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

Available data indicate that cardiovascular disease has become the leading cause of death in American Indians (2, 3, 4). Some Indian groups appear to be participating in the decline in CVD rates occurring within the overall U.S. population, but, among other Indians, rates appear to be increasing. In addition, when compared to data from other components of the U.S. population, there appears to be excessive mortality attributed to CVD in younger Indians.

Several problems have made it difficult to obtain adequate data on the prevalence and severity of CVD as a health problem among American Indians. The small size, relatively young age, cultural and anthropological diversity and the geographic dispersion of the American Indian population have made it impractical to include large numbers of subjects in research examinations and surveys of vital statistics. Excess mortality among younger Indians from noncardiovascular causes may have obscured the true risk of CVD in this population (5). Definitions of the term "Indian" are variable in published reports. 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 varied in different studies. In addition, health care services available to Indians vary considerably in different geographic areas, and possibly contribute to differences in reported CVD morbidity and mortality.

States with the largest Indian populations are Arizona, Oklahoma, California, New Mexico and North Carolina. Because the major concentrations of Indian tribal groups in the U.S. are located in the Southwest, more than half of the reported studies of CVD and CVD risk factors have been conducted in these groups. Studies have been reported in the Pima, Papago, Navajo, Apache, Hopi and other tribes in the Arizona-New Mexico region (6-19). In general, these studies have concluded that CVD rates are lower in these Indian groups than in the U.S. population.

Additional reports describe small and often incomplete surveys from Minnesota, Montana, Wyoming, Oklahoma, Florida and New York (20-23) and among Alaskan Natives (24). In general, CVD rates among Indians living in the North Central states appear to be substantially higher than rates found in the Southwest (25).
Although these rates are based upon small numbers, and thus, subject to fluctuation, some reports indicate CVD rates in this area may exceed those found in the U.S. White population (3). Despite the limitations and potential sources of error, available evidence suggests that there are major differences in CVD rates among Indian tribes from different geographic areas and between the majority of Indians and the general U.S. population.

The etiology, manifestations and natural history of CVD among Indians is not well known. Current information indicates 43 per cent of heart disease deaths among Native Americans are secondary to myocardial infarction and 32 per cent are due to chronic ischemic heart disease (26). Below the age of 35 years, the heart disease rate in Native Americans exceeded reported U.S. rates. A significant portion of this excess may be due to congenital heart disease (1).

Data on temporal trends in CVD prevalence and incidence in American Indians are limited. Sievers and Fisher have suggested that CVD rates may be increasing in some Southwestern tribal groups (27). Although coronary heart disease rates are still low among the Navajos, the largest U.S. tribal group and one in which traditional lifestyles have been maintained, these rates also appear to be increasing (18).

Several possible explanations exist for differences in apparent CVD rates and for potential differences in CVD risk factor distributions among U.S. Indians. American Indians have undergone rapid cultural changes during this century with many changes taking place during the last 40 to 50 years. Prior to 1940, over 90 per cent of Indians lived on reservations set aside by the Federal Government and, in many cases, constituted a “country within a country” with customs, diets and living conditions that differed dramatically from those of the surrounding white population (28). By the 1980 census, however, almost two thirds of the 1.4 million persons identifying themselves as Indian lived off reservations, tribal trust lands or other Indian lands. Over 50 per cent lived in metropolitan areas and 10 per cent reported living on or near reservations that were in or contiguous to metropolitan areas. Poverty remains widespread and the low socioeconomic status of the majority of Indians contributes to the patterns of disease seen in this subgroup of our population. Currently, the amount of cultural and genetic admixture of American Indians with the remaining U.S. population varies substantially and corresponds generally to the geographic location of tribal groups. Far more integration has taken place in the North Central states than in the Southwest (3). These changes may account for part of the apparent tribal (and geographic) variation in reported CVD rates. Sievers and Fisher believe that the lower CVD rates found in Indians may be explained by their higher degree of Indian blood and lower levels of acculturation compared to Indians living in other geographic areas (6). Changes in lifestyle associated with this acculturation would be expected to produce increases in cholesterol levels, lower ratios of high density lipoprotein cholesterol to low density lipoprotein cholesterol, increased frequency of cigarette smoking, decreases in physical activity and an increased frequency of diabetes, hypertension, and obesity. If the preliminary data of Sievers and Fisher are correct, rates of ischemic cardiovascular disease among American Indians may increase substantially in future decades.

