CARDIOVASCULAR DISEASE IN AMERICAN INDIANS
(PHASE II)

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 II)

Operational Manual
Volume One
GENERAL DESCRIPTION AND SURVEILLANCE PROCEDURES

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# Manual One

## General Description and Surveillance Procedures

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1. 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(1). 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 (2).

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 (2) and the high mortality rates from heart disease in younger Indians (those aged 25-44 years) (3). 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 - Phase I

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 initially for three years from October 1, 1989 to September 30, 1991 (1). The SHS is the largest study of CVD in American Indians ever undertaken. The SHS, which uses standardized methodology, is designed to estimate cardiovascular disease mortality and morbidity rates and the prevalence of known and suspected cardiovascular disease risk factors in American Indians. The study population consists of 13 tribes in three geographic areas: an area near Phoenix, Arizona, the southwestern area of Oklahoma, and the Aberdeen Area of North and South Dakota.

The SHS Phase I included three components. The first was a mortality survey to estimate cardiovascular disease mortality rates for 1984-1988 among tribal members aged 35-74 years. The second was a morbidity survey to estimate incidence of hospitalized myocardial infarction and stroke among tribal members aged 45-74 years in 1984-88. The third was a clinical examination of approximately 4,500 tribal members aged 45-74 years in order to estimate the prevalence of cardiovascular disease and its associations with risk factors. Medical history, family history, 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 include fasting and postload glucose, insulin, fasting lipids, apoproteins, fibrinogen, and glycated hemoglobin. Also measured were serum and urinary creatinine and urinary albumin. DNA from lymphocytes was isolated, frozen, and stored for future genetic studies.

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 Pimas 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 II of the Strong Heart Study.

The data confirming marked differences in CVD rates and prevalence of potential risk factors indicate that the SHS provides a unique opportunity to learn more about the importance of specific risk factors in American Indians (2). However, in a cross-sectional study, inferences with respect to etiology are limited. The contribution of various risk factors to the occurrence of CVD in the three groups of Indians will be better understood through a longitudinal study and for that reason, phase II proposes to follow prospectively the cohort of persons aged 45-74 who participated in the Phase I examination.

Comparative analysis of risk factors for CVD morbidity and mortality among the three centers will be done to determine why the rates of CVD differ. Since the Pimas have the highest rate of diabetes (over 65%) but the lowest rate of CVD, the study may identify protective factors that will have important implications for prevention of CVD (4). The SHS provides a unique opportunity to determine CVD risk factors in diabetic patients, because of the high prevalence of diabetes in all three groups. The high rates of CVD among the Sioux may be related to a high prevalence of smoking, hypercholesterolemia and diabetes in a population that has greater genetic admixture with non-Indians. A longitudinal study will allow these relationships to be defined more precisely in populations with high prevalence rates of obesity and diabetes and variable rates of other risk factors. Phase II of the SHS allows us to monitor changes in risk factor prevalence over time and to calculate incidence rates of CVD, diabetes, and hypertension among a large cohort of American Indian men and women whose CVD risk factors were uniformly assessed in Phase I examination.
Phase II of the SHS has four components:

1. A continuous mortality surveillance of the target populations (1989 - 1994);

2. A continuous morbidity surveillance of the Phase I examination cohort;

3. A re-examination of the Phase I cohort with an abbreviated personal interview, including a 24-hour dietary recall survey, echocardiography, pulmonary function tests, ultrasonography of the gallbladder, tuberculosis tests, peripheral neuropathy tests, additional laboratory tests, and a repeat of most of the tests done in the phase I examination;

4. Analysis and presentation of results from Phase I and II.
1.2 RESEARCH OBJECTIVES

The objective of the Strong Heart Study Phase II is to continue to obtain estimates of CVD mortality and morbidity rates using standardized methodology as well as to allow comparison of CVD risk factor levels among American Indian groups living in three different areas: Phoenix, Arizona, southwestern Oklahoma, and Aberdeen area, South and North Dakota.

The specific aims of the study are:

1. To determine cardiovascular disease (CVD) mortality and morbidity rates among American Indian men and women living in three different areas (Phoenix, Arizona; Southwestern Oklahoma; and Aberdeen Area, North and South Dakota) using a standardized methodology.

2. To determine CVD risk factors for these Indian groups in a longitudinal study that includes a follow-up examination of a cohort of American Indians aged 45-74 at the Phase I examination (1989-1991).

3. To compare CVD risk factors in the three centers and relate them to differences in the rates of CVD.

4. To compare risk factors for CVD among diabetic and non-diabetic participants.

5. To investigate structural and functional cardiac disease in three groups of American Indians by utilizing echocardiography.

6. To study pulmonary function among this cohort of Indians and to identify risk factors for pulmonary diseases and their relationships to CVD.

7. To study the prevalence of gallbladder disease (primarily cholelithiasis) and identify its risk factors.
1.3 STUDY DESIGN

Phase II of the Strong Heart Study has four parts; an extension of the mortality surveillance of the study target population from 1989-1994, a continuous morbidity surveillance of the Phase I examination cohort, a re-examination of the Phase I cohort, and analysis and presentation of results from Phases I and II. (See Figure 2).


Mortality and morbidity surveillance

Data analysis of Phase I and manual script preparation.

Development of protocol, manual, and data forms. Pretesting of forms.

Training session for Phase II examination.

Phase II exam.

Data Analysis.

Figure 1 Phase II Timetable

1.3.1 The Mortality Survey

In Phase II of the Strong Heart Study, surveillance activities include annual ascertainment of deaths in the entire target population (which includes the examination cohort) and identification of non-fatal events in the examination cohort.

