A Primer on Research

with the STRONG HEART STUDY as an Example
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Research Terms

Baseline Assessment – Assessment of a participant at the beginning of a study. In the STRONG HEART STUDY (SHS), this was Phase I, which was conducted from 1989-1991 and for the STRONG HEART FAMILY STUDY (SHFS) from 2001-2003 (except for approximately 900 examined between 1997 and 1998 in the family pilot study as part of SHS Phase III).

Code of Federal Regulations (CFR) – (US) a comprehensive set of regulatory requirements set forth by the Food and Drug Administration (FDA).

Common Rule – 1991 agreement to cover all federal sponsored research by a common set of regulations.

Confidence Interval – In general, a measure of confidence that an estimate and/or outcome are within a certain range.

Confidentiality - Prevention of disclosure, to other than authorized individuals, of a sponsor’s proprietary information or of a subject’s identity and medical information.

Contract – A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Data Management – The process of handling the data gathered during a study. This may also refer to the department responsible for managing data entry and database generation and/or maintenance. In the STRONG HEART STUDY, data management is done by the Coordinating Center at the University of Oklahoma.

Declaration of Helsinki – A series of guidelines adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964. The Declaration addressed ethical issues for physicians conducting biomedical research involving human participants. Recommendations include the procedures required to ensure subject safety in clinical trials, including informed consent and Institutional Review Board reviews.
Demographic Data – Refers to the characteristics of study participants, including gender, age, family medical history, and other characteristics relevant to the study in which they are enrolled.

Documentation – All forms of records that describe or document study methods, conduct and results, including any adverse events and actions taken.

Exclusion Criteria – Exclusion criteria refer to characteristics identified in the study protocol, which would prevent a participant from being enrolled in the study. In the STRONG HEART FAMILY STUDY, participants were excluded if they were not in the first phase of SHS or were not family members of those in the first phase and were not 18 years of age or older if recruited for the pilot phase or 15 years of age or older in Phase IV of SHS. In the current phase of SHS (Phase V), participants are excluded if they have not been enrolled in the earlier exams (pilot or Phase IV) of the STRONG HEART FAMILY STUDY.

Good Clinical Practice (GCP) – A Standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of studies that provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of study participants are protected.

Human Subjects – A patient or healthy individual participating in a research study. A living individual about whom an investigator obtains private information or data through intervention or interaction.

Inclusion Criteria – Characteristics, identified in the study protocol, which a subject must have in order to be enrolled in the study.

IEC/IRB approval – A written approval of a human research study protocol, informed consent form, advertisements for a clinical study, and any material to be distributed to subjects.

Informed Consent – A process by which a participant voluntarily confirms his or her willingness to be in a particular study after having been informed of all aspects of the study that are relevant to the participant’s decision to be in the study. Informed consent is documented by means of a written, signed and dated Informed Consent Form.
Informed Consent Form – The legal written record that the subject, or his/her representative, agrees to voluntarily participate in the investigation. Also referred to as “consent form” or “participant consent form.”

Institution – Location of research. The institution has the ultimate responsibility for human participant regulation compliance. There are five institutions participating in the STRONG HEART STUDY. They are MedStar Research Institute in Phoenix, AZ and Hyattsville, MD, University of Oklahoma in Lawton, Anadarko, and Oklahoma City, OK, Missouri Breaks Industries Research, Inc. in Eagle Butte and Pine Ridge, SD and Fort Totten, ND, Weill Medical College of Cornell University in New York, NY, and Southwest Foundation for Biomedical Research in San Antonio, TX.

Institutional Review Board (IRB) – An independent committee, which reviews and approves human research protocols, informed consent forms, study advertisements, and printed participant materials, to ensure that the rights and welfare of human subjects are protected. The board consists of at least five individuals, professionally competent in terms of knowledge and appreciation of an institution’s commitments and regulations, applicable law, and standards of ethical conduct and professional practice. At least one member must have a primary interest in a non-scientific area. In the STRONG HEART STUDY, the IRBs for the study are found in the 5 institutions named above in Institution plus the IRBs in the IHS area offices for each of the three geographic areas of SHS. Parenthetically, each of the 13 Tribes participating in SHS reviews and approves the study protocol, substudy proposals, manuscripts, etc.