A frequently overlooked but potentially important distinction is the heterogeneity of the American Indian population. Tribal groups now living within U.S. borders originated from several distinct migrations from Asia into North America over a 40,000 year period. Distinct subgroups of Indians of different origin can be identified.
both by linguistic analyses and by determination of genetic markers (29). Some Southwestern tribes are thought to have originated from early migrations and to have returned to the U.S. after initially migrating to Central America while other tribes now residing in the Northern United States are thought to be descendant from larger migrations which entered the U.S. from the North. The potential may still exist for comparing Indians of similar origin who have major differences in acculturation.

Limited data are available on current levels and time related changes in risk factors for ischemic cardiovascular disease among American Indians. Because of the absence of systematic surveys of defined populations and the lack of standardization of methodology employed in studies of different groups, it is difficult to interpret apparent increases in risk factors over time or to explain apparent differences in CVD rates by differences in risk factor distributions. Studies of current risk factor levels and distributions are of great importance, however, since they may provide the best estimates of the future relative risk of CVD within the Indian population.

Multiple factors may contribute to current risk factor levels in American Indians. Variations may exist among tribal groups, secondary to genetic admixture and to both the degree and duration of acculturation and in relation to attained socioeconomic status. It is important to recognize that generalizations about risk factors for CVD in American Indians are inappropriate and that available data only apply to groups with similar origins and history. Risk factor information now available is summarized below.

Rates of hypertension among Indians appear similar to rates observed in the U.S. white population (1,15,16,20,21,28,30,34,36). Rates may be increased in association with obesity and alcohol use (1).

Cholesterol levels among Indians are generally lower than those for U.S. Whites and generally lowest in Southwestern Indians (10,30,33). Limited studies of lipoprotein levels have indicated that Pima Indians have favorable HDL to LDL cholesterol ratios compared to levels observed in whites.

Excessive alcohol consumption is a well documented problem of the American Indians, particularly among males (13,34). Excessive alcohol consumption appears to increase rates of hypertension in Indians as has been shown in other populations.

Smoking prevalence rates vary greatly by tribal group and by region of county (35). In the Southwest, heavy cigarette smoking is rare although many Indians reported occasional smoking (13,36). Smoking habits of Indians in other locations were similar to those of the general population but are higher than U.S. rates in some North Central groups (25,30). These marked differences in smoking likely contribute to the differences in cardiovascular disease.

The prevalence of impaired glucose tolerance and diabetes is increased compared to both U.S. whites: and blacks among the majority of U.S. Indian tribes who have been surveyed except for those residing in Alaska (37,38). Diabetes appears to be almost exclusively of the Type II variety among full blooded Indians (39). Diabetes among Indians is highly associated with obesity and generally has an earlier age of onset than Type II diabetes seen in other populations (39). Diabetes is a risk factor for ischemic heart disease in Pima Indians, although observed rates in both diabetic and nondiabetic Pima remained lower than would be expected in comparable groups of U.S. whites (36).
In summary, studies to date indicate that rates of CVD in American Indians appear to vary up to fourfold by tribe and area of residence (3). Although studies are limited, conventional CVD risk factors appear to have expected associations with occurrence of CVD in Indians. Very limited studies suggest that rates of CVD are increasing, at least among some Indian groups.

1.2 RESEARCH OBJECTIVES

The objective of the Strong Heart Study is to employ standardized methodology to obtain estimates of CVD mortality and morbidity rates 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.

1.3 STUDY DESIGN

The study has three components: (1) a mortality survey to estimate the CVD mortality rate, (2) a morbidity survey to estimate the incidence rates of selected CVD, and (3) a clinical examination including personal interview and physical examination to estimate the prevalence of CVD and of CVD risk factors.

The study population includes members of the following tribes:

(1) The Pima/Maricopa Indians of central Arizona who live in the Gila River Indian Community (GRIC) and the Salt River Indian Community (SRIC).

(2) The Seven Tribes of southwestern Oklahoma: Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa and Wichita. These tribes live primarily in the southwestern Oklahoma including the following counties: Caddo, Comanche, Kiowa, Cotton, Tillman, Stephens, Washita, Jefferson, Grady, Custer, Blaine, Murray, Carter, Love, Garvin, McClain, Cleveland, Oklahoma, Canadian, Jackson, Beckham, Greer, and Harmon. The two major cities with IHS facilities in the area are Lawton and Anadarko.