For the mortality surveillance in the community, procedures similar to those used in Phase I will be continued. All deaths occurring among tribal members aged 35-74 in the three study areas between 1/1/89 and 12/31/94 are first identified through tribal records and other sources. Death certificates will be obtained and coded by a single nosologist. All death certificates with any mention of CVD will be further investigated. Medical records are reviewed and the cause of death confirmed independently. The causes of death of particular interest to the SHS are: myocardial infarction, stroke, sudden coronary death, and congestive heart failure (All participants in the Phase I exam will also be monitored for mortality, regardless of age).
1.3.2 The Morbidity Survey

Only those persons who participated in the Phase I physical examination will be followed for incident events of cardiovascular disease in Phase II. Because the interval between the Phase I and Phase II examination is relatively short (maximum, 6 years; minimum 1.5 years; mean 4 years), the major point at which the occurrence of new events will be ascertained will be at the Phase II examination. Determining the incidence of events at this time will allow for more thorough collection of data and for obtaining signed consent for review of medical records pertaining to the events of interest. In Phase II, the following incident events will be identified: myocardial infarction, stroke, congestive heart failure, angina, and peripheral vascular disease. The occurrence of coronary bypass surgery, angioplasty, or similar procedures will also be determined. Prevalence of the following conditions/indicators will also be ascertained at the Phase II examination: valvular heart disease, positive cardiac catheterization, positive treadmill test, left ventricular hypertrophy, other left ventricular dysfunction, cardiac wall motion abnormalities, and obstructive lung disease. The same definition and criteria for these events used in Phase I will be used in the Phase II study.

1.3.3 The Clinical Examination

The third component of the study consists of a personal interview, a limited physical examination, and laboratory tests for evidence of prevalent CVD, peripheral vascular disease (PVD) and risk factor assessment. Eligible persons will be participants of Strong Heart Study Phase I. Those eligible to participate will be contacted by the staff at each study center.

1. Personal Interview

Information on the following factors will be obtained from the personal interview:

(a) Demographic data
(b) Tobacco use and alcohol consumption
(c) Traditional values/culture
(d) Socioeconomic/stress evaluation
(e) Medical history, particularly CVD history
(f) Diet
2. Physical examination

The physical examination will include the following procedures:

(a) Height and weight
(b) Girth measurements: supine waist (abdominal) girth, erect hip girth, and upper arm circumference
(c) Measurements: of body fat using impedance meter
(d) Sitting arm blood pressure
(e) Ankle and arm blood pressures in supine position using the doppler
(f) A resting 12-lead ECG
(g) Examination of lungs
(h) Palpation of posterior tibial and pedal pulses
(i) Auscultation of femoral and carotid bruits
(j) Echocardiogram
(k) Pulmonary function test
(l) Ultrasonography of the gallbladder
(m) Assessment of peripheral neuropathy using monofilaments
(n) Skin testing for TB and coccidioidomycosis (AZ center only)

3. Laboratory measurements:

(a) Lipids: TC, TG, HDL-C, LDL-C, VLDL-C and VLDL-TG
(b) Fasting insulin
(c) Plasma creatinine
(d) Fasting glucose and 2-hour glucose tolerance test (GTT)
(e) Urinary albumin and creatinine
(f) Fibrinogen, plasminogen activator, inhibitor and C-protein
(g) Glycated hemoglobin (HbA1c)
(h) DNA extraction and storage
(i) Red blood cell typing for assessment of genetic admixture

1.3.4 Additional Measurements or Stored Samples from Phase I

Example:
1. Plasma Lp(a)
2. G(m) allotype
3. LDL size and density subclass
1.4 STUDY QUESTIONS

1.4.1 Mortality Survey

1. What are the CVD mortality rates (average annual rates for 1988-1994) in the three centers, and how do they compare to one another?

   a) Mortality rates will be estimated for acute myocardial infarction, stroke, congestive heart failure, total cardiovascular diseases, total mortality, diabetes*, cancer*, and external and other causes*.

   b) Estimated mortality rates will include the following:

      (1) Age-specific
      (2) Sex-specific
      (3) Age and sex-specific
      (4) Age-sex adjusted to U.S. population aged 35-74

* These will be collected by death certificate only. No attempt will be made to confirm cause of death.

2. How do these rates compare with reported rates for the U.S. population?

3. How do these rates compare with reported rates for Indians in these areas?

4. How do these rates compare among the tribes and among the three centers?

1.4.2 Morbidity Studies

Many of the study questions for Phase II are similar to those asked in Phase I. Some additional research questions of interest, based on Phase II data, include, but are not limited to, the following:

1) What are the four-year incidence rates of myocardial infarction, cerebrovascular disease (stroke), hypertension, congestive heart failure, large vessel peripheral arterial disease (PAD), diabetes, IGT, and hyperlipidemia?

2) Which risk factors have the strongest association with CVD incidence and prevalence?

3) Are the associations between risk factors and CVD similar in all three centers?
4) Are risk factors for CVD or PAD different among diabetics and non-diabetics?

5) Have the distributions of any risk factors changed over the follow-up period? Are the changes related to the development of CVD, PAD, diabetes, or IGT?

6) What is the rate of progression from IGT to diabetes mellitus?

7) Are diabetes and hyperinsulinemia independent risk factors for CVD?

8) Are diabetes and alcohol-consumption related to ventricular function as measured by echocardiography?

9) What is the relationship between ventricular function/mass and other evidence of CVD in this population?

10) What is the prevalence of rheumatic heart disease as determined by echocardiography?

11) What is the prevalence of abnormal pulmonary function and how does the prevalence relate to CVD, PVD, diabetes, and IGT?

12) What are the risk factors for abnormal pulmonary function?

13) What is the prevalence of gallstones?

14) What are the risk factors for gallstones?

15) What are the prevalence of TB and positive PPDs and their risk factors?

16) What are the risk factors for peripheral neuropathy?