Mean Value – The sum of the values of several observations or data points divided by the number of observations; an arithmetic average. For example the mean of 5, 6, 10 is 7 (5 + 6 + 10 = 21, 21 divided by 3 is 7).

Median – The middle value in a set of observations or data points; that is, just as many values are greater than the median as are less than the median. For example, the median of 10, 8, 5, 2, 15 is 8 (2 values are less than 8 and 2 values are greater than 8).

Observational Study Monitoring Board (OSMB) – Researchers, usually independent of the study they monitor, who periodically review data and progress of the monitored study. The OSMB for the STRONG HEART STUDY meets once a year to hear about the study, to give their comments and suggestions to the investigators and the funding agency (i.e., the National Heart, Lung, and Blood
Institute (NHLBI) for SHS), and to make a recommendation to NHLBI regarding whether funding for the study should be continued.

**Primary Investigator (PI) –** See Principal Investigator. May also refer to the lead investigator in a multi-center study.

**Principal Investigator (PI) –** The person(s) responsible for all aspects of the conduct of the study at each site. The STRONG HEART STUDY principal investigators are Dr. Barbara Howard at MedStar Research Institute, Dr. Elisa Lee at University of Oklahoma, Dr. Lyle Best at Missouri Breaks Industries Research, Inc., Drs. Richard Devereux and Mary Roman at Weill Medical College of Cornell University, and Drs. Shelley Cole and Jean MacCluer (Co-PIs) at Southwest Foundation for Biomedical Research

**Protocol** – A formal written document, which states the rationale, objectives, and statistical design/methodology of the study, with the conditions under which it is to be performed and managed. Also called “study protocol”.

**Protocol Amendment** – (1) A formal written document detailing changes to a protocol that has been approved by the relevant regulatory authorities. (2) Also refers to the addition of a study protocol not submitted in an original Investigational New Drug (IND) application.

**Publications** – Journal articles, books, or book chapters as well as abstracts, posters, and presentations at scientific and professional meetings. The publications for the STRONG HEART STUDY are posted on the web site (http://strongheart.ouhsc.edu/).

**Recruitment** – (1) Investigator: The process used by the sponsor to select investigators for a clinical study. (2) Participants: The process of identifying and screening potential participants for enrollment in a research study or clinical trial.

**Recruitment Period** – The time period during which participants can be entered into a research study. The recruitment period for the current phase of the STRONG HEART STUDY is May 2006 through June 2009.

**Recruitment Plan** – A summary of the steps to be taken to ensure recruitment of adequate numbers of participants within the target time frame. This might include, for example, pre-study chart review to identify potential participants, various kinds of advertisements after approval by the Institutional Review Board (IRB), or other permissible techniques to optimize recruitment.
**Recruitment Strategy** – A statement routinely included in the research plan which addresses the anticipated ease or difficulty in recruiting participants for a protocol, and the strategy to be adopted if recruitment targets are not being met.

**Recruitment Target** – The minimum number of participants who must be recruited to provide the number of evaluable subjects required for statistical significance after dropout loss. In the first phase of the STRONG HEART STUDY, the recruitment target was 4500. For the STRONG HEART FAMILY STUDY, the target was 3600.

**Reference Ranges** – Laboratory test values typical of specific subject populations used for comparison and evaluation of actual test results.

**Research** – Systematic investigation designed to develop or contribute to general knowledge. Includes Clinical and Non-Clinical Human Research, Laboratory, and Animal Research.

**Research Team** – Investigator, sub-investigator, and coordinator involved with the research study.

**Sponsor** – An individual, company, institution, or other organization, which takes responsibility for the initiation, management, and/or financing of a research study or clinical trial, but which does not actually conduct the investigation. The sponsor of the STRONG HEART STUDY is the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

**Study Coordinator** – Person who handles most of the administrative responsibilities of a clinical or other human research study; who may act as a liaison between the investigative site and the sponsor(s); and who reviews all data and records in a clinical study before visits of a study monitor.

