Manual of Operations

for STICH Protocol-Version 3 (11/01/04)

December 1, 2004

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STICH Telephone Numbers

Clinical Helpline and IVRS	Telephone Number
• US and Canada	1-888-871-6363
• Argentina	0-800-666-1645
• Australia	1-800-250-689
• Austria	0-800-293-592
• Belgium (Dom FF)	0-800-80965
• Brazil	0-800-891-7903
• Chile	1-230-020-3201
• Croatia	0-800-220-111
• Czech Republic	800-900-481
• Finland	0-800-112-599
• Germany (Dom FF)	0-800-752-2582
• Greece	00-800-441-40395
• Hong Kong (Dom FF)	300-21688
• Hungary	06-80-981-345
• Hungary (PSTN, non-toll free)	1-777-4750
• Israel	1-800-944-7874
• Italy	800-920-058
• Japan	813-357-08571
• Lithuania	8-800-30164
• Malaysia	1-800-880-131
• Netherlands (Dom FF)	0-800-022-2504
• New Zealand	0-800-448-602
• Norway (Dom FF)	800-40-941
• Poland	00-800-441-1611
• Romania	021-801-4442
• Russia (entire country, Rostelecom)	8-1080-0206-61049
• Russia (Moscow and St. Petersburg only)	7-095-545-0585
• Serbia (non-toll free)	00-36-1-777-4750
• Singapore	800-852-3534
• Slovakia	0-800-004-463
• Slovenia (non-toll free)	00-36-1-777-4750
• Sweden (Dom FF)	0-200-810-349
• Switzerland	0-800-561-144
• Taiwan	00-801-855-953
• Thailand	00-1-800-44-10503
• Turkey	00-800-12277
• United Kingdom (Dom FF)	0-800-028-8657

To obtain the most up to date country codes you can refer to the following link:
http://www.att.com/international_business/dialing_guide/country-diallist.cgi

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1. INTRODUCTION

The purpose of the STICH Manual of Operations is to define principles that result in best clinical research practice in compliance with the research plan of the STICH Trial described in the STICH Trial protocol. Both the Operations Manual and STICH Protocol are organized in a similar topical order with complementary but not redundant detail. The STICH Protocol provides the definitive description of the research plan. The Manual of Operations provides practical insights for accomplishing research plan objectives. A short summary of the STICH Trial research plan is available on the STICH web site www.stichtrial.org and included as Appendix 1 with this document.

Well-designed clinical trials must be conducted with attention to detail to provide high-quality data upon which conclusions can be reached that will influence critical decisions in the management of millions of patients. The issues addressed by the STICH Trial are some of the most basic and perplexing management questions in modern cardiology for patients with very advanced coronary artery disease (CAD) who are at high risk of death and disability. The trial seeks to define the evaluation and treatment strategy that promises the longest and most healthy life for the large and growing number of patients with Heart Failure (HF) and CAD. The major questions addressed by this trial include:

- In view of dramatic improvement in survival of advanced ischemic HF documented to result from use of ACE inhibition, beta blockade, and lipid-lowering medication, does revascularization by coronary artery bypass grafting (CABG) add survival advantage over modern medical therapy (MED)?
- In patients with regional dysfunction, does surgical ventricular restoration (SVR) designed to mechanically return the left ventricle to a more normal size and shape add survival to patients with CAD and HF beyond that realized from CABG alone?
- What is the role of noninvasive testing for identifying the specific medical or surgical therapy for an individual patient most likely to provide the longest survival with the best quality of life at the lowest cost?
- Can measurements made from blood samples add useful information for selecting and timing alternative treatments to optimize long-term outcome?

Trials designed primarily to evaluate the influence of major medical decisions, such as the choice of medical or surgical therapy on survival in patients with advanced disease often pose difficult recruitment challenges. Moreover, the STICH Trial incorporates a number of secondary management and mechanistic questions that require protocol-defined tests that often, but not always, are considered to be necessary in the care process. This manual describes usual modes of operation most likely to optimize patient recruitment and retention while achieving compliance with the STICH Trial protocol and accurate and complete data acquisition. This operational plan acknowledges the potential complexity of patient recruitment by providing alternate entry pathways that are those most commonly used in clinical practice. The value of these operational recommendations will increase when they are interpreted and applied with good judgment by the clinical site investigative team. As the source of this quality data, the principal investigator and study coordinator at each clinical site play a pivotal role in the success of the trial.

2. ORGANIZATION OF CLINICAL SITES

The STICH Trial seeks to recruit representative patients from a variety of clinical care environments to enhance generalizability of trial results. Large and small academic and private practice groups that share a common goal of high-quality clinical research while providing outstanding clinical care are invited to serve as STICH clinical sites. The specific structure of investigational work at a clinical site will be determined by the number of participating investigators and their interest in participating in either or both primary trial hypotheses. The scope of work undertaken will determine the number of investigators needed to fill specific leadership roles.

2.1 Leadership Roles

Principal Investigator: The principal investigator will be the individual recognized by the clinical site and the STICH Trial Coordinating Center and core laboratories as being responsible for conduct of the trial and appropriate disbursement of funds within the clinical site. Specific responsibilities include:

- Contract with the Coordinating Center as the individual responsible to the Coordinating Center and core laboratories for conduct of the trial at the clinical site in compliance with the STICH protocol at the reimbursement level specified.
- Negotiate the amount to be paid within the institution for all direct and indirect costs related to conducting the trial and appropriately disburse funds in compliance with policies of the institution.
- Serve as the clinical site representative on the STICH Trial Steering Committee (or designate a representative to serve in this capacity).
- Make definitive decisions on all clinical site operational policies in response to Coordinating Center or core laboratory inquiries.
- Coordinate activities of all other investigators at the clinical site.

Hypothesis 1 (myocardial revascularization) Co-Principal Investigator (may also serve the principal investigator role)**:**

- Establish and lead a research team for recruiting and following Hypothesis 1 patients.
- Develop research processes to optimally operationalize the research plan for Hypothesis 1 patients in compliance with the STICH protocol and manual of operations.
- Oversee fair distribution of funds within the institution generated by recruitment of patients into Hypothesis 1 and by follow-up work performed on any STICH patient.
- Review and sign all data forms on Hypothesis 1 patients.

Hypothesis 2 (surgical restoration) Co-Principal Investigator (may also serve the principal investigator role)**:**

- Establish and lead a research team for recruiting and following Hypothesis 2 patients.
- Develop research processes to optimally operationalize the research plan for Hypothesis 2 patients in compliance with the STICH protocol and manual of operations.
- Oversee fair distribution of funds within the institution generated by recruitment of patients into Hypothesis 2 and by follow-up work performed on any STICH patient.
- Review and sign all data forms on Hypothesis 2 patients.

Lead Cardiology Investigator (may also serve the principal investigator role)**:**

- Identify cardiologists at the site who are qualified to provide medical therapy to STICH Trial patients.
- Insure compliance with therapeutic protocols defined by the Medical Therapy Committee.
- Arrange continuous availability of qualified physician support for initiation and follow-up of medical therapy for STICH Trial patients.
- Assist the study coordinator in obtaining research information on STICH Trial patients who receive follow-up visits at other institutions.

Lead Cardiac Surgery Investigator (may also serve the principal investigator role)**:**

- Identify cardiac surgeons with the appropriate skills and training to serve as STICH Trial surgeons.
- Maintain surgical performance standards set by the Surgical Therapy Committee.
- Insure availability of surgical services by STICH Trial surgeons to support the trial protocol.

Lead Study Coordinator:

- Represent the clinical site at clinical coordinator meetings.
- Lead and support all other clinical coordinators working on the trial.
- Insure timely and accurate completion of all case report forms.
- Coordinate ongoing patient communication and follow-up visits.

Investigator*:* The clinical site principal investigator may designate any number of involved physicians to certify as STICH Trial investigators. The purpose of this designation is to facilitate communication at the clinical site and to acknowledge the contributions of all physicians who perform investigational work related to the trial. All interested investigators will be encouraged to attend the investigator meetings, participate in ancillary studies, and contribute to scientific aspects of the trial in their area of interest.

2.2 Types of Clinical Sites

Four different structures are possible for STICH clinical sites that are determined primarily by site interest in participation in either or both hypotheses and by the interest and qualifications of potential investigators. Specific leadership tasks remain constant among different types of sites, but single investigators can fill multiple roles if necessary. However, recruitment is encouraged of as large a group of investigators as justified by the interest and expertise at the site to facilitate the success of patient recruitment and to give clinical research leadership experience to young colleagues.

Comprehensive Clinical Sites: These sites will recruit into both primary hypotheses and cardiologists and cardiac surgeons will serve as investigators. Leadership roles needed for these sites include principal investigator, Hypothesis 1 co-principal investigator, Hypothesis 2 co-principal investigator, lead cardiologist, and lead surgeon. The minimal investigator participation required to qualify as a comprehensive clinical site includes a lead cardiologist and lead cardiac surgeon who would also fill the three principal investigators roles.

Hypothesis 1 Clinical Sites: These clinical sites focus recruitment work exclusively on Hypothesis 1 and include both cardiologists and cardiac surgeons as investigators. Leadership roles for these sites include principal investigator, Hypothesis 1 co-principal investigator, lead cardiologist, and lead cardiac surgeon. A lead cardiologist and lead cardiac surgeon represent the minimal number of investigators needed for the Hypothesis 1 clinical sites with either of these investigators also filling the leadership roles of the principal investigator and Hypothesis 1 co-principal investigator.

Hypothesis 2 Clinical Sites: These clinical sites focus recruitment work exclusively on Hypothesis 2 and include both cardiologists and cardiac surgeons as investigators. Leadership roles for these sites include principal investigator, Hypothesis 2 co-principal investigator, lead cardiologist, and lead cardiac surgeon. A lead cardiologist and lead cardiac surgeon represent the minimal number of investigators needed for the Hypothesis 2 clinical sites with either of these investigators also filling the leadership roles of the principal investigator and Hypothesis 2 co-principal investigator.

Cardiology Clinical Sites: These clinical sites can be established by a single cardiologist who performs all leadership duties of the principal investigator, the principal co-investigator for the hypotheses addressed, and of the lead cardiologist and lead cardiac surgeon. In settings without a lead cardiac surgeon, it is necessary that the principal investigator document that the surgeon to perform the surgical care of the STICH patient meets standards of quality established by the STICH Surgical Therapy Committee. Although the non-STICH surgeon will be responsible for obtaining informed consent for clinical care, the STICH investigator will be responsible for obtaining the consent for STICH Trial participation and for completing all case report forms, including the Surgical Therapy form.

2.3 Clinical Site Reimbursement

Reimbursement of the clinical site has been designed to promote overall trial efficiency and permit maximal flexibility to sites for use of funds. Reimbursement will occur when sites qualify to begin patient enrollment and as patients achieve specified evaluation points and the Coordinating Center has received an appropriate case report form that is accurate, complete, and error free. This approach of reimbursing for clean data optimizes the efficiency of Coordinating Center and site efforts. Clinical sites will be reimbursed monthly for receipt of documentation of all research work received by a pre-specified target day. In the event errors or missing data occur occasionally, sites will receive a notification and will be reimbursed for that work in the payment cycle when all queries are resolved. Site payments from the Coordinating Center made to the principal investigator represent total reimbursement for direct and indirect costs for all investigative work, including the work required to provide protocol-specified noninvasive studies and blood samples to core laboratories. Reimbursement levels assume that many of the protocol noninvasive studies will have been obtained during the usual clinical care process. The principal investigator will be responsible for redistributing funds to co-principal investigators and for negotiating appropriate redistribution of funds to reimburse clinical site laboratories for the technical component of those studies that must be acquired for research because they were not considered clinically necessary in the patient care process. Clinical site reimbursement was calculated to include appropriate levels of indirect costs for clinical research. Reimbursement sources tabulated to reflect patient-specific work tasks contributing to the total reimbursement provided monthly by the Coordinating Center will facilitate equitable distributions of funds at the site.

The STICH Trial is funded primarily from an NHLBI grant. However, funds from other sources also will defray a portion of clinical site costs. The clinical site budget is a subcontract between the Duke Clinical Research Institute (DCRI) and each clinical site. The clinical site budget is not a grant from the National Institutes of Health. Clinical sites should not anticipate receiving indirect costs at the NIH institutional level, but rather should be reimbursed for indirect costs as appropriate within the institution for contractual arrangements with non-governmental sources of clinical research funding. All principal investigators must comply with fund use and accounting policies of their institution. The DCRI will not require an accounting of use of the funds disbursed to the clinical site.