(3) The Oglala Sioux Tribe (Pine Ridge), and the Cheyenne River Sioux Tribe (Eagle Butte) of South Dakota and the Devil’s Lake Sioux Tribe (Ft. Totten) of North Dakota. The following communities surrounding Pine Ridge: Wanblee (includes Hisle, Interior, Kadoka), Kyle (includes American Horse Creek), Allen (includes Batesland), Manderson (includes Grass Creek and Wounded Knee), and Porcupine (includes Rockyford) and the following five communities on the Cheyenne River Sioux Reservation: Cherry Creek (includes Bridger), Red Scaffold, White Horse (includes Moreau River and Promise), Swift Bird (includes Four Bear, Laplant and Marksville), and Eagle Butte (includes Bear Creek and Green Grass) will be included in the study. The other community included is the Ft. Totten area where the Devil’s Lake Sioux Tribe of North Dakota live (see Appendix 4).
Residents who have lived in one of the study communities for at least 6 months prior to the CVD event or the physical examination will be eligible.

For the mortality surveys, resident tribal members who were 35-74 years old at the time of their death during the period from January 1, 1984 to December 31, 1988 constitute the study population for Arizona and Oklahoma. In the Dakotas, all the deaths occurring in residents of Wanblee, Porcupine, Allen, Kyle, Manderson, Swift Bird, Red Scaffold, White Horse, Cherry Creek, and the entire Devil's Lake Sioux Reservation will be included. A 50% random sample of the eligible persons from the Eagle Butte Community (living and dead) will be taken and the deaths in this random sample will be included in the mortality survey. This sampling methodology corresponds to the methodology used for the morbidity survey and for the clinical examination. For the morbidity survey, resident tribal members who were aged 45-74 years during the period from January 1, 1984 to December 31, 1988 constitute the study population. For the third component (clinical examination), tribal members who are local residents and between 45 and 74 years of age at the time of the examination will be invited to participate. Persons who are institutionalized will be excluded. Each study area is expected to recruit approximately 1500 subjects for the third component. In Arizona and Oklahoma, all persons who satisfy the above criteria will be invited. However, in the Dakotas only a representative sample will be invited due to limited resources and the large number of eligible persons. In the five communities of the Pine Ridge area, all eligible persons will be invited. Approximately 900 participants are expected. All of the eligible Cheyenne River Sioux in Cherry Creek, Red Scaffold, White Horse and Swift Bird and a 50% random sample of the eligible persons in the main community of Eagle Butte will be invited. A total of 400 persons are expected to participate in the study. Another 200 participants are expected to come from the Ft. Totten area, which will be a 100% sample. If insufficient participants are obtained, the size of the sample at Eagle Butte will be increased to provide at least 1500 participants in total.

In the calculation of the Center mortality and morbidity rates the total number of eligible persons will be estimated by using the December 31, 1988 tribal rolls taking into account the deaths occurring during 1984-1988 as confirmed by study center staff in consultation with the tribes. Every Center will compile a list of eligible persons. Steps for calculation of the denominator for mortality and morbidity rates are:

2. Confirm residence using IHS records and consultation with tribe.
3. Calculate person years for 35-74 years old (mortality survey) and 45-74 years old (morbidity survey) for each year from 1984-1988.
4. Include person years for all deaths.
5. Assume immigration equals emigration.
6. For denominator for morbidity incidence rates (for myocardial infarction and stroke) follow steps 1-5 for 45-74 years old and correct for prevalence of disease.
7. For prevalence rates, the denominator will be all those tribal members 45-74 years old who attend the clinical examination. Exclude individuals who are institutionalized for all of the examination period.
1.3.1 The Mortality Survey

For the mortality survey of the study all deaths occurring among eligible members aged 35 and 74 years in the three study areas between 1/1/84 and 12/31/88 will first be identified through tribal records and other sources. Death certificates will be obtained and coded by a central nosologist. All death certificates with any mention of CVD will be further reviewed and the cause of death confirmed independently. The confirmed CVD deaths will be used to calculate CVD mortality rates.