**Study Design** – An outline of the plan for answering the question(s) posed by the study.

**Sub-investigator** – Helps design and conduct the investigation at a study site.

**Total Grant Budget** – The amount spent to conduct the entire study.

**Variance** – Statistical term referring to how widely the values in a set of observations differ from the mean.
Overview of the STRONG HEART STUDY

The STRONG HEART STUDY and the STRONG HEART FAMILY STUDY are studies of cardiovascular disease (CVD: heart attacks, strokes, circulation problems) and its risk factors, and how genes and environment affect heart disease in American Indians from 13 communities in 3 geographic areas. CVD is increasing rapidly in American Indians, and it occurs more often in persons with diabetes. It is related in part to the dramatic changes in diet and lifestyle and in part to genetic determinants. Investigating CVD in American Indians provides information on how to improve treatment and prevention and to guide community health education programs. It also provides an excellent opportunity to identify genetic factors that interact with lifestyle and diet to influence the development of heart disease.

The STRONG HEART STUDY includes five institutions:

<table>
<thead>
<tr>
<th>Institution</th>
<th>Principal Investigator</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedStar Research Institute</td>
<td>Barbara V. Howard, PhD</td>
<td>Performs the field studies in Arizona and houses the Core Laboratory for blood and urine measures.</td>
</tr>
<tr>
<td>University of Oklahoma</td>
<td>Elisa Lee, PhD</td>
<td>Performs study coordination, data management, and the Oklahoma field studies.</td>
</tr>
<tr>
<td>Missouri Breaks Industries Research, Inc.</td>
<td>Lyle Best, MD</td>
<td>Performs the field studies in North and South Dakota.</td>
</tr>
<tr>
<td>Weill Medical College of Cornell University</td>
<td>Richard Devereux, MD, Mary Roman, MD</td>
<td>Oversees and processes all ultrasound (echo, carotid, and popliteal) studies and ECGs.</td>
</tr>
<tr>
<td>Southwest Foundation for Biomedical Research</td>
<td>Shelley Cole, PhD and Jean MacCluer, PhD (Co-PIs)</td>
<td>Advises the field centers regarding recruiting family members, pedigree and sample collection, receives, analyzes, and stores DNA samples, and performs the various genetic analyses.</td>
</tr>
</tbody>
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The goals of the STRONG HEART STUDY are to measure heart disease and risk factors in American Indians and to detect and map genes influencing variation in risk factors for heart disease and related disorders. Now in Phase V (2005-2010), family members are being re-examined as detailed in the sections that follow. These evaluations are being done so that changes in risk factors and heart problems can be analyzed and the effects of genes can be determined.
Recruitment is proceeding as in Phase IV. Meetings have been held with community leaders, and recruiters contact participants from Phase IV to explain why this follow-up exam is needed, what the exam will involve, the reasons for surveillance, the short- and long-term benefits, the consent forms, and the rules of confidentiality. This discussion is followed by a question-and-answer period. Our goal is to have everyone who is now living and was in the Phase III pilot family exam and/or the Phase IV exam participate in the Phase V exam.

Exams are conducted in the SHS offices, the SHS van, churches, community buildings, and other convenient sites throughout the communities. Most clinic personnel are community members who have been trained to schedule exams, provide transportation if needed, administer questionnaires, and do physical measurements. The SHS van that travels to each exam site houses equipment to make the ultrasound measurements.

Participants are asked not to eat or drink anything but water for 12 hours before their clinical exam. The clinical examination lasts approximately 3 hours. If possible, all components are completed during one visit. If an examination is not completed, every effort is made to complete the remaining components within 1 month.

After the clinical exams, the STRONG HEART STUDY staff members contact participants’ health care providers to communicate clinically relevant results and meet individually with participants to discuss their risk profiles and suggest behavioral changes to lower the risk of heart disease.
Follow-up (surveillance) Procedures

For the persons who attended either the Strong Heart or Strong Heart Family Study exams, follow-up data on all participants will be collected. We need to follow them to determine who has developed CVD problems. They are asked about health problems at the time of their examination, and their medical records are reviewed to determine whether they have had certain cardiovascular procedures, conditions, or surgeries since their initial exam. The relevant medical data include procedures (heart catheterization, stent, angioplasty, treadmill test), conditions (heart failure, heart attack, stroke), and surgeries (neck arteries, bypass surgery, valve repair/replacement, pacemaker). Photocopies of information in the participant's medical records related to cardiovascular events are sent to the STRONG HEART STUDY Morbidity and Mortality (M&M) Committee. The committee members review and code the information from all participants in a consistent way so that it can be analyzed.