17) What are the differences in diet among the 3 centers as measured by 24-hour recall?
1.5 STUDY MANAGEMENT

1.5.1 Introduction

The Strong Heart Study Phase II 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 (a). The operations of the study are directed by the Strong Heart Study Phase II Steering Committee, which includes members from each center and the NHLBI Project Manager (see Appendix 1 (b) for the members of Steering Committee). An organizational chart of the Strong Heart Study Phase II is given in Appendix 2. In addition to being a field center, the Oklahoma Center assumes the responsibility of the Coordinating Center, the Dakotas Center is the ECG Reading Center and the Arizona Center acts as the Core Laboratory. Echocardiogram are read at the Cornell University Medical Center under the direction of Dr. Richard Devereux, pulmonary function testing results are analyzed at the Arizona State University under the direction of Dr. Paul Enright. Analysis of the results of gallbladder ultrasonography is directed by Dr. James Everhart of NIDDK. Other key personnel at each center and consultants of the Study are listed in Appendix 3.

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 confidential pledge is given in Appendix 6 (b).

Completed data forms will be placed in locked file cabinets in offices assigned to the study at each study center and at the Coordinating 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, Echocardiography Reading Center, Pulmonary Function Testing Center, Ultrasonography Reading Center (NIH), 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:

FAX will be the major electronic mail facility to be used by all field centers, the Coordinating Center, Core Laboratory, ECG Reading Center, Echo Reading Center, Pulmonary Function Testing Center, Ultrasonography 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 acknowledgements of receipt of data.

3. Field Center Visits:

The Program Office and Staff from the Coordinating Center, ECG Reading Center, Echo Reading Center, Pulmonary Function Testing Center, Ultrasonography Center and Core Laboratory 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 second 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 Computype Inc. will be used.

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 4. Hospitals where the subject died or were 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 5. 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 6 (a). 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 sent to the Coordinating Center. The following are a few guidelines for form completion:

1. All forms should be filled in black pen. Print all information in block capital letters, with one letter only in each box, so that keypunch 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.

Example:

Name:  S M I T H  J R .  J O H N
If the address is a post office box or rural route, record in the field for "street number", as

\[
\begin{array}{c}
\text{R T 5 , B O X 5 4 A}
\end{array}
\]
or

\[
\begin{array}{c}
\text{1 4 7 3 S T A R S T R E E T}
\end{array}
\]

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

Example:

Triglyceride: \[
\begin{array}{c}
\text{1 6 7}
\end{array}
\]

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

Example:

Date of birth: \[
\begin{array}{c}
0 8 / 0 7 / 3 8
\end{array}
\]

mo \hspace{0.5cm} day \hspace{0.5cm} yr

5. When recording dates, use 99 for missing months, days or years.

6. To correct an error, draw a single line through the mistake and write the correct value above.

Example:

Age at Death: \[
\begin{array}{c}
6 4
\end{array}
\]

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.

Example:

16-18 months, midpoint = 17 months, record 17.
13-14 months, midpoint = 13.5 months, record 14.
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, do the following:

Time of death:

1.6.2 Monthly Mailings Of Data To The Coordinating Center

The Arizona Study Center will cease data collection at the close of operations on the first Friday of each month and prepare all recently collected data for shipment to the Coordinating Center. The Oklahoma Study Center will do the same on the second Friday of the month, as will the South Dakota Study Center on the third Friday of the month. This will allow for modular migration of data files to the Coordinating Center.

Preparation of the data for shipping will require a review of each data form for completeness (i.e. no missing responses or miscoded entries). Legible photocopies will be made of all original data forms. The photocopied forms will be separated by form type and sorted in ascending order by ID number. These forms should be packaged in a mailer made of corrugated cardboard and secured with the type of mailing tape that has fibre threads running through it. Each mailer should be labeled with large legible printing of the following address:

Strong Heart Study Coordinating Center
Center for Epidemiologic Research
University of Oklahoma Health Sciences Center
801 NE 13th Street
College of Health Building, #317
Oklahoma City, OK 73104

This label should be covered with clear adhesive tape to protect the label from moisture. The original data forms associated with this mailing should not be filed until the Coordinating Center acknowledges receipt of the photocopies. In the event that forms are lost in the mail, the Study Center must photocopy the originals a second time and repeat the above processing.
1.6.3 Procedures for data entry and verification of completeness

Each field center examines every data form for completeness and accuracy before sending it to the Coordinating Center. The Coordinating Center logs each form, laboratory result, and ECG report received in the Participant Forms Logbook. This is manually done. The ID number, participant's name, and date that the item is received are recorded. At the same time, the completeness of each form is checked. All the incomplete items (missing, questionable, unclear) are recorded and the corresponding field center is contacted to find out the reason. If the missing information can be obtained with additional effort, the form is returned to the field center. It may take several months for the field center to collect the missing information since it is very difficult to recall the participants. When these items are completed by the individual center and received by the Coordinating Center, the logbook is updated. Before the ECGs are Minnesota Coded, for interim reports and quick reference, both the machine reading and cardiologist's reading are coded according to the CAPOC MUSE Library Statement. Photocopies of the nosologist's codings of cause of death are made and sent back to each field center.

The complete data forms, ECG reports, and laboratory results are then given to the data manager for entry into the computer. The two data entry persons enter the data separately and exchange what they have entered and reenter. The two sets of the data are compared to identify data entry errors. Any inconsistent items are checked against the original data form to find out which one is correct and who made the mistake. After all the corrections are made, the error-free file is then appended to the permanent file which is used for data analysis. The lipid and glucose data received from the Core Laboratory on diskettes as ASCII files are directly converted into SAS datasets. However, before these data are merged into the permanent data files, they are checked against the values given by the laboratory on paper to ensure the conversion is correctly done. After data entry is completed, all the forms are stored in locked file cabinets.

After all the available data from the physical examination are entered into computer, the Coordinating Center also generates a Summary Report for each participant and sends the report to the field center. These summaries are then forwarded to the participant and his/her physician.

1.6.4 Data Backup:

Several backup procedures are used to ensure the safety of the SHS data files.

a. Daily backup: Two sets of diskettes 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 diskettes are rotated, each for every other week. Backup of the week's data set is done every Friday.

c. Tape backup: Additional permanent files are stored in the 486-computer, and backed-up every day by rotating two sets of tapes.

d. Storage of backup data: Diskettes and tapes are stored in locked file cabinets in different offices and one set of the weekly backup diskettes is stored in a different building.