3. CLINICAL SITE WORK PRIOR TO PATIENT ENROLLMENT

Prior to patient enrollment, each potential clinical site must document their qualifications and potential for contributing to the success of the STICH Trial to other STICH colleagues. Additionally, STICH Trial investigators must satisfy their own institution that all aspects of the overall trial research plan are ethical and that participation in the trial as a clinical site is compatible with overall institutional objectives. The Coordinating Center, as the representative of the STICH Trial to the NHLBI and other trial leadership, will assist clinical sites in every possible way to facilitate the process of certifying individual investigators to become qualified to begin patient enrollment. Submission of forms documenting completion of all necessary work to certify individual investigators and coordinators and to qualify the site for patient enrollment represents the first benchmark for clinical site reimbursement. These forms are available on the STICH web site (www.stichtrial.org) or from the Coordinating Center.

3.1. Certify Investigators and Coordinators

TABLE 1. Process for Qualification as a STICH Trial Clinical Site

Work to Complete	Documents Required For Payment
Certify Investigators and Coordinators (Section 3.1)	• Investigator Profile and CV for each Investigator (Section 3.2.6.1) • Profile for each Coordinator (Section 3.2.6.2) • Conflict of Interest Form for each Investigator (Section 3.2.6.3) • Documentation of Clinical Research Ethics Education for all trial related personnel (Separate document) (http://cme.nci.nih.gov) • Documentation of Surgical Experience Form for each Surgical Investigator (CABG – Section 3.2.6.5, SVR – Section 3.2.6.6)
Qualify Clinical Site (Section 3.2)	• Federal wide Assurance Number • Site Surgical Experience Form (Section 3.2.6.7) • Gender and Minority Patient Enrollment Projection Form (Section 3.2.6.8) • Identify site core laboratory investigators and contacts, initiate certification process. • IRB profile form and copy of IRB approval of protocol and approved consents (Section 3.2.6.9) • Signed contract with Coordinating Center (Appendix 2)

3.1.1 Certification Work for STICH Surgeons

High quality surgical care is essential for the STICH Trial to definitively address the two primary hypotheses comparing the benefit of medical and surgical therapies. The lead surgeon at each clinical site will certify themselves and other cardiac surgeons with the appropriate skills and training. The lead surgeon must complete the Certification Statement for individual surgeons qualified to perform the SVR, CABG, and SVR Operations forms (Sections 3.2.6.5 and 3.2.6.6) and submit these to the Coordinating Center confirming that each surgeon to be certified meets the operative experience qualifications defined by the Surgical Therapy Committee. Each site must retain records of data used to make this certification for review at the request of the Coordinating Center (Section 3.2.6.4 and appropriate clinical care documents). STICH surgeons may choose to certify to perform only CABG or may choose to meet qualification requirements for both CABG and SVR.

3.2 Qualify Clinical Site

3.2.1 Site Surgical Experience

Clinical sites may choose to qualify to enroll patients in all three strata from the outset of the trial or to enroll patients only in Stratum A or only in Stratum C. Clinical sites with one or more surgeons individually qualified to perform CABG and SVR whose composite experience meets criteria to qualify as a surgical site for performance of CABG and SVR may begin enrolling patients in all strata at the outset of the trial. Sites that qualify one or more investigators as meeting criteria for certification for performing the CABG operation and whose composite experience meets clinical site criteria for qualifying as a STICH surgical site for performing CABG may enroll patients only in Stratum A. The lead surgeon must complete either the Site Surgical Experience Form to qualify the site for CABG alone or forms for both CABG and SVR procedures.

3.2.2 Site Certification for Core Laboratory Studies

Each clinical site may invite colleagues with interest and expertise in areas represented by core laboratory activities to serve as STICH investigators. In addition to making scientific contributions, these investigators may assist the clinical site STICH team in obtaining and transmitting required core laboratory studies. In the absence of interested investigators in each discipline represented by core laboratories, the principal investigator or a designee must complete core laboratory certification and insure that core laboratory studies required for randomized patients are properly obtained and sent for analysis. Core laboratory certification documents should be returned directly to each individual core laboratory, and questions regarding the certification process should be directed to the designated contact person for each core laboratory (page 5). A manual for each core laboratory is available on the STICH web site (www.stichtrial.org).

3.2.3 Gender and Minority Patient Enrollment Projections

The STICH Trial proposes to recruit a relatively high percentage of women and minority patients because it is ethically important that all members of our society benefit equally from clinical research and because important scientific questions can be addressed most definitively with a heterogeneous patient cohort. Prior to final selection and receipt of any funding, each clinical site must set their own institution-specific recruitment goal for minorities as the number of patients projected to enter into the STICH Trial in each gender and minority category. In the final site selection process by the Coordinating Center and the NHLBI, preference will be given to sites with gender and minority recruitment goals reflective of the population mix of their institution. Moreover, performance relative to each institution-specific goal will be monitored throughout the period of patient entry. Therefore, these goals should represent reasonable projections of

anticipated recruitment at each site. Dr. Clyde Yancy, Chair of the STICH Minority Committee will advise the Coordinating Center and clinical sites on procedures most likely to achieve these stated goals. The Coordinating Center is responsible for achieving the stated goal for recruitment of 30% women and 20% minorities into the STICH Trial.

3.2.4 Institutional Review Board (IRB/ERB) Approval

Each institution must obtain local IRB/ERB approval of the STICH Protocol, informed consent and operational policies to be used for STICH Trial recruitment. The informed consent process is lengthy at many institutions and early attention to this work can greatly shorten the time required for site activation. Informed consent templates are available for reference on the STICH web site (www.stichtrial.org) or by request to the Coordinating Center. These templates may be used after modification to reflect local practice and local IRB/ERB requirements. The Coordinating Center staff will review the site – modified informed consents for ICH elements and HIPAA elements (US only) prior to submission to the local IRB/ERB. A current copy of IRB/ERB approval must be maintained by the clinical site and Coordinating Center throughout the duration of clinical site enrollment and follow-up. IRB/ERB review and approval of the protocol and consents are required on an annual basis.

3.2.5 Contract with Coordinating Center

A non-negotiable contract is offered to all principal investigators who accept the invitation to serve as a STICH Trial clinical site. The language of this contract should be reviewed for acceptability immediately upon receipt to identify any minor changes desired by the principal investigator of the contracting office of the institution. The contract with proposed changes should be returned promptly to the Coordinating Center principal investigator to avoid delay in preparing a final contract for signature.

3.2.6 Federal Wide Assurance Number

A federal wide assurance number is required for participation in NIH trials. The start-up packet contains information and the application needed for submission to the Office for Human Research Protections (OHRP). You may call the Coordinating Center for assistance or contact OHRP at http://ohrp.osophs.dhhs.gov.

3.3 Site Preparation for Patient Enrollment

During the waiting time intrinsic to the certification process, three concurrent areas of work should proceed to insure that patient enrollment can begin as soon as the certification process is complete. The three work objectives are:

1. Develop an integrated investigative team.
2. Develop a support team.
3. Define operational processes.

3.3.1 Develop an Integrated Investigative Team

The process of site certification requires definition of an investigative team that is properly trained. Transforming individuals into an efficient and productive integrated investigative team requires group knowledge of individual roles and definition of the cooperative processes needed to achieve the common goal. Team meetings should be convened on a regular basis to create structure and an effective working environment, and processes conducive to successful study conduct.

3.3.2 Develop an Integrated Support Team

Concurrent with the identification of the primary investigative team, a similar team spirit should be developed with colleagues who are not investigators but will contribute to the trial effort. Communication with individuals or groups of colleagues within the institution and its referral base regarding the objectives and research plan of the trial will be critical for developing a supportive attitude. The STICH web site (www.stichtrial.org) is an excellent resource of educational material that may be useful in these communications aimed at building general institutional support for the investigational team.

3.3.3 Learn to Use the STICH Web Site (www.stichtrial.org)

The STICH web site will be the focal point of communication for the STICH Trial. Throughout the seven-year trial period, a password-protected investigator area of the web site will be regularly updated with useful educational tools. The section of the web site open to the public has the objective of educating patients and care providers about the trial. Inquiries about STICH trial participation from patients and referring physicians coming to the Coordinating Center from the web site will be referred to investigators at appropriate clinical sites. Access to the secure section of the web site is provided to certified coordinators, investigators, and committee members with individualization of access determined by roles in the trial. This feature permits committees to conduct confidential work using the web site to enhance efficiency. All STICH working documents will reside on the web site and can be downloaded or printed. Slide sets and educational modules will be maintained and updated to provide instruction for new investigators or coordinators and to supplement lectures by investigators. The investigator portion of the site will also contain information on trial logistics and operations, participant directories, and bibliographies. Trial news will be updated regularly. Overall enrollment performance will be updated regularly, as will performance relative to minority and gender recruitment. The site will also provide a "real-time" forum for sharing details of specific approaches to patient screening and emphasis of principles responsible for their success. Space for informal interaction among investigators and coordinators will enhance communication among our entire STICH group and enhance deepening of professional relationships among us as colleagues.

3.3.4 Organize Recruitment Materials Provided by the Coordinating Center

Manual of Operations. The most current version of this document can be downloaded from the STICH web site or requested from the Coordinating Center. All Investigators and coordinators should carefully read this manual before enrolling patients.

Tools for Initial Evaluation and Follow-up Visits. A Tools binder is provided by the Coordinating Center for the study coordinator to organize the following materials:

- **Informed Consent**. Site specific IRB-approved informed consent forms should be stored in this binder by using the plastic sheet protectors provided.
- **Race and Ethnicity Survey**. This survey is to be used to obtain the most accurate race and ethnicity information from all patients enrolled in the trial.
- **Confidential Patient Information**. This form must be completed at the time of the initial evaluation for all patients enrolled in the trial including Initial Evaluation Log patients, registry patients, and randomized patients.
- **IVRS Worksheet**. This worksheet should be completed on each patient **before** calling the IVRS.
- **EQOL Summary and Questionnaire**. This questionnaire is to be administered to each randomized patient at the time of the initial evaluation using the instructions, Interview Guidelines, and Annotated Questionnaire, as needed.
- **EuroQOL**. This form is to be completed by randomized patients at the time of the initial evaluation and at specified intervals throughout the study.

- **6-Minute Walk Patient Worksheet**. The 6-Minute Walk instructions and the worksheets will aid proper performance and documentation of test results.
- **Patient Materials**. Wallet cards for randomized and registry patients and Quality-of-Life magnets are located in the clear plastic pouch in the Tools Binder.
- **Study Procedures**. The study procedure table will be a useful reference at the time of each patient follow-up visit.
- **Pocket Cards and Wall Posters**. Seven pocket cards and 3 wall posters are enclosed in the Start-up Kit. More can be requested at any time.
- **Recruitment Materials**. Pocket cards and two wall posters are enclosed for distribution to referring physicians.

3.3.5 Materials to be Organized by the Clinical Site

- **Case Report Forms (CRFs)**. CRF supplies are provided to serve needs specific to patients enrolled in the iInitial evaluation log and registry as well as for randomized patients.
- **Initial Evaluation CRF Pages Box**. This box contains 20 Initial Evaluation sets (pages 1-3) and submission and shipping supplies. One set is to be completed for each patient entered into the initial evaluation log, registry or randomized groups.
- **Clinical Follow-up CRF Pages Box**. This box contains 10 Clinical Follow-up CRF pages and all of the needed CRF submission and shipping supplies. This form must be completed for each randomized patient after each follow-up visit.
- **Additional CRF Pages Binder**. This binder contains visit-specific CRF pages for randomized patients.
- **CRF Storage Binder**. Two types of storage binders are provided. An individual binder will be provided for each randomized patient. The Registry and Initial Evaluation Patient CRF Storage binder will hold CRFs for 60 patients (pink copies).

A regulatory binder or file should be prepared to retain all required regulatory documents through the duration of the trial. Documents required in the certification process and those that require annual updates should be included.

4. PATIENT RECRUITMENT

4.1 Initial Evaluation of Patients Screened as Potentially Eligible

The best available and most recently performed LV assessment by either contrast (cardiac cath), gated SPECT, or CMR ventriculogram read at the clinical sites or a resting echocardiogram will identify patients meeting LV EF entry criteria. The CMR or gated SPECT, is strongly preferred as the study to use for definition of eligibility and definition of appropriate stratum for randomization. The contrast ventriculogram can be used to enroll patients but cannot be used as the baseline assessment of left ventricular function since it is not well suited to use to obtain the required 4- and 24-month follow up examinations. The echocardiogram should only be used as the baseline ventriculogram when the time required to obtain an additional test might jeopardize trial entry because of demands of clinical care.