We use local sources, community notices, and family members to identify participants who have died. Their medical records are reviewed by M&M committee members to determine the cause of death (including causes other than heart disease) and to code the cause(s) for scientific analysis as described above.
**STRAWG HEART STUDY Physical Measures**

**Body Mass Index (BMI)**
In most studies, body mass index (BMI), which takes into account both weight and height, is used as an indicator of overall body fatness. BMI is calculated as the body weight (in kilograms) divided by the height (in meters) squared. In the general US population, high levels of BMI are associated with high blood pressure, high cholesterol levels, diabetes and cardiovascular death.

**Sitting Arm Blood Pressure**
The normal range of blood pressure is wide. As blood pressure rises, so does the risk of heart disease and its complications. Even within the “normal range”, risk increases as the upper limits are approached. High blood pressure is an especially strong risk factor for stroke and, to a lesser extent, for peripheral vascular disease. Usually, blood pressures are expressed as systolic pressure/diastolic pressure. In the STRONG HEART STUDY, arm blood pressure is measured three times while sitting quietly. Within any one individual, variation in blood pressure can be large, even within a few minutes pressure changes can be large, particularly under conditions perceived as stressful. Use of a five-minute rest period and then spacing three readings over a five-minute period tends to reduce the influence of this short-term variation.
**Ankle Brachial Index (ABI)**
The Ankle Brachial Index (ABI) determination is a method for detecting the development of blockages in the arteries to the leg. These blockages are almost always due to atherosclerosis. ABI determination, therefore, is a technique capable of early detection of atherosclerosis. A Doppler instrument, instead of a stethoscope, is used to hear the blood flow. The Doppler probe is placed on the ankle as shown in the picture. The ABI is determined by dividing the ankle blood pressure by the arm blood pressure. When there are blockages in the arteries, a low ABI is found (usually less than 0.8). In individuals without blockages, ankle pressure is about the same or slightly higher than arm pressure (ABI usually 1.0 to 1.3).

**Bioelectrical Impedance Analysis (BIA)**
Bioelectrical Impedance Analysis (BIA) is a method to determine how much body fat a person has. Two electrodes are put on the participant's hand and two on the foot. Cables from the analyzer are connected to the electrodes. The test does not hurt. The analyzer measures the impedance or resistance to a small electrical current as it travels through the water that is found in muscle and fat. The more muscle a person has, the more water their body has. The more water in a person’s body, the easier it is for the current to pass through it. The more fat in a person’s body, the more resistance to the current. The analyzer gives a number for resistance. It is used to calculate the percent of fat in the participant's body.

**Electrocardiogram (ECG)**
Electrical impulses are produced by the heart. They cause the heart to contract which pumps blood through the body. The electrical impulses produce weak electrical currents throughout the body. The currents are picked up by electrodes put on the body in 10 specific places. An electrocardiogram (ECG) gives a picture of the electrical
currents. It is the most widely used screening test for noninvasive detection of problems with the heart.

**Carotid Artery, Heart, and Leg Ultrasound**

Ultrasound imaging, also called ultrasound scanning or sonography, is a method of obtaining images of organs and tissues inside the human body through the use of high-frequency sound waves. The reflected sound wave echoes are recorded and displayed on a monitor as a visual image. In the STRONG HEART STUDY, we scan the carotid (neck) arteries, the heart, and the arteries at the back of the legs. These scans are referred to as carotid ultrasound, echocardiogram and popliteal artery scans respectively. An ultrasound probe similar to the Doppler probe used for ABI measures is moved along the neck, chest, and legs. A moving image shows on a screen, and blockages in the arteries or abnormal heart movements can be seen. The recorded images are sent to the Reading Center at Cornell University for analysis. The participant later receives a letter with the results. With the permission of the participant, a referral to a doctor is made, if the results are abnormal.