1.6.5 Statistical Analysis

By July 1995, we will have collected CVD mortality data for the population over an eleven and one-half year interval (1/1/84-6/30/95). Age and sex specific mortality rates will be calculated using person-years accrued from 1984 to last contact or death. The 1988 tribal roll will be updated to provide denominators as of 1993.

Cardiovascular disease mortality rates will be compared with those of the U.S., the states where the participants reside, and other populations. For the examined cohort, standardized mortality ratios (SMR) will be calculated if the number of deaths is large enough. A proportional mortality ratio will be calculated also.

Morbidity data obtained from surveillance activities will allow us to estimate 4-year incidence density (using person-years computed from baseline examination) for the examined cohort. Since the date of first event will be available, we will also be able to use survival data analysis techniques to identify risk factors. For example, the distributions of disease-free time for different "exposure" groups can be estimated by the Kaplan-Meier method and compared by a two-sample or K-sample test (5). To evaluate the risk factors simultaneously, Cox's proportional hazards model will be used in a stepwise manner to rank the variables according to their relative importance (5,6).

Morbidity data obtained from the clinical examination will be examined cross-sectionally and prospectively when combined with Phase I (baseline) data. Cross-sectional analyses will be performed using statistical methods similar to those described for the Phase I data. These include summary statistics for each variable, correlation analyses between variables, and comparisons of risk factors between disease groups. Prospective analyses will include the calculation of four-year incidence of CVD, PAD, diabetes and IGT, the association of baseline risk factors with CVD outcome at follow-up, and an examination of changes in risk factors. In addition, prevalence of rheumatic heart disease, left ventricular dysfunction and wall motor abnormalities and abnormal pulmonary function and their associations with risk factors will be examined.
The 4-year incidence density of CVD, PVD, hypertension, diabetes, IGT and hyperlipidemia will be calculated by sex using person-years of follow-up from time of baseline examination to diagnosis or last contact. The numerator will be the number of new cases that are diagnosed during the follow-up period and the denominator will be the total person-years of follow-up of subjects who were free of the disease under study at baseline. The incidence density so obtained can be compared to that obtained by using the surveillance data. This will provide a comparison between designs with an ongoing surveillance and with a single disease ascertainment at the end of the follow-up period.

For the association of baseline risk factors and changes in risk factors with disease outcome at follow-up, we will begin with univariate analysis. For continuous variables (or risk factors), summary statistics will first be calculated for each variable to provide a preliminary understanding of the variables. Internal comparisons of the means or distributions of baseline variable between the diseased and the non-diseased will be performed by t-tests or nonparametric tests. Appropriate transformations may be used to stabilize the variance.

For categorical variables, histograms and contingency tables will be used to present the data. Disease incidence rates will be compared between different baseline "exposure" groups by chi-square tests. For example, incidence rates of myocardial infarction will be compared between smokers and nonsmokers as indicated at baseline (i.e., Phase I). For dichotomous variables, relative risks and odds ratios will also be computed. Many continuous variables will be dichotomized or polychotomized so that relative risk and odds ratio can be estimated and contingency table analyses performed. For example, systolic blood pressure can be dichotomized into two groups: < 140 mmHg and ≥ 140 mmHg and total cholesterol values can be classified into three groups: < 200 mm/dl, 200-239 mm/dl, and ≥240 mm/dl. To adjust for the possible effect of confounding factors, stratified analysis will be performed using the Mantel-Haenszel method (5). In addition, the linear logistic regression analysis will be performed to assess the relative importance of the risk factors, both continuous and categorical. Adjusted odds ratios will be obtained.

Changes in risk factors over the follow-up period will be assessed and related to disease outcome. The changes may be categorical (e.g., from smokers to nonsmokers) or numerical (e.g., cholesterol value being 50 mg/dl lower). Similar statistical methods will be used to assess the association between changes and disease status at follow-up. Progression from IGT to diabetes and from normal glucose tolerance to IGT will be examined.

As in Phase I, we will analyze the risk factor data periodically during the clinical examination period for abstracts to be submitted to professional conferences. The risk factors will be examined for linear and nonlinear relationships, and interactions. Multiple regression analysis will also be performed to examine multiple variables simultaneously.
1.7 PUBLICATION POLICY

Overall responsibility for manuscript and abstract generation and approval for the Strong Heart Study lies with the Steering Committee, which also serves as the Publication Committee. This committee has developed procedures for generating manuscripts and abstracts as well as the formal requirements for manuscript approval prior to submission for publication or abstract submission before presentations.

The overall aim of this process is to encourage the preparation of manuscripts and abstracts while also providing appropriate control over their quality and content.

This section discusses the procedures for both the generation phase and the approval phase. It reviews the different types of possible publications and presentations, authorship, and general strategy for preparation of manuscripts and abstracts, and describes in more detail the requirements for each type of publication or presentation.

1.7.1 Types of Publications and Presentations

There are several types of publications and presentations for which approval procedures are established. These include:

(1) Major descriptions of the design and conduct of the study.

(2) Descriptions of results, based on data from all field centers, addressing the objectives of the study.

(3) Descriptions of results based on data collected from a single field center.

(4) Descriptions of methodological developments required to meet the needs of the study.

(5) Articles to appear in proceedings of meetings for which no abstract was required.

(6) Invited presentations.

(7) The draft outline

(8) Press releases or discussions with the media.

The Steering Committee is responsible for resolving any uncertainties as to which category a specific presentation or publication belongs.
1.7.2 Outline of the Preparation and Approval Process

The basic steps for the generation and approval of publications and presentations are listed below:

(1) The Steering Committee designates a topic.

(2) The Steering Committee selects a writing group and its chairperson. A member of the Coordinating Center will be included in each writing group.

(3) The writing group prepares specifications for the manuscript and obtains Steering Committee approval.