4.2 Obtaining Informed Consent

After responsible physicians agree, patients can be approached for informed consent for randomized treatment selection within the STICH Trial strata for which they qualify. Patients should be encouraged to have supportive family members and other advocates present during the informed consent process. Additionally, they should be given full access to all physicians involved in their care to aid in their deliberation on trial entry.

Patients should be approached for informed consent to receive only the alternative therapies possible within the randomization stratum for which they are eligible. Patients in Stratum B are also eligible for randomization in Stratum A. Those who decline randomization in Stratum B are appropriate to randomize in Stratum A if consent is given. The overall informed consent process should be conducted in a non-threatening way and the patient should be reassured that failure to consent to enter the trial will in no way compromise any aspect of their ongoing care. Patients should be informed that consent can be withdrawn at any time and for unstated reasons. This information should be balanced with the caution that unless they are truly willing to accept any randomized treatment for which they are eligible, they should be honest at the outset and decline randomization.

5. RANDOMIZATION

Although care providers who are not STICH investigators may be involved in the informed consent process, STICH investigators or coordinators will also need to be involved with the randomization process to complete the Confidential Patient Information and Initial Evaluation Forms. Receipt of these forms by the Coordinating Center initiates clinical site reimbursement for investigator work in enrolling randomized patients.

5.1 The Interactive Voice Response System (IVRS)

An IVRS Worksheet with evidence that the patient meets inclusion/exclusion criteria and a signed Informed Consent Form should be completed prior to initiating a call to the DCRI randomization center to obtain the treatment assignment for the patient. The IVRS system will prompt the caller to enter and confirm all information needed for the randomization to occur. After confirmation, the patient will be randomized to a treatment and assigned an 8-digit randomization number. The randomization number will be assigned as a site specific unique identifier and will consist of the first four digits being the site number and the fifth digit being a "0" for randomized patients; "1" for registry patients; and "2" for Initial Evaluation patients. Anytime during the IVRS, pressing the "0" key will transfer the call to a randomization attendant. The IVRS will also let clinical sites practice enrolling patients and will identify this procedure as a practice enrollment. Site identification number 9999 is reserved for this purpose.

5.2 STICH Clinical Helpline 888-871-6363

A physician will be available 24 hours a day to answer urgent questions about recruitment, enrollment, and patient management by selecting the "Technical Support" option. Sites are encouraged to call the Clinical Helpline to seek assistance on unclear issues that arise when applying of the research plan to specific patients. Use of this Helpline is especially important before randomization of patients with any question of eligibility.

5.3 Baseline Work After Randomization

Table 2 summarizes baseline work to be completed in patients in the three strata. Studies completed prior to randomization (within 3 months) in compliance with core laboratory standards do not need to be repeated. All tests must be completed prior to initiation of therapy.

Table 2. Baseline Evaluation Studies

Patient Characteristics	Stratum A	Stratum B	Stratum C
All Consenting Patients	• ECHO to Core • QOL to Core • EuroQOL to Core • CMR, Gated SPECT, or ECHO for LV function	• ECHO to Core • QOL to Core • EuroQOL to Core • CMR, Gated SPECT, or ECHO for LV function	• ECHO to Core • QOL to Core • EuroQOL to Core • CMR, Gated SPECT, or ECHO for LV function
When Feasible	• NCG Blood to Core • Myocardial Viability to Core	• NCG Blood to Core • Myocardial Viability to Core	• NCG Blood to Core
Patients ABLE	• 6-minute Walk • Exercise Stress	• 6-minute Walk • Exercise Stress	• 6-minute Walk • Exercise Stress

6. TREATMENT

Study therapy allocated by randomization should be initiated as soon as feasible but no later than Day 14. Intensive medical treatment (MED) will be initiated after completion of the baseline evaluation in all randomized to MED. Patients randomized to surgical treatment will undergo operation as soon as possible after completion of the baseline evaluation but within 14 days in all patients. In surgical patients, MED will be initiated after operation as soon as postoperative recovery permits but should be optimized in all patients by the 4-month visit.

6.1 CABG

CABG will be performed using at least one internal mammary graft in all patients unless this conduit is unavailable or has inadequate flow. Unequivocally needed reparative procedures, such as aortic valvular repair or replacement or thoracic aortic aneurysmectomy, are exclusion criteria at entry. However, patients with secondary mitral regurgitation identified by echocardiography who are judged to need mitral valve repair may undergo this procedure combined with CABG with or without SVR. Therefore, use of CABG or CABG + SVR throughout the STICH protocol implies that mitral repair for regurgitation secondary to ischemic HF may be included in the operative strategy at the discretion of the operating surgeon.

6.2 CABG with SVR

The two criteria used by the Surgical Therapy Committee to define the acceptable range of specific operative maneuvers essential to be considered an acceptable technical SVR operation for the STICH Trial will be any ventricular reconstruction method that consistently results in: 1) a low operative mortality; and 2) an average EF increase of $\geq$ 10% and average LVESVI decrease of $\geq$ 30% as assessed on the four-month postoperative CMR measurements. SVR may be performed with or without cardioplegic arrest. In general, the SVR is begun after completion of the CABG. The region of dysfunction identified by preoperative CMR will be incised regardless of the epicardial appearance. The border separating the dysfunctional from contracting myocardium identified by palpation will guide placement of sutures and a patch, if necessary, to purse string the endocardial scar, thereby decreasing LV size without distorting the LV shape.

6.3 MED

6.3.1 General Management

The most effective general measure in the management of HF is close attention and follow-up. Noncompliance with diet and medications can rapidly and profoundly affect the clinical status of patients. Increases in body weight and minor changes in symptoms commonly precede by several days the occurrence of major clinical episodes that require emergency care. Patient education and close supervision can reduce the likelihood of noncompliance and detect changes in body weight or clinical status early enough to allow an opportunity to begin treatments that can prevent clinical deterioration.

In addition to the visits designated by the STICH protocol, patients with HF will commonly be evaluated by physicians who are not STICH investigators at intervals appropriate to the severity of their illness (every 2-3 months in class II, every 4-12 weeks in class III and every 7-28 days in class IV patients). At all times, patients and their families should be encouraged to conduct home surveillance, including daily weights and monitoring of signs and symptoms. Significant changes should prompt patient-initiated changes in therapy (as agreed upon with a physician) or a timely call to the patient's health care professional.

6.3.1.1 Recommended Outpatient Evaluations

Assessment of Clinical Status. During each visit physicians should inquire about symptoms and should note all medications (and their doses), including the use of over-the-counter drugs and nutritional supplements. Discrepancies with prescribed regimens should be identified and addressed.

Assessment of Volume Status. Physicians must evaluate the volume status of patients during each follow-up visit. This assessment plays a pivotal role in determining the dose of diuretic and in detecting sodium excesses or deficits that may limit the efficacy and decrease the tolerability of drugs used to treat HF. At each visit physicians should record the patient's body weight and determine the degree of jugular venous distension (and its response to abdominal pressure), the presence and severity of organ congestion (pulmonary rales and hepatomegaly), and the magnitude of peripheral edema (in the legs, abdomen, presacral area or scrotum).

The most reliable physical sign of volume overload is jugular venous distension. Patients with peripheral edema should also be considered to have volume overload, although the possibility of noncardiac causes for edema may limit the utility of this sign in some patients. Most patients with chronic HF do not have pulmonary rales, even those with end-stage disease who have markedly elevated left-sided filling pressures. The presence of rales generally reflects the rapidity of onset rather than the degree of volume overload; hence, the finding of clear lung fields should not suggest that fluid retention has been adequately treated.

Of available measures, short-term *changes* in fluid status in the individual patient are most reliably gauged by measuring short-term *changes* in body weight. However, changes in weight may be less reliable during long periods of follow-up, since many patients lose skeletal muscle mass and body fat as the disease advances (cardiac cachexia). Although some have proposed that the serial measurement of circulating levels of brain natriuretic peptide may be useful in estimating the degree of volume overload, the utility of such measurements has not been established.

Laboratory Assessment. Serum electrolytes and renal function should be routinely monitored. Of particular importance is the serial measurement of serum potassium concentration, since drugs used for HF can produce both hypokalemia (diuretics) and hyperkalemia (ACE inhibitors and spironolactone). Many believe that serum potassium concentrations in the range of 3.5-3.8 mmol/L or 5.2-5.5 mmol/L should be avoided in patients with HF, even though such values may be in the normal range for many laboratories.

Renal dysfunction may result from volume depletion, renal hypoperfusion (due to worsening HF), treatment with an ACE inhibitor, intrinsic kidney disease, or a combination of these factors. Because worsening renal function may have several causes, physicians should not assume that increases in blood urea nitrogen (even when disappropriate to increases in serum creatinine) are related to volume depletion. Deterioration of renal function (regardless of cause) may require downward adjustment in the doses of digoxin or upward adjustment of the doses of diuretics.

6.3.1.2 Diet General Measures

Moderate sodium restriction is recommended to permit effective use of lower and safer doses of diuretic drugs. Some (but not all) patients require potassium supplements to maintain serum potassium concentration between 3.8 to 5.2 mmol/L. When severe, correction of potassium deficits may require supplementation of magnesium as well as potassium. In patients receiving ACE inhibitors alone or in combination with spironolactone, the routine prescription of potassium salts may be unnecessary and potentially deleterious. Water restriction is not indicated in most patients with HF, except those with severe hyponatremia.

Exercise. Although patients should not participate in heavy labor or exhaustive sports, physical activity should be encouraged (except during periods of acute decompensation) to prevent physical deconditioning. Controlled clinical trials has shown exercise training to decrease symptoms, increase exercise capacity, and improve quality of life. This improvement was additive to the benefits of ACE inhibitors and beta-blockers.

Minimization of Exacerbating Factors. Patients should be strongly advised about the hazards of smoking, alcohol, cocaine, and other illicit drugs. Obese patients should be advised to lose weight. Immunization with influenza and pneumococcal vaccines may reduce the risk of a respiratory infection and are strongly recommended. Physicians should treat other diseases that may adversely affect the heart, e.g., anemia, thyroid disorders.

Drugs to be Avoided for Patients with Heart Failure. Four classes of drugs can exacerbate the syndrome of HF and should be avoided:

a. Antiarrhythmic agents. These drugs can exert cardio-depressant and proarrhythmic effects. Of available agents, only amiodarone has been shown not to adversely affect survival.
b. Calcium channel blockers. These drugs can lead to worsening HF and have been associated with an increased risk of cardiovascular events. Of available agents, only amlodipine has been shown not to adversely affect survival, although experience with the drug in HF is limited to patients not receiving beta-blockers.
c. Nonsteroidal anti-inflammatory drugs (including COX-2 specific inhibitors). These drugs can cause sodium retention and peripheral vasoconstriction and can attenuate the efficacy of and enhance the toxicity of diuretics and ACE inhibitors.
d. Anti-cytokine agents. Drugs that block the actions of tumor necrosis factor (such as infliximab) have been reported to worsen HF and should not be used.

Nutritional Supplements and Hormonal Therapies. Nutritional supplements (e.g., coenzyme Q10, carnitine, antioxidants) or hormonal therapies (e.g., growth or thyroid hormone) has not been shown to be effective in HF. Furthermore, the safety of these supplements has not been evaluated, and the use of some agents may have deleterious effects on the heart or interact adversely with drugs known to be of value. Therefore, nutritional supplements or hormonal therapies are not recommended for the treatment of HF. Since patients can initiate such treatments without a prescription, physicians should routinely inquire about and discourage their use.

6.3.2 Drugs Recommended for Routine Use in the STICH Trial (Required Unless Contraindicated)

Patients in the STICH Trial should be routinely managed with a diuretic, an ACE inhibitor, and a beta-adrenergic blocker. Patients with evidence of fluid retention should receive a diuretic until an euvolemic state is achieved, and diuretic therapy should be continued to prevent the recurrence of fluid retention. Even if the patient has responded favorably to the diuretic, treatment with both an ACE inhibitor and a beta-blocker should be initiated and maintained in patients who can tolerate them, since they have been shown to favorably influence the long-term prognosis of HF.