Hardenings of the arteries, or atherosclerosis, are terms for the general disease that causes blockages in arteries. Arteries have muscular walls that change shape as the blockages get bigger so that the area carrying blood stays the same. Because of these changes, people do not have symptoms during the early stages of atherosclerosis. The problem may continue to go unnoticed for decades as the risk for heart attacks, strokes and kidney disease grows.

One of the measures from the scan is intima-media thickness (IMT), or thickness of the artery wall. IMT increases with age and also with atherosclerosis. The ultrasound also shows the presence of plaque. Plaque is a build-up of fat, cholesterol, calcium, and other substances in the blood on the inner walls of the artery. The plaque can block the flow of blood. In the neck we look at a total of 8 areas of the arteries (4 on the right and 4 on the left) to see if plaque is present or absent. We also determine how thick the plaque is. Sometimes plaque is present but it is not thick enough to block the flow of blood.

It has been shown that an increased IMT and the presence of plaque in the carotid arteries are associated with an increased risk of heart attacks and strokes. These scans can show abnormalities before a person has symptoms. If there are abnormalities, it is important to stop smoking, eat healthy foods, get regular exercise, and take medications as prescribed by your doctor. This could prevent heart attacks and strokes in the future.
This is an ultrasound picture of a carotid artery. The internal and external carotid arteries (on the right of the picture), merge into the common carotid artery and carry blood to the brain. The arrows are pointing to plaque.

**Pedometer**
Physical Activity is thought to be an important factor in cardiovascular health. The pedometer (see picture, below right) is worn on the waistband of clothing (as shown in the picture, below left) or on a belt. It provides a measure of physical activity by counting the number of steps taken by the participant each day.
STRONG HEART STUDY Laboratory Measures

Blood is drawn and urine is collected from all participants. They are asked not to eat or drink anything except water for 12 hours before blood is drawn. Some of the tests that we run are explained below.

**Blood Fats**
The two most common blood fats are cholesterol and triglycerides. Both are necessary for body function, but excess cholesterol has been shown to cause atherosclerosis (hardening of the arteries) and heart disease. Cholesterol is carried on particles called lipoproteins. **LDL** (low-density lipoprotein) cholesterol is the "bad" cholesterol. It is the main source of cholesterol buildup and blockage in the arteries. **HDL** (high-density lipoprotein) cholesterol is the "good" cholesterol. It helps keep cholesterol from building up in the arteries. **Triglycerides** are another form of fat in the blood. High levels of triglycerides may lead to heart disease.

**Blood Glucose (sugar) and Insulin**
Diabetes (high blood sugar) is an important risk factor for cardiovascular disease, as well as damage to the kidneys, eyes, and nerves. The STRONG HEART STUDY screens for diabetes by measuring blood sugar. Anyone found to have a high blood sugar will also have a blood test known as “hemoglobin A1c” or just “A1c”, which is a measure of how elevated the blood sugar has been during the previous few months. Insulin, which is the hormone that the body produces to use blood sugar, is also measured.

**Chemistry Profile**
Several blood measures are made to screen for problems with liver and kidney function. Other elements such as proteins, calcium, potassium, and sodium are measured. These values, in addition to personal medical history, a physical examination, and other tests help to determine the overall state of the participant's health.

**Urine**
Urine is collected for measurement of albumin and creatinine, which are substances normally found in the urine in small amounts. The proportion of albumin to creatinine (ACR) is calculated. This test is useful in identifying kidney disease.
Overview of Publication Process

After an investigator analyzes data, he/she usually wants to publish the findings. Many times the investigator first submits an abstract (a short description of the findings) for a scientific meeting and shows the findings at a poster session or during a short talk. Then the investigator often will write a paper about the findings and submit it to a journal to be published. The STRONG HEART STUDY Publications and Presentations (P&P) Committee reviews and approves or disapproves all paper proposals. Once an abstract or a manuscript has been written, it will be submitted to the National Heart, Lung, and Blood Institute for review and comment prior to submission to a meeting or to a journal, if an NHLBI staff is a co-author of the paper. At the same time a manuscript is sent to the NHLBI for review, it is sent to the Chairs of the 13 Tribes and to the IRBs of the 3 area IHS offices for approval prior to publication. The authors must obtain all of these approvals before they can publish their paper.