(4) The writing group prepares and communicates computational specifications to the Coordinating Center.

(5) The Coordinating Center prepares statistical computations according to priorities specified by the Steering Committee.

(6) The writing group prepares, reviews internally, and submits the completed document to the Steering Committee for review and approval.

(7) The draft article is submitted to NHLBI, IHS and tribal groups for review and approval.

(8) The manuscript is formally submitted to a journal or abstract selection process.

The overall responsibility for managing the entire process lies with the Steering Committee.

1.7.3 Authorship

The authorship policy varies according to the type of publication or presentation being considered. In all cases, the persons preparing the manuscript are listed as authors. Some abstracts and presentations can be listed as presented by someone for the study. The person assuming the primary responsibility will be listed as the first author. In addition, the phrase "Strong Heart Study" is to be included in the title and listed as a "keyword" whenever possible.

The Steering Committee is responsible for resolving any conflict or confusion that occurs with respect to appropriate recognition of authorship.
1.7.4 Manuscript and Abstract Generation

The general procedure for generating manuscripts or abstracts is for the Steering Committee to designate a writing group with the charge to develop the manuscript for publication or presentation. The impetus for this designation may come directly from the Steering Committee or may be in response to a request or suggestion from outside the committee. Once it is decided that a specific manuscript will be developed, the writing group and its chairperson will be specified.

Under normal circumstances the chairperson, who has the lead responsibility for this task, will also be listed as the first author. The chairperson also has the responsibility for listing the co-authors in the appropriate order. As indicated above, the Steering Committee serves as final arbitrator of any conflicts.

Individuals interested in preparing a manuscript or abstract on a specific topic must submit their proposal, which should include suggestions for writing group members, to the Steering Committee for approval. The proposal must include a clear statement of the nature of the publication, and should, if appropriate, also include the hypotheses to be addressed and the types of statistical computations or data summarizations likely to be required.

The Steering Committee has the responsibility for reviewing these proposals, both for appropriateness and for a priority designation. The Steering Committee also ensures that the different participating centers and groups are appropriately represented and that appropriate recognition is provided.

Once the specifications for the manuscript have been approved, the requirements for statistical computing can be formally communicated to the Coordinating Center. Requests will be processed according to the priorities specified by the Steering Committee. The Coordinating Center has representation on the writing group whenever possible and this person serves as the liaison to the writing group both for communications about computing issues and for providing or obtaining appropriate statistical input.

The Steering Committee reviews the progress that each writing group is making toward the completion of its task and makes those changes required for the timely completion of each manuscript or abstract.

1.7.5 Approval Procedures

A manuscript stemming from the Strong Heart Study is submitted to the chairperson of the Steering Committee, who sends copies of the manuscript to all Steering Committee members for their critique. Upon receiving the critiques, two courses of action are possible: (1) If the chairperson deems the reviewers suggestions to be mainly editorial in nature, she may approve the manuscript and request that the authors incorporate
suggested changes to the final version, or submit in writing reasons for not doing so. No further action is needed from the Steering Committee; or (2) If, in the chairperson's judgment, critiques entail substantive changes, the revised manuscript must be further reviewed by the primary reviewers. Approval by NHLBI, IHS and tribes will next be initiated. Each center will be responsible for obtaining local IHS and tribal approval. The Dakotas Center, on behalf of the three centers, will also submit the manuscript to IHS headquarters for approval of the manuscript.

1.7.6 Press Releases and Media Discussions

In general, scientific findings from the Study made available to the media will involve those findings being presented at scientific meetings and being published in the scientific literature. Such presentations and publications require prior clearance as noted above. In some circumstances, media discussions and press releases may be appropriate to clarify scientific findings for the lay public, but they should not be used as forums to release new information. Investigators are requested to keep the Program Office informed of contacts with representatives of the major national media and of major national media coverage of information which they have supplied. If a situation arises in which it appears desirable to release to the media new information not otherwise cleared for presentation or publication, prior clearance from both the Steering Committee and the Program Office is required.

Release of general descriptive information about the study for local use (such as a local newspaper, university newsletter or state medical society journal) does not require prior approval. Use of centrally prepared materials for such purposes is encouraged. A copy of any resultant article should be sent to the Program Office and the participating tribes. All those communicating with the media will be sensitive of the special needs and concerns of the Indian Communities involved. Any interviews or photographs involving tribal members must have prior approval of the tribe.
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.

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

1.8.6 Analysis and Publication of Results of Ancillary Studies

The 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 will be required to sign a confidentiality statement (Appendix 6). In addition the investigation 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.
2. Mortality Survey

2.1 ELIGIBILITY CRITERIA

Fatal events are selected according to the following eligibility criteria:

(1) Age. Only deaths at ages 35 to 74 and participants of SHS-I are included.
(2) Tribal Affiliation. The decedent must have been enrolled in one of study tribes.
(3) Place of Residence. The decedent must have lived within the study community. The residence recorded on the death certificate determines eligibility. People institutionalized at the time of death will be included.
(4) Time. Only deaths occurring between January 1, 1989 and December 31, 1994 are eligible.

2.2 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

All death certificates will be coded by the study nosologist. After coding the following ICD codes will be utilized to identify subjects for detailed mortality review: possible cardiovascular disease 250, 390-448, 518.4, 585, 789 and 799.

Criteria used for defining the primary CVD deaths are the International Diagnostic criteria for acute myocardial infarction and acute stroke (7) and criteria for fatal CHF of the Framingham study (8).

2.2.1 Definite fatal myocardial infarction (MI)

1a 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

1b Acute MI diagnosed by autopsy

AND

2 No known nonatherosclerotic or noncardiac-atherosclerotic process that was probably lethal according to death certificate, autopsy report, hospital records, or physician records.

2.2.2 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 1a in Section 2.2.1 for criteria for definite MI)

AND

3 No known nonatherosclerotic or noncardiac-atherosclerotic process that was probably lethal according to death certificate, autopsy report, hospital records, or physician report.
2.2.3  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 nonatherosclerotic or noncardiac-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 2.3.