6.3.2.1 Diuretics

Recommendations for Use. All patients in the STICH Trial should be receiving long-term treatment with a diuretic, unless there is a specific contraindication to its use. Few patients with HF will be able to maintain dry weight without the use of diuretics, and appropriate use of diuretics is a key element in the success of other drugs used for the treatment of HF. The use of inappropriately low doses of diuretics will cause fluid retention, which can diminish the response to ACE inhibitors and increase the risk of treatment with beta-blockers. The use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension with ACE inhibitors and vasodilators and the risk of renal insufficiency with ACE inhibitors and angiotensin II receptor antagonists.

Because of their greater efficacy (particularly in patients with poor renal perfusion), the loop diuretics (bumetanide, furosemide and torsemide) have emerged as the preferred duretics for patients with heart failure. The most commonly used loop diuretic for the treatment of HF is furosemide. Furosemide is the agent preferred by the members of the Medical Therapy Committee and is the designated diuretic for the STICH Trial.

Practical Use of Diuretic Therapy Initiation and Maintenance. In patients with fluid retention, therapy is commonly initiated with low doses of a diuretic and the dose is increased until urine output increases and weight decreases, generally by 0.5-1.0 kg daily. Further increases in the dose or frequency of diuretic administration may be required to maintain an active diuresis and sustain the loss of weight. The ultimate goal of treatment is to eliminate physical signs of fluid retention, either by restoring jugular venous pressures toward normal or by eliminating the presence of edema, or both. Diuretics are generally combined with moderate dietary sodium restriction (< 3g daily).

If electrolyte imbalances are seen, these should be treated aggressively and the diuresis continued. If hypotension or azotemia are observed before the goals of treatment are achieved, the physician may elect to slow the rapidity of diuresis, but diuresis should nevertheless be maintained until fluid retention is eliminated as long as the patient remains asymptomatic even if this strategy results in mild or moderate decreases in blood pressure or renal function. Excessive concern about hypotension and azotemia can lead to the under utilization of diuretics and a state of persistent volume overload, which may not only exacerbate symptoms but may also limit the efficacy and compromise the safety of other drugs used for heart failure.

Once fluid retention has resolved, treatment with the diuretic should be maintained to prevent the recurrence of volume overload. Although patients are commonly prescribed a fixed dose of diuretic, the dose should be adjusted periodically to maintain euvolemia. In many cases this adjustment can be accomplished by having the patient record his/her weight each day and allowing the patient to make changes in dose if the weight increases or decreases beyond a specified range.

Patients may become unresponsive to high doses of diuretic drugs if they (1) consume large amounts of dietary sodium; (2) are receiving agents that can block the effects of diuretics (e.g., nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors); or (3) have a significant impairment of renal function or perfusion. Diuretic resistance can generally be overcome by (1) the intravenous administration of diuretics (including the use of continuous infusions); (2) the use of two or more diuretics in combination (e.g., furosemide and metolazone); or (3) the use of diuretics together with drugs that increase renal blood flow (e.g., positive inotropic agents).

Electrolyte depletion. Potassium deficits should be corrected by the short-term use of potassium supplements, or if severe, by the addition of magnesium supplements. Concomitant administration of ACE inhibitors alone or in combination with potassium-retaining agents (such as spironolactone) can prevent electrolyte depletion in most patients with heart failure receiving a loop diuretic. When these drugs are prescribed, long-term oral potassium supplementation is frequently not needed and may be deleterious.

Hypotension and azotemia. Excessive use of diuretics can decrease blood pressure and impair renal function, but hypotension and azotemia may also occur as a result of worsening HF, which may be exacerbated by a reduction in the dose of diuretics. If there are no signs of fluid retention, hypotension and azotemia are likely to be related to volume depletion and may resolve following a decrease in diuretic dose. If fluid retention is present, hypotension and azotemia are likely to reflect worsening HF and a decline in peripheral perfusion. Such patients should be managed by maintaining the dose of diuretic and improving end-organ perfusion (e.g., with the short-term use of an intravenous positive inotropic agent).

6.3.2.2 Angiotensin Converting Enzyme Inhibitors

Recommendations for Use. All patients in the STICH Trial should be receiving long-term treatment with an ACE inhibitor, unless there is a specific contraindication or the patient has been shown to be unable to tolerate treatment with the drug. ACE inhibitors are preferred over the use of angiotensin II receptor antagonists or direct-acting vasodilators (e.g., hydralazine plus isosorbide dinitrate).

Appropriate reasons for not using an ACE inhibitor include: (1) pregnancy; (2) history of a life-threatening adverse reaction (e.g., angioedema or anuric renal failure) during earlier exposure to an ACE inhibitor; and (3) intolerable cough (which has been shown to be due to ACE inhibition by a process of withdrawal and rechallenge). Patients with very low systemic blood pressures (systolic blood pressure <80 mm Hg), markedly increased serum levels of creatinine (>3 mg/dl), bilateral renal artery stenosis or elevated levels of serum potassium (>5.5 mmol/l) remain candidates for the cautious use of ACE inhibitors.

Which ACE inhibitor should be preferred? Few trials have compared the relative efficacy and safety of ACE inhibitors in the treatment of heart failure. In severely ill patients, treatment is frequently initiated with a short-acting agent (e.g., captopril) to minimize the risk of symptomatic hypotension or renal insufficiency. For long-term treatment, preference should be given to ACE inhibitors that have been shown to reduce morbidity and mortality in clinical trials (captopril, enalapril, lisinopril and ramipril), since these studies have defined a dose that is effective in modifying the natural history of the disease. Some physicians prefer ACE inhibitors that have a high affinity for ACE in the tissues (e.g., ramipril and quinapril), and such ACE inhibitors produce greater effects on some physiologic variables than ACE inhibitors that primarily act on serum ACE**.**

Trandolapril. In addition to a generous grant to the clinical site reimbursement budget, Abbott Laboratories will supply without cost, the ACE Inhibitor trandolapril, ("Mavik")™, to STICH randomized patients in the United States. The Medical Therapy Committee has designated trandolapril as the preferred ACE inhibitor for the STICH trial. Use of this drug is strongly encouraged to standardize medical therapy and to remove cost as a barrier to patient compliance. However, use of this specific ACE inhibitor is not mandated by the STICH protocol, and alternate ACE inhibitors may be used if preferred by the patient or responsible physician.

Abbott Laboratory representatives will coordinate drug shipments to activated US (only) clinical sites who must assume responsibility for tracking the receipt, dispensation and return of unused trandolapril upon completion of the trial. Trandolapril is available in strengths of 1, 2, and 4 mgms.

Practical Use of ACE Inhibitors

Initiation and Maintenance. Practical Use of ACE Inhibitors - ACE inhibitors should be initiated at very low doses followed by gradual increments in dose if lower doses have been tolerated. Renal function and serum potassium should be assessed periodically.

What dose of an ACE inhibitor should physicians try to achieve? In clinical trials, the dose of the ACE inhibitor was not determined by a patient's therapeutic response but was increased until a target dose was reached. Low or intermediate doses were prescribed if higher doses could not be tolerated. In a large multicenter trial, high doses of an ACE inhibitor were somewhat better than low doses in reducing the risk of hospitalization, but the two doses had similar effects on symptoms and mortality. These findings suggest that: (1) physicians should attempt to prescribe doses of an ACE inhibitor that have been shown to reduce the risk of cardiovascular events in

clinical trials; (2) if these target doses of an ACE inhibitor are poorly tolerated, then lower doses should be utilized with the expectation that there are probably only small differences in efficacy between low and high doses.

Every effort should be made to minimize the occurrence of sodium retention or depletion before and during long-term treatment with an ACE inhibitor, since changes in salt and water balance can exaggerate or attenuate the cardiovascular and renal effects of treatment. Fluid retention can minimize the symptomatic benefits of ACE inhibition, whereas fluid loss increases the risk of hypotension and azotemia. Nonsteroidal anti-inflammatory drugs (including COX-2 specific agents) can block the favorable effects and enhance the adverse effects of ACE inhibitors in patients with heart failure and should be avoided.

Retrospective analyses of large-scale trials suggest that aspirin might also interfere with the benefits of ACE inhibition in patients with heart failure. Aspirin can attenuate the hemodynamic actions of ACE inhibitors, an effect not seen with non-aspirin anti-platelet agents (e.g., clopidogrel). In several multicenter trials, use of aspirin was associated with a diminution of the effect of ACE inhibitors on survival and on cardiovascular morbidity. Despite these findings, many believe that the data supporting the existence of an adverse interaction between aspirin and ACE inhibitors are not sufficiently compelling to justify altering the current practice of prescribing the two agents together. In contrast, many physicians would consider the use of an alternative antiplatelet agent such as clopidogrel (which does not interact with ACE inhibitors and may have superior effects in preventing ischemic events).

Risks of Treatment

Hypotension. Hypotension is seen most frequently during the first few days of initiation of or increments in therapy, particularly in patients with hypovolemia, a recent marked diuresis or severe hyponatremia (serum Na <130 mmol/L). Hypotension is generally a concern only if accompanied by postural symptoms, worsening renal function, blurred vision or syncope. The risk of hypotension may be minimized by reducing the dose of diuretics, liberalizing salt, or both as long as the patient does not have significant fluid retention. Most patients who experience symptomatic hypotension remain excellent candidates for long-term ACE inhibition if appropriate measures are taken to minimize recurrent hypotensive reactions.

Worsening renal function. ACE inhibitors can worsen renal function, particularly in patients who have severe symptoms, hyponatremia or bilateral renal artery stenosis or who are receiving non-steroidal anti-inflammatory drugs. Renal function usually improves following a reduction in the dose of concomitantly administered diuretics, and thus, can generally be managed without the need to withdraw the ACE inhibitor. However, if the dose of diuretic cannot be reduced because the patient has fluid retention, the patient may need to tolerate mild to moderate degrees of azotemia to maintain therapy with the ACE inhibitor.

Potassium retention. In general, hyperkalemia is seen in patients whose renal function deteriorates or who are taking potassium supplements or potassium-sparing diuretics, especially if they have diabetes.

Cough. The cough associated with ACE inhibitors is characteristically nonproductive; is accompanied by a persistent "tickle" in the back of the throat; usually appears within the first months of therapy; disappears within 1-2 weeks of discontinuing treatment; and recurs within days of rechallenge. Other causes of cough must be considered (especially pulmonary congestion), and the ACE inhibitor be implicated only after these have been excluded. Before abandoning treatment, physicians should demonstrate that the cough disappears following drug withdrawal and recurs following rechallenge. Physicians should encourage patients to continue taking these drugs if the cough is not severe. Only if the cough proves to be persistent and troublesome should the physician consider withdrawal of the ACE inhibitor and the use of alternative medications (e.g., angiotensin receptor antagonist).

Angioedema. Because its occurrence may be life-threatening, the clinical suspicion of this reaction justifies subsequent avoidance of all ACE inhibitors for the lifetime of the patient.

6.3.2.3 Beta-Adrenergic Receptor Blockers

Recommendations for Use. All patients in the STICH Trial should be receiving long-term treatment with a beta-blocker, unless there is a specific contraindication or the patient has been shown to be unable to tolerate treatment with these drugs. Patients need not be receiving high doses of ACE inhibitors before being considered for treatment with a beta-blocker, since most patients enrolled in the beta-blocker trials were not receiving high doses of ACE inhibitors. Furthermore, in patients receiving a low dose of an ACE inhibitor, the addition of a beta-blocker produces a greater improvement in symptoms and reduction in the risk of death than an increase in the dose of the ACE inhibitor.

Appropriate reasons for not using a beta-blocker include: (1) symptomatic or severe bradycardia or advanced heart block (unless treated with a pacemaker); (2) reactive airways disease; or (3) peripheral vascular disease that may jeopardize limb viability. Beta-blockers should not be initiated in patients who require intensive care, have evidence of fluid overload or have recently required treatment with an intravenous positive inotropic agent. Such patients should first receive intensified treatment with other drugs for heart failure (e.g., diuretics) and then be re-evaluated for beta-blockade after clinical stability has been achieved. Patients who have had fluid retention or worsening heart failure during a prior exposure to beta-blockade remain good candidates for long-term beta-blockade. Beta-blockers are not contraindicated in patients with diabetes mellitus or chronic pulmonary disease (without a bronchospastic component).

Practical Use of Beta-Blockers

Initiation and Maintenance. Treatment with a beta-blocker should be initiated at very low doses followed by gradual increments in dose if lower doses have been tolerated. Patients should be monitored closely for changes in vital signs and symptoms and increase in body weight during this uptitration period.