1.3.2 The Morbidity Survey

Possible cases of CVD will be identified in the three study areas through the review of hospital records. Persons eligible will be tribal members aged 45-74 years at any time during 1/1/84-12/31/88 who were discharged from the hospital with a diagnosis of CVD between 1/1/84-12/31/88. Relevant information from the medical record will be abstracted to allow independent confirmation of the diagnosis of an incident or recurrent case. CVD events to be ascertained include the following:

1. Acute myocardial infarction (ICD9 410)
2. Stroke (ICD9 431,432,434,436)

Incident rates, incidence density, as well as total incidence (40) will be estimated.

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 tribal members aged 45-74 at the time of the examination. Those eligible to participate will be contacted by the staff at each study center.

1. Personal Interview

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

(a) Demographic data: age, sex, quantum of Indian blood and quantum of Indian blood of subject’s parents and grandparents.
(b) Education
(c) Family history of CVD
(d) Tobacco use and alcohol consumption
(e) Traditional values/culture
(f) Socioeconomic/stress evaluation
(g) Physical activity
(h) Medical history, particularly CVD history
(i) Diet - This will be done on a random sample if extra support is found.
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 heart and lungs
(h) Palpation of posterior tibial and pedal pulses
(i) Auscultation of femoral and carotid bruits

3. Laboratory measurements:

(a) Lipids: TC, TG, HDL-C, LDL-C, VLDL-C and VLDL-TG
(b) Apolipoproteins: ApoB, ApoA-I, Lp(a), Apo E phenotype
(c) Fasting insulin
(d) Plasma creatinine
(e) Fasting glucose and 2-hour glucose tolerance test (GTT)
(f) Urinary albumin and creatinine
(g) Fibrinogen
(h) Glycated hemoglobin (HbA1c)
(i) DNA extraction and storage

1.4 STUDY QUESTIONS

1.4.1 Mortality Survey

1. What are the CVD mortality rates (average annual rates for 1984-1988) 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 (four 10-year age group)
(2) Sex-specific
(3) Age and sex-specific (8 groups)
(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 Survey

1. Incidence Rates

(a) What are the CVD incidence rates (average annual rates for 1984-1988) in the three centers, and how do they compare to one another?

(1) Incidence rates and total incidence will be estimated for hospitalized acute myocardial infarction, and stroke.
(2) Estimated incidence rates will include the following:

(i) Age-specific (three 10-year age group)
(ii) Sex-specific
(iii) Age and sex-specific (6 groups)
(iv) Age-sex adjusted to U.S. population

(b) How do these rates compare to published rates of other population (e.g., Framingham, Minnesota Heart Study, etc.)?

1.4.3 Clinical Examination

1. Prevalence Rates by Examination

(a) What are the prevalence rates of CVD and related diseases in the three centers, and how do they compare to one another?

(1) Prevalence rates will be estimated for angina, ischemic heart disease with a history of myocardial infarction, cerebrovascular disease with a history of stroke, congestive heart failure, diabetes, impaired glucose tolerance, ECG abnormalities, large vessel peripheral arterial disease, and hypertension.

(2) Estimated prevalence rates will include the following:

(i) Age specific (three 10 year age groups)
(ii) Sex specific
(iii) Age and sex-specific (6 groups)
(iv) By degree of Indian blood (e.g. $\leq \frac{1}{4}$, $\frac{1}{4}$-$\frac{1}{2}$, $\frac{1}{2}$-$\frac{3}{4}$, $>\frac{3}{4}$)
(v) Age-sex adjusted to U.S. population

(b) How do these rates compare to those from other studies?
2. Risk Factor Analysis

(a) What are the prevalence rates or distributions of the following risk factors in each of the three centers, and how do they compare to one another?
   1. Hypertension
   2. Tobacco use
   3. Lipids (TC, TG, LDL-C, VLDL-C, VLDL-TG, HDL-C)
   4. Obesity (% body fat)
   5. Diabetes, impaired glucose tolerance (IGT)
   6. Concentrations of insulin, HbA1c, glucose
   8. Fibrinogen
   9. Alcohol consumption
  10. Physical Activity
  11. Diet
  12. Degree of Indian blood
  13. Family history of CVD
  14. Acculturation
  15. Education/Socioeconomic status
  16. Intake of dietary fat, cholesterol, animal protein, fiber and total calories

(b) What individual risk factors and/or combinations of risk factors are associated with CVD prevalence? What is the degree of association?

(c) What are the most important risk factors associated with CVD prevalence in each of the three centers, and how do the centers differ from one another?