2.2.4 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 nonatherosclerotic or noncardiac-atherosclerotic process that was probably lethal according to death certificate, autopsy report, hospital records, or physician records.
2.2.5 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.

2.2.6 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).
2.2.7 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 ≥ 120/min)

**Major or Minor criterion**

Weight loss ≥ 4.5 kg in 5 days in response to treatment. No know noncardiac process leading to massive fluid overload such as renal failure.

2.2.8 Possible Fatal CHF

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

1. Definite 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) Adequate documentation in medical records

2. Possible other fatal CVD
   Death certificate with consistent underlying or immediate cause, but does not satisfy any of the above criteria.

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

2.3.1 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 - V5); lateral (I, aVL, V6); or inferior (II, III, aVF)] 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.
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 ≥ 0.5 mm. and flat or downsloping ST segment depression followed by a record with an equivocal Q wave PLUS ST Junction and flat or downsloping 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.)

2.3.2 Abnormal Enzyme

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 enzyme values recorded 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.
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 enzymes 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:
### Total CK

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

### 2.3.3 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.

### 2.4 Identification and Confirmation of CVD Deaths

Fatal events will continue to be identified and investigated during Phase II using the same protocol as was used in Phase I. Procedures for abstracting and coding death certificates and for the mortality review are described in detail on pages 22-34 and 149-203 in the Strong Heart Study (SHS) Phase I manual. In Phase II, all deaths occurring in the population during the calendar years 1989 through 1994 will be identified. Additional information will be obtained for those death certificates with any mention of cardiovascular disease. These data will be reviewed for assignment of the underlying cause of death.

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, IHS, tribal and BIA records. Near the end of 1995, the final year of data acquisition in Phase II, 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.
2.4.1 Procedure

The identification and confirmation of CVD deaths will involve the following steps: (1) identification of all deaths occurring in the eligible population during 1989-94, (2) obtaining all death certificates, (3) coding of all death certificates by the central nosologist, (4) identification of potential CVD deaths, (5) obtaining Coroner's/Medical Examiner's report, (6) review autopsy reports, (7) chart review, and (8) independent confirmation of CVD deaths by the Mortality/Morbidity Review Committee comprised of Dr. Maurice Sievers, Dr. Wm. James Howard, and Dr. Arvo Oopik.

STEP 1: Identification of all deaths

All deaths that satisfy the Eligibility Criteria (1) - (4) in Section 2.1 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 mailed 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: Identification of potential CVD deaths

Potential CVD deaths will be identified by each Study Center after receiving the codes from the Coordinating Center.

A potential CVD death is defined as having mention of any of the following anywhere on the death certificate.

- Any type of cardiovascular disease
- Diabetes
- Acute edema of lung
- Renal disease
- Sudden death, cause unknown

If there is any question as to whether a death should be considered a potential CVD death, the P.I. should be consulted.

The following steps are for the potential CVD deaths only.

STEP 5: Obtaining Coroner's/Medical Examiner's Report

If it is indicated on the death certificate that an autopsy was performed, the Coroner's/Medical Examiner's Report will be obtained by each study center. Photocopy the autopsy report, complete the Mortality Medical Records Abstract Form, attach both to the death certificate, and send the entire package, including Final Decision Form, to Dr. Sievers for confirmation.

STEP 6:

Review medical chart to see if the decedent was hospitalized within one year prior to death and fill out Mortality Survey Medical Records Abstract Form (Appendix 9) in order to identify possible CVD events between 1989 and 1994. The Chart Request Form in Appendix 16 can be used to record charts needed from each involved hospital. Note that if the decedent was a participant in phase I exam, all hospital admissions between exam and death must be reviewed.

STEP 7: Confirmation of CVD deaths

a. If the decedent was hospitalized within one year prior to death, the Mortality Survey Medical Records Abstract Form will be completed. The Medical Records Abstract Form, the death certificate and the Coroner's/Medical Examiner's report, if available, will be sent to Dr. Sievers for confirmation.
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, and an informant will be identified from the death certificate or other sources and contacted for an interview. The Physician's Questionnaire (Appendix 10), Informant Interview Form (Appendix 11), and the Medical Records Abstract Form will be completed. These three forms as well as the death certificate and coroner's/medical examiner's report (if available) will be forwarded to Dr. Sievers. A Final Decision Form (Appendix 12) will also be mailed to Dr. Sievers from the study center for recording his final decision. The study center will stamp the ID number and fill out the patient's name on the Final Decision Form for Dr. Sievers. Dr. Sievers will return the completed Final Decision Form to the Coordinating Center for data entry. The Coordinating Center will forward a copy of the Decision Form to the Study Center. For any equivocal cases Dr. Sievers will forward all information to Dr. Wm. James Howard for independent classification. In addition, Dr. Wm. James Howard will independently reclassify 33 percent of deaths, and other will independently reclassify the rest 67 percent.

A flowchart describing the procedure outlined above and a checklist which should be followed to assure that all steps are completed are given in Appendices 13 and 14, respectively.

2.4.2 Review of Medical Charts of the Decedents

Unless the Coroner's report is conclusive, medical records of the decedent will be reviewed and pertinent data abstracted and photocopied using the Medical Records Abstract Form. 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 to complete the Medical Record Abstract Form. Discharge summaries, ECGs, X-ray reports, etc. will be photocopied and attached to the Form. If the patient died in a hospital as an in-patient, data accumulated in the period of hospitalization will be reviewed and abstracted. 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 and abstracted.

2.4.3 Informant Interview

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., son, daughter, or sibling) of the decedent, or someone else who witnessed the death. 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 (Appendix 15 a and b) 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.