What dose of a beta-blocker should physicians try to achieve? As in the case of ACE inhibitors, the dose of beta-blockers in controlled clinical trials was not determined by a patient's therapeutic response but was increased until the patient received a prespecified target dose. Low or intermediate doses were prescribed if higher doses could not be tolerated. Only one trial (with carvedilol) compared the effects of different doses of a beta-blocker. Although high doses produced greater increases in ejection fraction than low doses in this study, both doses improved cardiac function and were associated with a lower risk of death or hospitalization. Nevertheless,

physicians should make every effort to achieve the target doses of the beta-blockers shown to be effective in major clinical trials.

Risks of Treatment

Fluid retention and worsening heart failure. Initiation of a beta-blocker can cause fluid retention, which is usually apparent as asymptomatic weight gain, but may lead to worsening heart failure. Patients with fluid retention before treatment are at greatest risk of fluid retention during treatment; thus, beta-blockers should not be started in those patients who are volume overloaded. Following initiation of treatment, physicians should monitor patients closely for increases in weight and, if weight increases, should augment the dose of diuretic until the patient's weight is restored to pretreatment levels, whether or not other signs or symptoms of worsening heart failure are present. The occurrence of fluid retention or worsening HF is not generally a reason for the permanent withdrawal of treatment. Such patients generally respond favorably to intensification of diuretics, and once treated, such patients remain excellent candidates for long-term treatment with a beta-blocker.

Fatigue. Beta-blockers can cause general fatigue or weakness. In many cases, these symptoms resolve spontaneously without treatment, but in others, they may be severe enough to limit increments in dose. Treatment with the beta-blocker should be discontinued if the syndrome of weakness is accompanied by evidence of peripheral hypoperfusion.

Bradycardia and heart block. The slowing of heart rate and cardiac conduction produced by beta-blockers is generally asymptomatic and requires no treatment. However, if the bradycardia leads to dizziness or lightheadedness or if second or third degree heart block occurs, physicians should decrease the dose of the beta-blocker. Physicians should also consider the possibility of drug interactions, since other drugs can cause bradycardia or heart block and may be discontinued. In selected patients the benefits of beta-blockers may be deemed to be so important that, if low doses cause symptomatic bradycardia or heart block, cardiac pacing could be considered to allow the use of beta-blockers.

Hypotension. Beta-blockers (especially those that also block α_1-receptors) can produce hypotension, which is usually asymptomatic but may lead to dizziness, lightheadedness or blurred vision. These vasodilatory side effects are generally seen within 24-48 hours of the first increments in dose and usually subside with repeated dosing without any change in dose. Physicians may minimize the risk of hypotension by administering the beta-blocker and ACE inhibitor at different times during the day or by a temporary reduction in the dose of the ACE inhibitor. Hypotensive symptoms may also resolve following a decrease in the dose of diuretics in patients who are volume depleted, but in the absence of such depletion, relaxation of diuretic therapy may increase the risk or consequences of fluid retention.

6.3.3 Interventions to Be Considered in Selected Patients in STICH (appropriate but not required)

6.3.3.1 Digoxin

Digoxin improves the symptoms and clinical status of patients with HF, when used in conjunction with conventional drugs. In addition, in a large-scale trial, digoxin reduced the risk of hospitalization for heart failure, but did not prolong life. In this study, use of digoxin was associated with an increased frequency of hospitalizations for cardiovascular events other than HF and an increased risk of death due to arrhythmias or myocardial infarction. These effects may have neutralized any benefit on survival which might otherwise have been seen as a result of the drug's favorable effect on HF.

Digoxin is commonly initiated and maintained at a dose of 0.125-0.25 mg daily. Lower doses (0.125 mg daily or every other day) should be used if the patient is over 70 years old, has impaired renal function or has a low lean body mass. Higher doses (e.g., 0.375-0.50 mg daily) are rarely used or needed for heart failure. Digoxin should be used cautiously for patients receiving other drugs that can depress sinus or AV nodal function or are known to increase serum levels of the drug (e.g., amiodarone and spironolactone). Although some have advocated using serum levels to guide dosing, the radioimmunoassay for digoxin was developed to assist in the evaluation of the toxicity (and not the efficacy) of the drug. There may be little relationship between the serum digoxin level and the drug's therapeutic effects in HF.

Recommendations for Use. Most patients in the STICH Trial are expected to receive long-term treatment with digoxin. Digoxin may be used early to reduce symptoms for patients who have been started on but have not yet responded symptomatically to an ACE inhibitor or a beta-blocker. Alternatively, digoxin may be delayed until the patient's response to ACE inhibitors and beta-blockers has been defined and used only for patients who remain symptomatic despite therapy with the neurohormonal antagonists.

6.3.3.2 Aldosterone Antagonists (Spironolactone)

In a large-scale trial, the addition of low doses of spironolactone to patients with recent or current class IV symptoms who were receiving an ACE inhibitor reduced the risk of death and hospitalization. The most marked effects were seen in patients who were also receiving digitalis and beta-blockers. Adverse reactions included hyperkalemia and gynecomastia (in men).

Recommendations for Use. The addition of spironolactone (25 mg daily) should be considered for patients with recent or current symptoms at rest despite the use of digoxin, diuretics, an ACE inhibitor and a beta-blocker. Patients should have a serum potassium < 5.0 mmol/L and a serum creatinine < 2.5 mg/dL before initiating therapy, and both variables should be monitored closely during treatment. Hyperkalemia may complicate treatment at any time and lead to life-threatening bradyarrhythmias. It is therefore prudent to reduce or stop potassium supplements when therapy with spironolactone is started. If the serum potassium increases to a level > 5.4 mmol/L, physicians should reduce the dose of spironolactone. The drug should be stopped if hyperkalemia or painful gynecomastia develop.

The role of spironolactone for patients with mild-to-moderate HF has not been defined, and use of the drug is not recommended in such individuals.

6.3.3.3 Angiotensin Receptor Blockers

Experience with angiotensin receptor blockers in controlled clinical trials of patients with HF is less than with ACE inhibitors. In one trial patients tended to have a better survival with an ACE inhibitor than with an angiotensin receptor blocker. In a second study, the addition of the angiotensin receptor antagonist valsartan (target dose 160 mg twice daily) to conventional therapy reduced the combined endpoint of death and hospitalization for HF but did not improve survival. Subgroup analysis indicated that (1) most of the benefit was seen in patients not receiving an ACE inhibitor; (2) the benefit of adding valsartan to patients receiving an ACE inhibitor was small; and (3) the drug exerted an adverse effect on both morbidity and mortality in patients receiving both an ACE inhibitor and a beta-blocker.

Recommendations for Use. Angiotensin receptor blockers should not be considered equivalent or superior to ACE inhibitors in the treatment of HF. Thus, they should not be used for the treatment of HF in patients who have no prior use of an ACE inhibitor and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty. Angiotensin receptor blockers should be considered primarily in patients who are intolerant of ACE inhibitors due to angioedema or intractable cough. Beta-blockers (rather than angiotensin receptor antagonists) should be added to patients receiving an ACE inhibitor, and angiotensin receptor antagonists should not be added to patients receiving an ACE inhibitor and a beta-blocker.

6.3.3.4 Hydralazine and Isosorbide Dinitrate

In a placebo-controlled trial, the combination of hydralazine (target dose 300 mg daily) and isosorbide dinitrate (target dose 160 mg daily) reduced mortality (but not hospitalizations) in patients with HF treated with digoxin and diuretics but not an ACE inhibitor or beta-blocker. However, in another study that compared the vasodilator combination with an ACE inhibitor, the ACE inhibitor produced more favorable effects on survival. In both trials, the use of hydralazine and isosorbide dinitrate produced frequent adverse reactions (primarily headache and gastrointestinal complaints), and many patients could not be maintained on treatment at target doses. There is no controlled experience with the addition of hydralazine and isosorbide dinitrate to patients receiving an ACE inhibitor or a beta-blocker.

Recommendations for Use. The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of HF in patients who have no prior use of an ACE inhibitor and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty. Despite the lack of data with the vasodilator combination in patients who are intolerant of ACE inhibitors, the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in patients who cannot take an ACE inhibitor because of hypotension or renal insufficiency. However, compliance with this combination has generally been poor due to the large number of tablets required and the high incidence of adverse reactions. Furthermore, since there are no controlled trials evaluating the utility of the hydralazine and isosorbide dinitrate combination in patients already receiving an ACE inhibitor, other agents (e.g., beta-blockers) should be considered first in such patients.

6.3.3.5 Synchronized Biventricular Pacing

Some patients with HF have asynchronous ventricular electrical activation (as reflected by a prolonged QRS duration on the ECG), which may contribute to the hemodynamic and clinical abnormalities of the syndrome. Such asynchronous contraction can be corrected by electrically activating the right and left ventricles in a synchronized manner with a pacemaker. In a controlled trial of 6 months' duration, synchronized biventricular pacing improved symptoms and exercise tolerance in patients with class III or IV symptoms and a QRS duration > 130 msec. However, implantation of a resynchronization device carries an important risk of coronary sinus perforation. Furthermore, the long-term efficacy and safety of cardiac resynchronization are unknown.

Recommendations for Use. Synchronized biventricular pacing may be considered in conjunction with drug therapy to improve symptoms in patients with class III or IV symptoms and a QRS > 130 msec.

6.3.4 Interventions in the Hospitalized Patient

Patients with decompensated HF characteristically have symptoms at rest or on minimal exertion and typically require hospitalization for intensive management. These individuals should be considered for specialized treatment strategies such as aggressive fluid management and intravenous pharmacological support, and if at the end-stage of the disease, for cardiac transplantation and mechanical circulatory support.

6.3.4.1 Aggressive Fluid Management

Most patients with decompensated or end-stage HF have symptoms that are related to the retention of salt and water and will respond favorably to interventions designed to restore sodium balance. Control of fluid retention may require progressive increments in the dose of an intravenously administered loop diuretic and frequently the addition of a second diuretic that has a complementary mode of action (e.g., metolazone) or a drug that can increase renal blood flow (e.g., intravenous dopamine and dobutamine). Attempts to elicit a diuresis may lead to worsening azotemia, but as long as renal function stabilizes, small or moderate elevations of blood urea nitrogen and serum creatinine should not lead to efforts to minimize the intensity of therapy. If the degree of renal dysfunction is severe or if the edema becomes resistant to treatment, ultrafiltration or hemofiltration may be needed to achieve control of fluid retention.

In general, patients should not be discharged from the hospital until a stable and effective diuretic regimen is established, and ideally, not until euvolemia is achieved. Patients who are sent home before these goals are reached are at high risk of recurrence of fluid retention and early readmission, because unresolved edema may itself attenuate the response to diuretics.

6.3.4.2 Cautious Use of Neurohormonal Inhibitors

Controlled trials suggest that patients with advanced HF respond favorably to treatment with both ACE inhibitors and beta-blockers in a manner similar to those with mild-to-moderate disease. However, because neurohormonal mechanisms play an important role to support circulatory homeostasis as HF progresses, neurohormonal antagonism may be less well tolerated by patients with severe symptoms than by patients with mild symptoms. Specifically, patients who have decompensated or end-stage HF are at particular risk of developing hypotension and renal insufficiency following the administration of an ACE inhibitor and of experiencing worsening HF following treatment with a beta-blocker.

What should physicians do when patients receiving long-term treatment with ACE inhibitors and beta-blockers are hospitalized for worsening HF? If the exacerbation is mild, both classes of drugs can be continued while concomitant therapy is intensified. However, if patients are hemodynamically unstable or responding poorly to diuretics, treatment with the ACE inhibitor and beta-blocker should be withheld until the status of the patient stabilizes. Once stability is achieved, treatment with an ACE inhibitor and beta-blocker should be reinitiated to reduce the risk of future exacerbations; patients should be started on very low doses and followed closely for signs or symptoms of intolerance. Patients with decompensated or end-stage HF may tolerate only small doses of neurohormonal antagonists; however, clinical trials with lisinopril and carvedilol suggest that even low doses of these drugs may provide meaningful benefits.