(d) Can the data for mortality, morbidity and risk factors be combined and analyzed collectively?

(e) What are the relationships among risk factors in each centers and how do they compare among the centers?

1.5 STUDY MANAGEMENT

1.5.1 Introduction

The Strong Heart Study 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 Steering Committee, which includes members from each center and the NHLBI Project Manager. An organizational chart of the Strong Heart Study 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. 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, 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 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 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.
In the interest of standardization of the data management process, the following guidelines are recommended:

a. All data collected by the three Study Centers will be entered, managed and analyzed by the Coordinating Center.

b. All file restorations will be performed on IBM personal computers or on IBM compatible computers.

c. Removable diskette drive A: of the computer will be of the 3.5 inch hard cased 1.44 megabyte format type.

d. The operating system for the computer will be DOS 3.3 or any operating system that reliably emulates DOS 3.3.

e. The set of DOS programs will be located on the C: hard disk drive in the directory C:\DOS; directory C:\DOS will be included in the DOS path list.

f. Each Study Center will license SAS software for the personal computer that minimally will include the SAS/BASE programs.

g. SAS software will be located on the C: hard disk in directory C:\SAS and will be installed as recommended by SAS Institute.

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). The ID number is a six digit number: the first digit is the center code (1 = the Dakota Study Center, 2 = the Oklahoma Study Center, and 3 = the Arizona Study Center), the second digit indicates the vital status of the subject (1 = dead and 0 = alive), and the last 4 digits are for the local identification number. For convenience, for subjects in the mortality study (deaths) the last four digits will start from 0001, and those in the morbidity study (living participants) will have numbers beginning with 2001. For example, 110001 will be the ID number of the first death identified at the Dakota Study Center and 302001 the ID number of the first living participant at the Arizona Study Center. The ID number will be stamped on every page of all forms at each center. For laboratory specimens, Computype brand labels will be used. Page 12a gives examples of how to assign ID numbers.

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. 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 out 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: \[ \underline{A} . \underline{D} . \underline{H} \underline{A} \underline{R} \underline{J} \underline{O} \]

If the address is a post office box or rural route, record in the field for “street number”, as

\[
\begin{array}{c}
\text{P O BOX} \\
\text{or} \\
\text{ROUTE} \\
\end{array}
\]

205

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

Example:
Triglyceride: \[ \underline{2} \underline{0} \underline{5} \]

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: \[ \underline{0} \underline{5} \underline{0} \underline{8} \underline{2} \underline{9} \]
mo day 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: \[ \underline{7} \underline{8} \]
ASSIGNMENT OF ID NUMBERS FOR STRONG HEART STUDY

This is a procedure for assigning numbers to Strong Heart Study participants and for individuals who are morbid, or mortal cases but do not participate in the study. Examples given below are using Darkotas participants.

1. Participants in the physical examination will be assigned as they have been in the past with the following sequences:

   102000 - 102999: Pine Ridge
   103000 - 103499: Eagle Butte
   103500 - 103699: Fort Totten

   The same number will be used for the morbidity forms if the participant was hospitalized for cardiovascular disease. Using the same identification number, a separate morbidity form must be completed for each hospitalization with ICD-9 discharge diagnoses 402, 410-414, 427, 428, 518.4, or 430-458.

2. Deceased tribal members who died between 1984 and 1988 will be assigned the following numbers for the mortality surveillance.

   110000 - 110999: Pine Ridge
   111000 - 111499: Eagle Butte
   111500 - 111700: Fort Totten

   If a deceased person had previously been hospitalized and has discharge codes as noted above (see #1), the last four digits will remain the same but the second digit will be changed from 1 to 5 when filling out the morbidity forms. A separate morbidity form must be completed for each hospitalization using the same identification number. For example,

   if 111047 had CVD event, then the ID for the morbidity for would be 151047.

3. Individuals who are alive, December 31, 1988 but who refuse to participate or who are not eligible to participate, and have morbid events will be assigned numbers as follows:

   106000 - 106999: Pine Ridge
   107000 - 107499: Eagle Butte
   107500 - 107699: Fort Totten

   Non-participant forms should also be assigned numbers according to this sequence when they are completed. If an eligible person decides to participate after being assigned a non-participant number, he/she should be assigned a number according to (#1) above and the data center should be requested to delete the data entered on the non-participant form and to change the number on any other forms. This persons non-participant number can then be reassigned to the next non-participant.