2.4.4 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, we will attempt to obtain an abstract or summary from the hospitals where they died and interview an informant. Their local medical charts will also be reviewed.
3. Morbidity Survey

3.1 ELIGIBLE POPULATION

Only those persons who participated in the Phase I physical examination will be followed for incident events of cardiovascular disease in Phase II. Because the interval between the Phase I and Phase II examinations is relatively short (maximum, 6 years; minimum 1.5 years; mean 4 years), the major point at which the occurrence of new events will be ascertained will be at the Phase II examination. Determining the incidence of events at this time will allow for more thorough collection of data and for obtaining signed consent for review of medical records pertaining to the events of interest. In Phase II, the following incident events will be identified: myocardial infarction, stroke, congestive heart failure, angina and peripheral vascular disease. The occurrence of coronary bypass surgery, angioplasty or similar procedures will also be determined. Prevalence of the following conditions/indicators will also be ascertained at the Phase II exam: valvular heart disease, positive cardiac catheterization, positive treadmill test, left ventricular hypertrophy, other left ventricular dysfunction, cardiac wall motion abnormalities, and obstructive lung disease. The same definitions and criteria for these events used in Phase I will be used in Phase II.

3.2 SURVEILLANCE EVENTS

Two types of frequency measures will be used, total incidence and incidence rate. All cases of MI and stroke, as well as new cases (first occurrence), occurring during the study interval will be ascertained. Data obtained from review of medical records will be used to calculate total incidence and incidence rates of acute myocardial infarction and stroke. Only information for those events with discharge diagnoses between 1989 and 1995 and for participants in the Strong Heart Study Phase I examination will be abstracted. The following types of CVD will be ascertained:

1. Acute Myocardial Infarction (ICD-9 code 410)
2. Stroke (ICD-9 codes 431-432, 434, 436)
3. Coronary Heart Disease
4. All other Cardiovascular Disease
3.3 DIAGNOSTIC CRITERIA - NON-FATAL CARDIOVASCULAR DISEASE

1. **Definite Myocardial Infarction (MI)**

   Minnesota codes 1.1.x or 1.2.x except 1.26. and 1.28 with no 7.1 or 7.4
   History of MI verified by chart review as definite MI

2. **Possible Myocardial Infarction**

   Minnesota codes 1.3.x, 1.2.6, or 1.2.8 with no 7.1 or 7.4
   History of MI verified by chart review as possible MI

3. **Definite Coronary Heart Disease (CHD)**

   Definite MI, or
   Definite CHD verified by chart review to include cardiac cath,
   proven coronary artery disease, PTCA, coronary artery bypass grafting, or
   abnormal stress ECG plus abnormal imaging (i.e., both must be abnormal), or
   Angina Pectoris plus LBBB (7.1.1) or
   ST changes (4.1) or
   T wave changes (5.1), or
   verified possible MI.

4. **Possible Coronary Heart Disease**

   Possible MI by ECG (1.3.x, 1.2.6, 1.2.8), or verified by chart review, or
   Minnesota codes in one of the following 7.1, 4.1, 4.2, 5.1, 5.2, 7.4, or
   Positive functional test of ischemia (such as treadmill) without invasive confirmation, or
   Possible ECG or imaging in scintigraphic studies (not both), or
   Unconfirmed self reported history of MI, or
   Self reported Angina Pectoris.

5. **Other Non-fatal Cardiovascular Disease**

   Any CHD
   Congestive Heart Failure
   Cardiomyopathy
   Valvular Heart Disease
   Left ventricular Hypertrophy by Echocardiogram
   Left ventricular Hypertrophy by ECG (3.1 or 3.3 plus 4.1-4.3 or 5.1-5.3)
   Ankle Arm Index <= 0.8
   Atrial Fibrillation
   Minnesota codes 4.1, 5.1, 6.1, 6.2, 6.8, 7.1, 7.2, 7.4
Noncoronary heart surgery or carotid or other vascular surgery
Pacemaker implantation
Bruit by physical examination
Intermittent Claudication by Rose Questionnaire
Positive non-coronary angiography

3.4 PROCEDURE FOR IDENTIFICATION OF INCIDENT AND RECURRENT CASES

Data on the incidence and prevalence of endpoints of interest will be obtained primarily at the time of the Phase II examination. Other sources of this information include: IHS user listings and discharge records of other community hospitals. Relevant information will be collected from the medical record for each documented event to allow independent confirmation of the diagnosis of a case.

STEP 1: Identification of potentially eligible cases.

Participants at the clinical examination will be asked if they had an MI, stroke or any other heart or circulation problems during 1989-95. Positive answers will be confirmed by chart review. When reviewing IHS user lists or hospital discharge listings, names, chart numbers and other relevant information for pulling charts for review should be recorded on the Chart Request Form (Appendix 16). The following ICD-9 codes are associated with events of interest.

1. MYOCARDIAL INFARCTION (ICD-9 codes 402, 410-414, 427-428, 518.4)

402 Hypertensive heart disease
410 Acute myocardial infarction
411 Other acute and subacute forms of ischemic heart disease
411.0 Postmyocardial infarction syndrome
411.1 Intermediate coronary syndrome
411.2 Other - includes coronary insufficiency (acute), microinfarct of heart, subendocardial ischemia
412 Old myocardial infarction
413 Angina pectoris
414 Other chronic ischemic heart disease
427 Cardiac dysrhythmia
428 Heart failure
428.0 Congestive heart failure
428.1 Left heart failure
428.9 Heart failure, unspecified
518.4 Acute edema of lung, unspecified
2. CEREBROVASCULAR DISEASE (ICD-9 430-438)

430 Subarachnoid hemorrhage
431 Intracerebral hemorrhage
432 Other and unspecified intracranial hemorrhage
433 Occlusion and stenosis of precerebral arteries - includes embolism, narrowing, obstruction or thrombosis of basilar, carotid, and vertebral arteries
434 Occlusion of cerebral arteries
435 Transient cerebral ischemia
436 Acute, but ill-defined, cerebrovascular disease - includes CVA NOS, Stroke
437 Other and ill-defined cerebrovascular disease - includes cerebral atherosclerosis, chronic cerebral ischemia, hypertensive encephalopathy, cerebrovascular disease or lesion not otherwise specified.
438 Late effects of cerebrovascular disease

STEP 2: Review of medical record for eligibility

If the examination participant reports a history of MI, stroke or diagnostic procedures or treatments of interest between 1989 and re-examination, they will be asked at which hospital they were cared for so that records can be obtained. Release of clinical information forms will be obtained for all non-IHS facilities, if required by local Institutional Review Board (IRB) and the standard IHS Authorization For Release of Information may be used.