6.3.4.3 Intravenous Peripheral Vasodilators and Positive Inotropic Agents

Patients hospitalized with refractory HF commonly receive infusions of positive inotropic agents (dobutamine, dopamine or milrinone) or vasodilator drugs (nitroglycerin or nitroprusside) alone or in combination to improve cardiac performance, facilitate diuresis and promote clinical stability. The use of these drugs may be guided by hemodynamic measurements obtained through a pulmonary artery catheter. Some physicians have proposed the use of invasive hemodynamic measurements to guide the selection and dosing of agents for oral therapy as well, but such an approach has been questioned since many useful drugs for HF produce benefits by mechanisms that cannot be evaluated by measuring their short-term hemodynamic effects. Regardless of whether invasive hemodynamic monitoring is used, every effort should be made to devise an oral regimen that can maintain the symptomatic improvement achieved with intravenous drugs and reduce the subsequent risk of deterioration.

Patients who cannot be weaned from intravenous onto oral therapy on multiple occasions may require placement of an indwelling line to allow for the continuous infusion of dobutamine or milrinone. Such a strategy is commonly used in patients who are awaiting cardiac transplantation, but it may also be utilized in the outpatient setting in patients who otherwise cannot be discharged from the hospital. The use of continuous intravenous inotropic support to allow hospital discharge should be distinguished from the administration of *intermittent* infusions of positive inotropic agents to patients who have been successfully weaned from inotropic support. The long-term use of regularly scheduled intermittent infusions at home, in an outpatient clinic, or in a short-stay unit is strongly discouraged, even in advanced HF.

6.3.4.4 Mechanical and Surgical Strategies

Surgical and mechanical approaches for the treatment of end-stage HF include; (1) cardiac transplantation; (2) extra-corporeal devices for patients who are expected to recover from a major cardiac insult or to receive a definitive treatment for HF; and (3) left ventricular assist devices as a bridge to transplant or as destination therapy.

6.3.5 Management of Concomitant Disorders

Appropriate management of concomitant illnesses may produce symptomatic and prognostic benefits that may be as important as the treatment of HF itself.

6.3.5.1 Coronary Artery Disease and the Prevention of Ischemic Events

Since all patients in the STICH Trial will have CAD, physicians should seek to control vascular risk in all patients enrolled in the study.

6.3.5.1.1 Management of Lipid Disorders. Therapy with a statin has been shown to reduce the risk of death and of HF in patients with a history of myocardial infarction but without HF, even in patients without elevated levels of serum cholesterol. However, little is known about the benefits of treating hypercholesterolemia in patients with established symptoms of HF. The lack of such data is noteworthy, since (1) the progression of HF is frequently associated with decreases in serum lipids (as a result of cardiac cachexia); and (2) the benefits of lipid lowering may be seen only during periods of treatment that exceed the expected lifespan of many patients with HF. Nevertheless, it is prudent to manage hypercholesterolemia in patients with HF as if patients did not have HF.

6.3.5.1.2 Prevention of Ischemic Events. Aspirin has been shown to reduce the risk of major cardiovascular events in patients without HF, but its ability to do so in patients with HF has not been established and concerns have been raised that aspirin may attenuate the hemodynamic and prognostic benefits of ACE inhibitors, For these reasons, the role of aspirin in preventing ischemic events in patients with chronic HF remains controversial. Alternative antiplatelet agents (e.g., clopidogrel) may not interact adversely with ACE inhibitors and may have superior effects in preventing clinical events.

6.3.5.1.3 Management of Hypertension. Physicians should seek to lower both systolic and diastolic blood pressure in accordance with published guidelines. Target levels of blood pressure are lower in patients with associated major cardiovascular risk factors (e.g., diabetes). An appropriate antihypertensive regimen frequently consists of several drugs used in combination. In devising such a regimen, drugs that are useful for the treatment of both hypertension and HF are preferred (e.g., diuretics, ACE inhibitors and β-blockers). Physicians should avoid the use of most calcium channel blockers (due to their cardiodepressant effects) or potent direct-acting vasodilators (due to their sodium retaining effects).

6.3.5.1.4 Management of Diabetes Mellitus. Physicians should make every effort to control hyperglycemia in patients with diabetes mellitus, although such control has not yet been shown to favorably affect the course of HF. Among available agents, the thiazolidinediones (e.g., rosiglitazone and pioglitazone) should be used with caution since they can cause sodium retention and may worsen HF. In addition to the control of blood glucose, diabetic patients should receive ACE inhibitors, which have been shown to prevent the development of renal disease and to lower the likelihood of cardiovascular death, myocardial infarction and HF in diabetic patients, even in those who do not have hypertension.

The drugs used in the management of HF in non-diabetic patients should be administered to those with diabetes, since ACE inhibitors and beta-blockers slow the progression of HF and prolong life in diabetic patients as well as in nondiabetic patients. Physicians should not avoid the use of beta-blockers in diabetic patients, despite fears that these drugs may mask symptoms of hypoglycemia produced by antidiabetic therapy or may exacerbate glucose intolerance or insulin resistance.

6.3.5.1.5 Management of Angina Pectoris. Patients who have both angina pectoris and HF should receive drugs that relieve angina along with drugs that are appropriate in the management of HF (e.g., nitrates and beta-blockers). Yet, the combination of the two drugs may produce little improvement in angina unless fluid retention is adequately controlled with diuretics. Most calcium channel blockers should be avoided in HF.

There is no evidence that pharmacological efforts to minimize the occurrence or severity of asymptomatic myocardial ischemia can exert meaningful benefits in patients with HF.

6.3.5.2 Cardiac Arrhythmias and the Prevention of Sudden Death

6.3.5.2.1 Supraventricular Arrhythmias. In most patients with HF, control of the ventricular rate is the primary goal of the treatment of supraventricular arrhythmia. The agent most commonly used to slow the ventricular response in patients with HF and atrial fibrillation is digoxin, but this drug slows AV conduction primarily at rest and not during exercise, and thus, it does not block the excessive exercise-induced tachycardia that may contribute to exercise tolerance. Beta-blockers are effective both at rest and during exercise and are preferred because of their favorable effects on the natural history of HF. Although both verapamil and diltiazem can also suppress the ventricular response during exercise, they can increase the risk of HF and should be avoided. If beta-blockers are ineffective or contraindicated, amiodarone may be a useful alternative, and AV nodal ablation may be needed if tachycardia persists despite pharmacologic therapy. Regardless of the intervention, every effort should be made to reduce the ventricular response to less than 80-90 beats/min at rest and less than 110-130 beats/min during moderate exercise. Control of ventricular rate should be combined with warfarin, which can reduce the risk of thromboembolic events in patients with atrial fibrillation.

Should patients with HF and atrial fibrillation be converted to and maintained in sinus rhythm? The benefits of restoring sinus rhythm remain unclear, and the difficulties and risks of doing so are considerable. Most patients who are electrically converted to sinus rhythm will revert to atrial fibrillation within a short time, unless they are treated with a Class I or Class III antiarrhythmic drug. However, patients with HF are not likely to respond favorably to Class I drugs and may be particularly predisposed to their cardio-depressant and proarrhythmic effects. Class III anti-arrhythmic agents (e.g., sotalol, dofetilide and amiodarone) can maintain sinus rhythm in some patients, but treatment with these drugs is associated with an increased risk of organ toxicity (amiodarone), proarrhythmia (dofetilide) or death (D-sotalol). Restoration of sinus rhythm is primarily warranted in patients in whom recurrent or sustained atrial arrhythmias are associated with worsening symptoms that can be directly attributed to the loss of atrial transport function.

6.3.5.2.2 Ventricular Arrhythmias and Prevention of Sudden Death. Patients with HF are at great risk for sudden death, but it is not clear whether the complex ventricular arrhythmias commonly found in such patients contribute to the high frequency of sudden death. In many patients sudden death is due to an acute ischemic event or to a bradyarrhythmia or electrical-mechanical dissociation; in others, lethal ventricular tachyarrhythmias may occur in patients without a history of worrisome arrhythmias. Nevertheless, some physicians have advocated the aggressive detection of ambulatory arrhythmias and the routine or selective use of antiarrhythmic interventions in patients with advanced ventricular dysfunction. However, such a strategy has not led to a reduction in the risk of sudden death in controlled clinical trials. Furthermore, most antiarrhythmic drugs have proarrhythmic and negative inotropic effects, particularly in patients with systolic dysfunction. As a result, physicians should not use ambulatory electrocardiographic monitoring to detect asymptomatic ventricular arrhythmias in patients with HF, and they should not

attempt to treat such arrhythmias if detected. However, physicians should make every effort to prevent the occurrence of sudden death. Three types of interventions may be used to accomplish this goal: (1) beta-adrenergic blocking drugs; (2) amiodarone; and (3) implantable cardioverter-defibrillator (ICD).

Beta-Adrenergic Blocking Drugs. Beta-blockers reduce the risk of sudden death (as well as all-cause mortality) in both post-infarction patients and in patients with HF. As a result, patients with ventricular systolic dysfunction should routinely receive long-term treatment with a beta-blocker, unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs.

Amiodarone. In one randomized open-label trial, amiodarone therapy was associated with a significant reduction in the risk of death, but in a second double-blind trial, amiodarone had little effect on all-cause mortality or on the combined risk of death or hospitalization for HF, except possibly in patients with a nonischemic cardiomyopathy. Because of uncertainty surrounding its benefits and concerns about its toxicity, the routine use of amiodarone to prevent sudden death is not recommended. The drug may be useful primarily in suppressing the recurrence of a lethal ventricular arrhythmia (alone or in conjunction with a beta-blocker and an ICD) in patients with a history of sudden death, ventricular fibrillation or sustained or hemodynamically destabilizing ventricular tachycardia.

Implantable Cardioverter-Defibrillator (ICD). Implantation of an ICD has been shown to reduce mortality in cardiac arrest survivors and in patients who have a history of a myocardial infarction and a reduced ejection fraction, whether or not nonsustained ventricular tachycardia is found on ambulatory monitoring or a sustained ventricular tachyarrhythmia can be induced during electrophysiologic testing. However, it is unclear whether these results can be extrapolated to the general population of patients with established HF. A large-scale, long-term trial of defibrillator therapy in a broad population of patients with chronic HF is now ongoing. Until this trial is completed, implantable cardioverter-defibrillators should be used when indicated.

6.3.5.3 Cardiac Thrombi and the Prevention of Thromboembolic Events

There have been no controlled trials of antithrombotic agents in patients with HF. Although patients with HF are at increased risk of thromboembolic events, the risk of thromboembolism in clinically stable patients is low (1-3% per year), even in those with very depressed ejection fractions and echocardiographic evidence for intracardiac thrombi. These rates may be sufficiently low to limit the detectable benefit of anticoagulation. In several retrospective analyses, the use of warfarin was not associated with a lower risk of thromboembolic events. In patients with HF, warfarin therapy was associated with a reduction in major cardiovascular events in one retrospective analysis but not in another.

Despite the lack of supportive data, some physicians prescribe anticoagulants to all patients with markedly depressed ejection fractions and dilated hearts. Others advocate the use of warfarin in patients who harbor a cardiac thrombus, even though many thrombi detected by echocardiography do not embolize and many embolic events are probably related to thrombi that are not visualized. Anticoagulation with warfarin is most justified in patients who have experienced a previous embolic event or who have paroxysmal or chronic atrial fibrillation.

6.3.5.4 Noncardiovascular Disorders

Renal Insufficiency. Most patients with HF tolerate mild to moderate degrees of functional renal impairment without difficulty. In most individuals, changes in blood urea nitrogen and serum creatinine are generally clinically insignificant and can be managed without the withdrawal of drugs needed to slow the progression of HF. However, if the serum creatinine increases to > 3 mg/dl, the presence of renal insufficiency can limit the efficacy and enhance the toxicity of established treatments. In patients with a serum creatinine > 5 mg/dl, hemofiltration or dialysis may be needed to control fluid retention, minimize the risk of uremia and allow the patient to respond to and tolerate the drugs used for the management of HF.

Pulmonary Disease. Some drugs used to treat HF can produce or exacerbate pulmonary symptoms. ACE inhibitors can cause a persistent nonproductive cough that can be confused with a respiratory infection, and conversely, ACE inhibitors may be inappropriately stopped in patients with pulmonary causes for cough. Beta-blockers (regardless of their selectivity) can aggravate bronchospastic symptoms in patients with asthma and should not be given to patients with reactive airways disease. However, most patients with chronic obstructive pulmonary disease do not have a bronchospastic component to their illness and remain reasonable candidates for selective and nonselective beta-blockade.