4. These individuals are assigned numbers in this sequence so that the study will be able to keep track of which category they are in. The last four (4) numbers should be unique for each individual in the study.
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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:

Dr. Elisa T. Lee  
Strong Heart Study  
Department of Biostatistics and Epidemiology  
OUHSC -CHB 301  
P.O. BOX 26901  
Oklahoma City, OK 73190

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 Restoration of Coordinating Center Backup Diskettes

After receipt of data forms from a Study Center, the Coordinating Center will forward monthly to that Study Center diskettes which contain backup copies of the databases. The first diskette (in case of multiple diskettes) will be labelled with the command line that must be typed at the DOS prompt in order to RESTORE the databases at the Study Center. A typical example of such a command line is given by the following:

```
C:\DOS\RESTORE A: C:\AZ89JUL\*.* /S
```

In this example, the data of the Arizona (AZ) Study Center for the year 1989 (89) and the month July (JUL) is to be restored from the Coordinating Center backup. The first diskette would be placed into the A: drive and the command given on the diskette label (above) would be typed and the ENTER key pressed.

1.6.4 Statistical Analysis

(1) Mortality rate (or mortality density)

Mortality events can be grouped into three classes: (1) death due to CVD, i.e., CVD is the immediate cause of death, (2) death due to causes other than CVD in patients with CVD, i.e., CVD is the underlying or contributing cause of death, and (3) death due to causes other than CVD in patients without CVD, i.e. CVD is not mentioned on the death certificate. Classes (1) and (2) are of interest to this study. Let D represent the number of these events occurring between 1984 and 1988. To determine the CVD mortality rate, the total number of deaths will be the numerator and the total population-time (or person-year) contributed by all eligible participants (living and dead) the denominator. Thus, the estimated mortality rate due to CVD for 1984-88 is

$$\text{MR}_{(1984-88)} = \frac{D}{PT}$$

where $PT = \sum_{i=1}^{n} \Delta t_i$, $n$ is the total number of eligible persons and $\Delta t_i$ is the follow-up period for the $i$th individual from the time he/she satisfies the age criteria to death (for the deceased) or to December 31, 1988 (for the living participants). Since the December 31, 1988 tribal roll will be used to estimate the total number of eligible persons and information of those who migrated out of the area is unavailable, losses-to-follow-up will be ignored. Eligible members are tribal members who were 35 to 74 years old during 1984-88 (born between January 1, 1910 and December 31, 1953). The December 31, 1988 tribal roll will be used to estimate the number. The $\Delta t_i$ will be computed as follows:

<table>
<thead>
<tr>
<th>Birth Date</th>
<th>$\Delta t_i$ (contribution to PT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/10 to 12/31/10</td>
<td>$\leq 1$ year, from birthdate to death or to 12/31/84</td>
</tr>
</tbody>
</table>
1/1/11 to 12/31/11 ≤ 2 years, from birthdate to death
           or to 12/31/85
1/1/12 to 12/31/12 ≤ 3 years, from birthdate to death
           or to 12/31/86
1/1/13 to 12/31/13 ≤ 4 years, from birthdate to death
           or to 12/31/87
1/1/14 to 12/31/49 ≤ 5 years, from birthdate to death
           or to 12/31/88
1/1/50 to 12/31/50 ≤ 4 years, from birthdate to death
           or to 12/31/88
1/1/51 to 12/31/51 ≤ 3 years, from birthdate to death
           or to 12/31/88
1/1/52 to 12/31/52 ≤ 2 years, from birthdate to death
           or to 12/31/88
1/1/53 to 12/31/53 ≤ 1 year, from birthdate to death
           or to 12/31/88

Age and sex specific CVD mortality rates will be estimated in a similar way.

(2) Incidence rate (or incidence density) and Total incidence

Average five-year incidence rates of acute myocardial infarction and stroke
will be estimated in a manner analogous to the mortality rate:

\[ IR(1984-88) = \frac{I}{PT} \]

where I is the number of new cases that occurred during the calendar period
1984-88, PT is the amount of population-time (person-year) accrued

by the eligible CVD free study population, \( PT = \sum_{i=1}^{n} \Delta t_i \). The eligible
population consists of tribal members who reside in Study Communities and
who were between 45 and 74 years old (born between January 1, 1910 and
December 31, 1943). The December 31, 1988 tribal roll plus the deaths
occurring during 1984-88 minus the number of prevalent cases will be used to
estimate the number. In the Dakotas random sampling is used to determine
the eligible population in the town of Eagle Butte and the Ft. Totten service
unit as described in the mortality study design. The number of prevalent
cases will be obtained from the clinical examination and medical record
review. The individual contribution (\( \Delta t_i \)) to the calculation of PT is similar
to that in the estimation of mortality rates.