If required by the local IRB, consent for release of clinical information will be obtained from the participant or the next-of-kin before any charts are reviewed.

STEP 3: Confirmation of event occurrence and incident status.

Because discharge diagnoses may be improperly recorded and a variety of associated codes will be screened, it is important to confirm that one of the events of interest has, in fact, occurred. Information in the record pertaining to the admission by which the potential case was identified (the index admission) should be reviewed. Check the discharge diagnoses listed on the face sheet of the admission and read the discharge summary.
Myocardial infarction and stroke are defined as "new" if the participants gave a negative history during the Phase I examination and there was no mention in the medical record of a previous episode. An event is "new" only if it first occurred after the Phase I examination. All events of interest occurring during the study interval should be abstracted.

**STEP 4:** Medical record abstract for incident cases.

If the index admission is for one of the study events (whether or not it is the first occurrence), an appropriate medical record abstract form for that admission should be completed (Appendix 17(a)). If evidence is present suggesting that one or more myocardial infarctions or strokes occurred, a separate chart abstract form will be completed for each event. Separate events must have a 28 day period when the patient is discharged from an acute care facility after a previous event. (If the participant is a study death, the abstract of medical records for decedents should also be completed.) If the medical record is not eligible for abstraction, the reason for exclusion (i.e., event occurred outside of the calendar years of the study, not a study event) should be noted on the front on the SHMORB.

Photocopy checklists for MI, stroke, and/or cardiovascular procedures and tests should be completed, depending on the material that is being collected. High resolution photocopies of ECGs taken as evidence of a myocardial infarction (see Section 3.3.3) should be arranged in chronological order from earliest to latest. ECG series for each case will be sent to the ECG Reading Center (Fitzsimons) with a completed Possible Myocardial Infarction ECG Analysis Field Sheet (Appendix 17(b)) and a blank ECG Center Sheet (Appendix 17(c)) with ID number stamped. The ECG series will be reviewed independently by three cardiologists and results recorded on the ECG Center Sheet which will then be returned to the Coordinating Center.

The Morbidity Survey Medical Records Abstract form, Photocopy Checklists, the ECG Analysis Field Sheet, the ECG Analysis ECG Center Sheet and the Morbidity Survey Decision form (Appendix 17(d)) will be sent by the Coordinating Center to Dr. Arvo Oopik for confirmation. Dr. Oopik will return the entire package with the completed Decision form to the Coordinating Center. For any equivocal cases Dr. Oopik will forward all information to Dr. Wm. James Howard for independent confirmation. In addition, Dr. Wm. James Howard will independently reclassify a random ten percent of cases.
Table 1. Endpoints

<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</td>
</tr>
<tr>
<td>Stroke</td>
<td>I</td>
<td>S, E</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>I</td>
<td>S, E</td>
</tr>
<tr>
<td>ECG evidence of new MI</td>
<td>I</td>
<td>E</td>
</tr>
<tr>
<td>Coronary bypass surgery/angioplasty</td>
<td>I</td>
<td>S, E*</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</td>
</tr>
<tr>
<td>Angina</td>
<td>I</td>
<td>E</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>I</td>
<td>E</td>
</tr>
<tr>
<td>Cardiac catheterization, positive</td>
<td>P</td>
<td>S, E*</td>
</tr>
<tr>
<td>Positive treadmill test</td>
<td>P</td>
<td>S, E*</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (LVH)</td>
<td>P</td>
<td>E</td>
</tr>
<tr>
<td>Global evaluation of LV function</td>
<td>P</td>
<td>E</td>
</tr>
<tr>
<td>Cardiac wall motion abnormalities</td>
<td>P</td>
<td>E</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
<td>P</td>
<td>E</td>
</tr>
<tr>
<td>(Ratio FEV1/FVC or FEV1/SVC)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I = Incidence         P = Prevalence
S = Surveillance contact     E = Examination, Phase II
E* = 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.
4. Procedures for Training & Quality Control 
of Mortality & Morbidity Surveillance

4.1 TRAINING

Interviewers and data abstractors will be centrally trained at the July 1993 training meeting in South Dakota. Training will include instructions in reviewing and abstracting of charts and instructions in transcribing of information on death certificates and medical examiner reports. Training will include:

1. Adherence to the standardized protocol
2. Techniques for locating information in the charts
3. Dealing with problems encountered in the charts
4. Post-abstraction responsibility for the data

The training sessions will consist of:

1. Explanation of the procedure for abstracting
2. Demonstration by the instructor of abstraction procedures
3. Performance of abstraction by the trainee with instructor observing
4. Abstraction of records by both the trainee and the instructor with verification for completeness, consistency and accuracy

4.2 QUALITY CONTROL

4.2.1 Ascertainment of Cause of Death

In the mortality study, duplicated records will be sent to the Mortality Review Committee by each center. Each reviewer will independently make a judgement as to the cause of death and fill out Decision Form I or II. The Coordinating Center will then compare the results from both physicians. In addition, if a decision on a death is equivocal, the records will be sent to a third reviewer. The mortality review committee will arrive at a joint decision for all cases of non-concordance.

4.2.2 Data Abstraction

To assure consistency and accuracy in the chart abstractions and death certificate and medical examiner reports, a chart for morbidity, a chart for mortality, a death certificate and a medical examiner report will be circulated by the Coordinating Center to each center quarterly with personal identifiers deleted. All data abstract personnel will complete the necessary forms related to that circulated material and they will be judged at a central source for consistency and completeness.
REFERENCES