Pain (arthritic and non-arthritic). Pain in patients with HF should be treated with acetaminophen, or if severe, with a combination of acetaminophen and codeine. Nonsteroidal anti-inflammatory drugs (including high doses of aspirin and COX-2 specific inhibitors) should be avoided, since they can cause fluid retention, systemic vasoconstriction and worsening renal function and may interfere with the actions of diuretics and ACE inhibitors. In addition, agents that block the actions of tumor necrosis factor (e.g., infliximab) have been reported to worsen HF and should be avoided. Corticosteroids can cause both sodium retention and potassium depletion and should be used at the lowest possible dose for the shortest possible time.

6.4 Monitoring Safety of Therapies Compared in the STICH Trial

6.4.1 Principles for Monitoring Safety

Clinical practice suggests the following assumptions are reasonable considerations in developing principles for monitoring the safety of three therapies during patient enrollment:

- The advanced ischemic heart disease characteristic of all STICH patients suggests that as many as 10% of patients may have serious adverse events within the first 30 days of treatment.

- The two surgical therapies are expected to have adverse events clustered near the time of operation with subsequent diminution of the rate as benefit is realized from the procedure. In comparison, MED is expected to have a lower adverse event rate than surgical therapy but with time this event rate may persist and exceed that of the surgical therapies.

- The additive design of the trial that requires all SVR patients to also receive CABG and MED and all CABG patients to also receive MED suggests that MED should have the least and CABG + SVR + MED should have the most short-term adverse outcomes.

- The negative impact of an adverse therapy may be amplified by the therapy with which it is combined. For example, renal dysfunction associated with ACE inhibitor therapy may be of greater seriousness in a surgical patient than a patient treated with MED alone.

- The potential adverse effect of one therapy may be masked by the acute beneficial effect of another therapy with which it is combined. For example, postoperative worsening of left ventricular dysfunction associated with a CABG operation may be less apparent if a SVR operation is also done to acutely restore a more normal left ventricular chamber size.

The complexity of these five reasonable assumptions about the occurrence of serious adverse events in STICH Trial patients leads to the following practical principles for monitoring the safety of therapies compared in the STICH Trial:

- A strategy of monitoring rates of occurrence of adverse events among therapies will be preferable to a strategy of urgent reporting of isolated adverse events.

- The severity of adverse events must be evaluated in addition to the rates of occurrence.

- Expected rates of occurrence of adverse events in the MED population can be readily derived from reported adverse events in clinical trials in patient groups with characteristics similar to STICH patients who were treated with similar drug regimens to those planned for use in the STICH Trial.

- Expected rates of adverse CABG events can be derived from large standardized clinical databases, such as the STS and New York State experience.

- Attention to reporting and adjudication of details of the occurrence of serious adverse events should be reserved for those adverse events that occur above the prespecified threshold for any monitoring interval.

6.4.2 Approach to Defining and Monitoring Serious Adverse Events

All serious adverse events in this high risk population will be monitored and collected. The rate of SAE's will be used to assess the safety of the treatment. SAE's will be reported in the following manner:

- Those that are serious, unexpected, and protocol related will require expedited reporting (within 24-72 hours) to the DCRI Safety Surveillance Desk and the Regional Coordinating Center if ex-US.

The following events will be collected in all STICH patients receiving randomized treatments and will be reported to the Coordinating Center with the CRF Visit Form:

- Worsening renal insufficiency.
- Acute myocardial infarction.
- Need for left ventricular assist device or heart transplantation.
- Stroke

In addition to the adverse events listed above the following adverse events will be collected on patients receiving surgical treatments and will be reported to the Coordinating Center with the CRF Visit Form:

- Return to the operating room for bleeding
- Return to the operating room for other reason
- Mediastinitis

The DSMB will be provided data from documented sources supporting the best available estimates of anticipated rates of occurrence of these serious adverse events to be monitored.

Because of anticipated differences in baseline characteristics associated with disease severity among the three randomization strata, serious adverse event monitoring will compare treatment event rates within strata as well as total event rates by overall treatment assignment. The first observation of event rates will be reported to the DSMB when ten patients have been enrolled in each comparative treatment within a stratum and when enrollment within any stratum totals 50 patients. This reporting interval will also summarize events for each of the three treatment groups.

After review of these initial data, the DSMB will define the frequency of reporting intervals for the duration of the trial.

Whenever the DSMB has sufficient concern about safety of any treatment upon review of serious adverse event rates, a directive to the study chairman and principal investigator defining the serious adverse event of concern will prompt immediate notification of all clinical sites that the subsequent occurrence of this adverse event will require completion of a serious adverse event form. Information on this serious adverse event form and associated documentation will be reviewed by a group of Coordinating Center cardiovascular physicians not associated with the STICH Trial. Information will be summarized in a form suitable for review by the external Endpoints Committee that will adjudicate all events and submit their report to the DSMB.

6.4.3 Reporting Unexpected Protocol Related Serious Adverse Events

All adverse events that occur from randomization through the follow up period that result in death and/or **unexpected protocol related SAEs** are to be reported by fax in an expedited fashion (24-72 hours) to the DCRI Safety Surveillance Department on an “Serious Unexpected SAE Form”, in addition, deaths should be reported on an “End of Study Form”.

Examples of serious, unexpected, protocol related major events include, but are not limited to:

- Major, disabling stroke.
- New, acute renal insufficiency requiring dialysis.
- Ventricular rupture.
- New Ventricular Septal Defect.
- Peripheral arterial embolization requiring surgery or percutaneous intervention.
- Death
- Other – defined by the PI, as meeting above SAE definition.

7. PATIENT FOLLOW-UP

At each four month follow-up interval, a Clinical Follow-up CRF will be completed. Additional studies required at 4, 12, 24, 36 and 48 months are summarized in Table 3. It is recommended that the patient be seen by the physician at each 4 month visit. In situations when patients cannot or will not return for follow up in clinic, an interview by telephone should be used to obtain all requested information except that requiring direct patient contact. The final four month visit will require completion of the End of Study Form.

Table 3. Follow-up Evaluation Studies

Interval	Patient Characteristics	Stratum A	Stratum B	Stratum C
4 Months	All Patients	ECHO to Core EuroQOL to Core	ECHO to Core EuroQOL to Core V-gram to Core (CMR, SPECT, or Echo)	ECHO to Core EuroQOL to Core V-gram to Core (CMR, SPECT, or Echo)
	When Feasible	NCG Blood to Core	NCG Blood to Core	NCG Blood to Core
	Patients ABLE	6-minute Walk	6-minute Walk	6-minute Walk
12 Months	All Patients	EuroQOL to Core	EuroQOL to Core	EuroQOL to Core
	Patients ABLE	6-minute Walk	6-minute Walk	6-minute Walk
24 Months	All Patients	ECHO to Core EuroQOL to Core	ECHO to Core EuroQOL to Core V-gram to Core (CMR, SPECT, or Echo)	ECHO to Core EuroQOL to Core V-gram to Core (CMR, SPECT, or Echo)
	Patients ABLE	6-minute Walk Exercise Stress	6-minute Walk Exercise Stress	6-minute Walk Exercise Stress
36 Months	All Patients	EuroQOL to Core	EuroQOL to Core	EuroQOL to Core
	Patients ABLE	6-minute Walk	6-minute Walk	6-minute Walk
48 Months	All Patients	EuroQOL to Core	EuroQOL to Core	EuroQOL to Core
	Patients ABLE	6-minute Walk	6-minute Walk	6-minute Walk

8. DATA MANAGEMENT

8.1 Data Collection Process

Database management and quality control for the STICH trial are the responsibility of the DCRI. Clinical Site Investigators must collect all information required by the protocol on an appropriate STICH Case Report Form (CRF). The CRFs will be printed on three-part no-carbon-required (NCR) paper. All entries to the CRF must be made clearly with a black ballpoint pen to ensure the legibility of self-copying pages. Corrections are made, initialed and dated by an authorized member of the Clinical Site Core Team by placing a single horizontal line through the incorrect entry, so that the original entry remains visible, and placing the correct entry beside it. Correction fluid (white out) or correction tape should not be used. Additional CRF insert pages are available in the Additional Pages Binder. All data on the CRF must be verifiable from a source document (the original record form or report where patient information is written or reported). Examples of source documents include hospital/clinic records, patient diaries, discharge summary, transfer

records, ambulance records, laboratory reports, ECGs, x-rays, and worksheets. When submitting **source documents**, blacken or mark out all patient identifying information (patient name, address, medical record number) but **do not** blacken out dates or times. Attach a label and record the patient identifiers (patient number and patient initials) on each page of the documents submitted.

8.2 Recording Information on CRF Page and Source Documents

To insure patient confidentiality, all data forms and source documents are identified by a unique site and patient number. Therefore, routine data management tasks can be completed easily while maintaining patient anonymity. This approach requires numbering of every page of every CRF and source document.

Patient number: Record the 4-digit site number that identifies your site and the 4-digit patient number written on the IVRS worksheet at the time the patient number is assigned from the IVRS.

Patient Initials: Record as First Middle Last. If there is no middle initial, record a dash (-). For hyphenated last names, record the initial of the first part of the hyphenated name. Record initials consistently throughout the CRF.

Do not leave blanks for any expected data fields; e.g., when Yes is checked, all subquestions must be completed.

Record dates using numbers for the day and year, and the three letter abbreviation for the month (e.g.) February 9, 2002 = 09/FEB/2002). If part or all of the date is unknown, record ND in the appropriate blank(s).

January = JAN	April = APR	July = JUL	October = OCT
February = FEB	May = MAY	August = AUG	November = NOV
March = MAR	June = JUN	September = SEP	December = DEC

Record time using a 24-hour clock from 00:00 (midnight) to 23:59. DO NOT RECORD 24:00.

Midnight = 00:00
15 minutes after noon = 12:15
Last entry on a day = 23:59

8.3 Submitting Case Report Forms

The investigator must sign each CRF before submitting it to the DCRI. Envelopes and Federal Express airbills will be provided to sites for the submission of CRFs and source documents. The Confidential Patient Information page should be placed in separately provided confidential envelopes and submitted to the DCRI. Upon completion, the CRFs are separated into two parts, with the site retaining the pink copy in their study files and forwarding the white and yellow copies to the DCRI (see Table 4 for submission timeline). When patients die during the study, refer to the CRF instructions to determine the specific CRF pages that must be completed and submitted. Send the STICH submission envelope by Federal Express as instructed in the CRF instructions. Indicate the contents on the outside of the STICH submission envelope. Photocopy the Forms Submission Form to file in the patient study file before enclosing it in the submission envelope.

Table 4 Summarizes the title, categorical content and submission event for each STICH trial Case Report Form. Any change or correction found necessary to correct the original information previously submitted to the Coordinating Center must be made on the Data Clarification Forms (DCFs) and not on the original CRF pages. DCFs are obtained from the Coordinating Center monitor and when complete with the corrected entry and signed are submitted in the same manner as a CRF.

8.4 Maintaining the Clinical Site Patient File

Keep the following documents in the clinical site patient study file for each patient entered in the STICH trial.

- Copy of Confidential Patient Information page
- STICH IVRS Worksheet
- Original signed Consent Form
- Site copy of submitted CRF pages and the site copies of all Forms Submission Forms
- Copies of all submitted source documents
- Completed and signed Data Clarification Forms
- Patient information related to core laboratory studies
- Initial Evaluation – within 5 days
- Baseline – within five days
- Treatment (medical therapy/surgery) – within 30 days
- Hospitalization End of Study – within 30 days
- Follow Up – within 5 days

TABLE 4. STICH Trial Case Report Forms

Form Title	Categorical Content	CRF Completion and Submission Guidelines
Confidential Patient Information	Patient identification Secondary residence Alternative contact Referring physician	Complete at patient enrollment (enrollment = signing ICF). Submit within 5 days.
Initial Evaluation	Demographics and vital signs Medical history Procedure history Current medications Laboratory studies Qualifying HF Cardiac catheterization LV dysfunction documentation studies Stratum qualification for all patients Disposition	Complete at randomization. Submit within 5 days of randomization.
Baseline	Core laboratory studies Exercise studies Stratum	Complete at randomization. Submit within 5 days.
Medical Treatment	Current medications Events after randomization until hospital discharge or within 30 days Endpoints Patient initially treated in hospital or as outpatient	Treatment to Discharge – 30 days (or 30 Days). Submit within 60 days of randomization.
Surgical Treatment	Events before surgery Endpoints before surgery Surgical data Efficiency data Current medications Events after surgery Endpoints after surgery Discharge information	Complete at Discharge or 30 days post randomization (whichever occurs first). Submit within 60 days post randomization.
Clinical Follow-up	Type of visit/contact History and vital signs Current medications Medical utilization	Complete at visit. Submit within 5 days.
4 Month Studies	Core laboratory studies EuroQOL 6 minute walk Study required on Strata B and C patients	Complete at visit. Submit within 5 days.
12, 36, or 48 Month Studies	EuroQOL 6 minute walk	Complete at visit. Submit within 5 days.
24 Month Studies	EuroQOL 6 minute walk Treadmill core laboratory studies Study required on Strata B and C patients	Complete at visit. Submit within 5 days.
Hospitalization	Reason for admission Procedures	Complete and submit within 30 days of admission.
End of Study	Reason for end of study	Death. Submit with SAE Form. Final visit, consent withdrawn. Complete and submit within 5 days.
Unexpected Protocol Related Serious Adverse Event	Serious reporting criteria SAE condition SAE onset date Outcome Narrative Information source	Faxed within 24-72 hours of investigators knowledge of event.