Since myocardial infarction and stroke may occur more than once within an
individual, the total incidence will also be estimated. Let T be the total
number of new and recurrent events (MI or stroke) that occurred during the
calendar period 1984-88 and TPT be the total amount of population-time
(person-year) accrued by the eligible study population, the total incidence is
estimated as follows:

\[ 1/1/1989 \quad 1/1/1991 \]
\[ 12/31/74 \quad 12/31/79 \quad t_i \quad 12/31/1996 \]
\[ 12/31/1975 \quad 1/1/1994 \]
\[ T_{I(1984-88)} = \frac{T}{TPT}. \]

The calculation of TPT is slightly different from PT:

\[ TPT = \sum_{i=1}^{n} T_i \]

where \( n \) is the total number of eligible persons and \( T_i \) is the total follow-up time of the \( i \)-th person, from the time he/she is eligible for the Study to death or December 31, 1988.

(3) Prevalence rate

Cases identified in the examination from persons between 45 and 74 years of age will allow us to estimate the point prevalence rate. The point estimate is calculated by:

\[ P_t = \frac{C_t}{N_t} \]

where \( C_t \) is the number of CVD cases found and \( N_t \) the size of the sample or study population, at time \( t \). A function of the point prevalence, namely, the prevalence odds (probability of being a case divided by the probability of not being a case at time \( t \)) can also be calculated. In addition, age, sex and exposure-specific prevalence rates will be obtained.

Since this is a cross-sectional study, the following prevalence ratio can be used to compare CVD prevalence between centers and between subgroups (or exposure groups in a broad sense, such as smokers and nonsmokers)

\[ PR_i = \frac{P_i}{P_0} \]

where \( P_i \) and \( P_0 \) are the estimated prevalence rates, respectively, for the center (or exposure group) and the reference center (or reference exposure group) (40).

(4) Risk Factor Assessment

Risk factors for each subtype of CVD in each center will be identified and compared with those identified in other centers. Both univariate and multivariate methods will be employed to examine associations between potential risk factors and morbidity endpoints. Cardiovascular disease rates will be estimated for the “exposed” and “unexposed” groups and tested for equality by chi-square methods. Odds ratios (OR) and 95% confidence intervals will also be obtained. For continuous variables, such as cholesterol concentration, the t-test will be used to compare means between the CVD cases and non-CVD persons within each center and for all centers. If the distribution of a variable is skewed, a logarithmic transformation will be considered or a nonparametric test (e.g. the Mann-Whitney U test) may be used.
If the number of non-responders is large, we will examine the characteristics of the nonresponder obtained from chart. Nonparticipation fractions for each of the four exposure-disease cells can then be estimated and the OR corrected according to methods described by Kleinbaum et al (41). Nonresponse bias will also be estimated.

In evaluating a possible risk factor, one must consider potential confounding variables. For example, in assessing the association of blood pressure and coronary heart disease, one must consider the extraneous effect of age. One method to control for confounding factors is stratified analysis. Decisions needed to be made include the determination of the variables to be used to stratify and the selection of ways to form strata. The Mantel-Haenszel Method (42) will be used to estimate summary odds ratios and to test for significant association.

Another method to be used for control of confounding variables is multivariate mathematical modeling. This method will enable us to control for several confounding variables simultaneously, to estimate overall effect and to test for overall association. The most commonly used model is the linear logistic regression (40,43). Odds ratios and confidence intervals will be estimated from this model for the various exposure factors and each subtype of CVD.

Significant risk factors identified from the above methods for each center will then be compared. Factors which appear to act across the centers and those which appear to act only in a specific population will be identified.

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) 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 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 and IHS will next be initiated. Each center will be responsible for obtaining local IHS approval. The Dakotas Center, on behalf of the three centers, will also submit the manuscript to IHS headquarters for approval for the Study.
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.

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. Manuscripts resulting from ancillary studies will require approval by the Steering Committee and by NHLBI 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 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.