme values meet any of the following criteria:

   1a) CK-MB is "present" (if laboratory uses the criterion of "present" or "absent" without reporting a more specific value) or the CK-MB (heart fraction) is at least twice the upper limits of normal (if hospital uses quantitative criteria) or 10% of the total CK value, and total CK is at least twice the upper limit of normal.

   AND

   1b) There is no known non-ischemic cause (cardiac surgery, severe muscle trauma, rhabdomyolysis) for the elevated enzyme value.

   OR

   2a) The ratio $\text{LDH}_1 : \text{LDH}_2 > 1$

   AND

   2b) There is no evidence of hemolytic disease.

   OR

   3a) Total CK and LDH are both at least twice the upper limits of normal. (These increases do not have to occur on the same day.)

   AND

   3b) There is no known non-ischemic cause (cardiac surgery, severe muscle trauma, rhabdomyolysis) for the elevated enzyme value and no evidence of hemolytic disease.

2. Equivocal Cardiac Enzyme

   Enzymes are classed as "equivocal" if the criteria for abnormal are not met and if:
1) Either total CK or total LDH are at least twice the upper limits of normal.

**OR**

2) Both total CK and total LDH are between the upper limits of normal and twice the upper limits of normal. (These increases do not have to occur on the same day.)

**OR**

3) CK-MB = 5-9% of total CK or is "weakly present".

A summary of the enzyme diagnostic criteria, as related to total CK and LDH is given in the following algorithm:

<table>
<thead>
<tr>
<th>Twice Upper Limit of Normal</th>
<th>Equivocal</th>
<th>Equivocal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL LDH Upper Limit of Normal</td>
<td>Normal</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Normal Upper Limit of Normal</td>
<td>Upper Limit of Normal</td>
<td>Twice Upper Limit of Normal</td>
<td></td>
</tr>
</tbody>
</table>

**3.3.3 Prolonged Cardiac Pain**

Pain having the following characteristics: Occurring anywhere in the anterior chest, left arm or jaw, which may also involve the back, shoulder, right arm, or abdomen on one or both sides and lasting for more than 20 minutes.

**3.4 MORTALITY SURVEY FORMS**

1. **Mortality Survey Death Certificate Form:** This form codes relevant information directly from the death certificate. Data from the form are entered on computer by the M&M Coordinator at each center and forwarded electronically to the Coordinating Center.
2. **Final Decision Form I - Autopsy Report Form:** This form is designed to capture the underlying cause of death as designated by the pathologist, medical examiner or coroner when an autopsy has been performed. The form is completed by Dr. Sievers when an autopsy report accompanies the mortality packet. The form is completed by transcribing the relevant information from the autopsy report, and does not involve decision-making.

3. **Photocopy Checklist for Medical Records Review - Mortality Surveillance - CVD and Non-CVD:** This checklist is intended to assist the field staff in collecting the appropriate medical records information for review of the cause of death in SHS participants. It also serves as a computerized record of the materials collected to support the mortality review for each event. The form is completed by the field staff collecting information on a SHS death.

4. **Mortality Survey - Final Decision Form:** This form records the judgment of the SHS Mortality Review Committee member as to the underlying and contributory causes of death. The form is completed independently by two reviewers for each death in the SHS cohort that is not due to an intentional or unintentional injury. Completed forms are forwarded to the Coordinating Center for data entry and review to identify discrepancies in assigned causes.

**SPECIAL COMMENTS:**

**Assigning Codes for Causes of Death -** Section A of the Final Decision Form includes codes for the underlying cause of death (only 1 is allowed) and for up to 2 contributing causes. Codes 01 through 09 are used for CVD and codes 21 through 33 are used for major, non-CVD causes. Code 88 should be used to designate a cause other than those listed, and the exact "other" cause should be printed in the space provided. Code 99 is used to designate death due to indeterminate causes. When a vascular disease was a contributory cause of death, the code associated with a "definite" occurrence should be used, i.e., codes 01, 03, 05 or 07.

The remainder of the form is used to indicate the types of evidence on which the designation of CVD was based. For non-CVD deaths, up to 3 evidence codes are provided to record the type of information on which the decision regarding cause of death was based.

5. **Mortality Survey Packet Checklist:** This form is used by the field staff to organize materials for the mortality packets prior to forwarding the packet to Dr. Sievers for review.

6. **Master List of Hospitalizations and Outpatient Visits:** This form is used by the field staff to record both in-patient and out-patient visits for which the medical records need to be reviewed. This would include any event of interest to the SHS or may be used by the centers to keep a log of all hospitalizations or out-patient visits. The intent of the form is to be useful to the field staff for organizing the events that require review for any given participant.