8.5 Coordinating Center Processing of CRF

The Coordinating Center will log receipt of the CRF and promptly evaluate completeness and accuracy of data to facilitate prompt reimbursement to the clinical site. Queries generated at any stage of the data management process either by missing data noted upon receipt or inconsistencies or omissions identified by automated and manual data-validated checks will prompt a Data Clarification Forms (DCFs) to be sent by fax or mail to clinical sites for resolution. The site receiving the DCF should review the issue identified by referring to appropriate source documents, complete the DCF, sign, and return to the Coordinating Center. Quality-control methods will be used throughout to maintain data integrity and audits will be performed at designated times during the study.

9. CLINICAL SITE MONITORING

9.1 Background

The monitoring of clinical sites ensures that:

- The study is conducted according to the protocol and in compliance with applicable regulations.
- There are adequate resources at the sites to conduct the trial.
- The required data are collected and recorded accurately.

To accomplish these goals, a DCRI site monitor will perform on-site visits during the enrollment phase of the trial. A visit will be made shortly after the first few patients are enrolled at each site and again at the end of enrollment to insure that patient enrollment and data collection proceeds properly. In the interim, telephone visits will be made annually. The monitor will determine the amount of time required for the visit based on the anticipated number of forms requiring review, but clinical site personnel should allow at least one full day for each visit. During the visit, the monitor will:

- Answer questions about the protocol, forms completion and endpoints.
- Assist with enrollment strategies for appropriate patients.
- Verify that the trial is proceeding according to protocol.
- Verify certain source data.
- Help ensure completion of and collection of late data forms.
- Review the regulatory documents file, including IRB approval.

Appendix 3 shows a complete list of items reviewed by the monitor during these visits.

In the STICH Trial, at least 10% of all case report forms (CRFs) will be randomly selected for source document verification. All information on each CRF selected (and available follow-up forms) will be verified against source medical records. In addition, Informed Consents and critical variables will be verified on all patients. The first 2 patients will be 100% source verified. Critical variables and ICFs will be verified for all patients randomized. For the STICH trial, critical variables will include, but are not limited to:

- Informed Consent Forms
- Inclusion/Exclusion Criteria
- Treatment Assignment
- SAEs

9.2 Monitoring Visits

After 3-5 patients are enrolled, the monitor will call to schedule a monitoring visit at a mutually convenient time. When the monitor calls to set an appointment, he or she will ask that all completed CRFs for patients enrolled since the previous monitoring visit be available for review. Signed Informed Consent Forms and hospital records also will be needed for these patients, to permit CRF data to be verified against the source data. This process not only ensures that the data being submitted are accurate but also enables the monitor to identify discrepancies that may require additional explanation.

The following arrangements will help the monitor work efficiently:

- Identify a quiet place for the monitor to work (an office, conference room, medical records department) that provides access to a phone, a fax and a copy machine.
- Complete the appropriate CRFs before the visit.
- Obtain the medical records for the patients identified for review.
- Obtain transfer records from outside hospitals, when applicable.
- Organize the regulatory document files for review.
- Confirm that all copies of the signed Informed Consent Forms for all patients enrolled at your site are available for review.
- Schedule time for the study coordinator to meet with the monitor to review all data forms monitored during the visit and to discuss the general progress of the trial (that is, enrollment strategies, ideas for generating enthusiasm, protocol adherence, etc.).
- Schedule time for the principal investigator to meet with the monitor to review the findings. About 30 minutes at the end of the day is recommended for this meeting.

9.2.1 Recording of Monitoring Visits

At the end of the visit, the monitor will review findings with both the study coordinator and principal investigator to assess if process change is needed, and will complete the Monitoring Log. A follow up letter will be sent to the principal investigator and study coordinator reviewing findings, action items and time frame for completion.

9.2.2 Source Documents

Source documents refer to the original information on the patient's condition before, during and after the trial. Source documents may include the following:

Medical history	Pharmacy records	Ambulance records
Physical exam forms	Medication records	Life flight records
Progress notes	Clinical worksheets	Transfer records
Laboratory results	Enrollment forms	
Diagnostic tests results	Autopsy reports	

9.2.3 Patient Recruitment Reports

During patient enrollment, enrollment reports will be provided to report on the status of site performance. Site specific enrollment data will be reviewed by the DCRI on a regular basis. If patient recruitment drops below one patient per month at any site, the Study Coordinator will be contacted and provided with suggestions on how to meet recruitment goals. The Study Leadership will contact Principal Investigators as appropriate to discuss more aggressive methods of improving enrollment.

9.2.4 Close-Out

When the study is completed, the monitor will conduct a phone close-out visit at each site. All CRFs, data clarifications and final review of the regulatory file must be completed at the time of this visit. Once the close-out procedure is completed the Principal Investigator must submit a letter informing the IRB that the clinical site has completed the trial. The STICH Trial Coordinating Center should be sent a copy of this letter.

10. ENDPOINTS

10.1 Required Source Documents for Endpoints

Clinical events identified by the investigator as possible primary or secondary endpoints will be adjudicated by the Endpoints Committee, who will not be blinded to treatment assignment. Study Coordinators are required to forward specific source documents described below to assist the Endpoints Committee in adjudicating events.

10.2 Death

All deaths will be adjudicated for cause. All deaths shall be considered cardiovascular unless an unequivocal noncardiovascular cause can be established. Deaths will be classified into the following categories: Arrhythmia/sudden death, HF, fatal MI, other cardiac death and noncardiovascular death.

In order to facilitate adjudication of deaths, study coordinators should forward the following source documents along with the CRF to the Coordinating Center.

- Sudden death – hospital discharge/death summary, autopsy report if available.
- Heart failure – hospital discharge/death summary, autopsy report if available.
- Fatal MI – hospital discharge/death summary, ECG performed during event, report of cardiac enzymes drawn during the event, autopsy report if available.
- Fatal stroke – hospital discharge/death summary, MRI or CAT Scan, autopsy report if available.
- Other cardiovascular – hospital discharge/death summary, autopsy report if available.
- Noncardiovascular – hospital discharge/death summary, autopsy report if available.

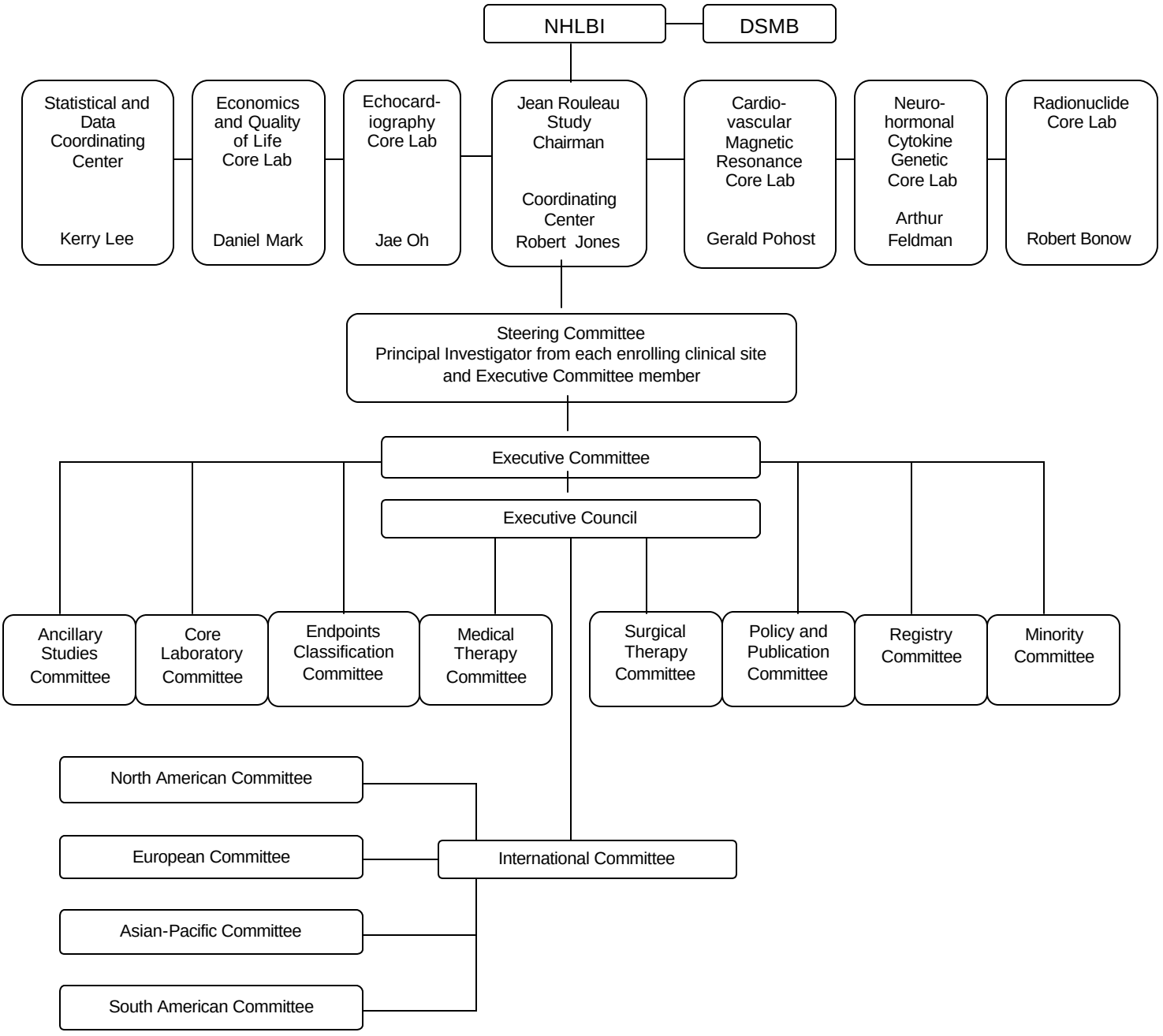
A clinical summary, signed by the principal investigator, may be used in place of a discharge summary when one is not available.

10.3 Hospitalization

Hospitalization is defined as inpatient status for >24 hours or an emergency department visit that spans >24 hours. All hospitalizations will be adjudicated through the first cardiac-cause hospitalization for each patient. To aid in the adjudication of hospitalizations, coordinators should send a hospital discharge summary for each new hospitalization to the Coordinating Center. For instances where the discharge summary (submit with CRF Hospitalization form) is not available, the investigator will complete a "Clinical Summary" and send to the Coordinating Center. When submitting discharge summaries, patient's name, medical record number, or other identifying numbers (e.g., social security number) must be blacked out. Place completed label on document to identify by site and patient number.

11. TRIAL ORGANIZATION

Figure 1. STICH Trial Organization



11.1 Overview of Organization

Opportunities to interact with peers in leadership roles represent one of the strongest motivations for young investigators to participate in a randomized trial. Moreover, an interactive network of peers setting an expectation of high quality enhances performance among all clinical sites. For these reasons, an integrated participatory leadership structure is important as well as for the coalescence of good decisions it brings to trial processes. Leadership opportunities will be given preferentially to investigators from high-enrolling sites, and positions will be held for pre-specified terms to permit participation of a large number of investigators over the course of the trial. The original leadership structure is being revised to reflect the global nature of the trial (Figure 1). The Executive and Steering Committees are now complemented by the addition of an International Committee comprised of chairmen of four regional committees (North American, European, Asian-Pacific, South American). The overall purpose of the regional international committees will be to mentor and support clinical sites within the regions named in all aspects of STICH Trial activation and patient recruitment work.