1. Chapter 1: Study Overview

Cardiovascular diseases remain the leading cause of death and a major cause of morbidity and disability among both men and women in the United States, with an estimated 13 million people reported as having symptomatic coronary heart disease (CHD). Approximately 1.5 million myocardial infarctions (MI) occur each year, with over 1/2 million deaths from MI (AHA, 1992). In 1993, an estimated 745,000 persons were hospitalized for MI alone. The direct and indirect costs of heart disease in the United States exceed $100 billion per year.

Recent data show that psychosocial factors, such as lack of social support and depression, are important predictors of morbidity and mortality in CHD patients (Ahern et al., 1990; Berkman et al., 1992; Carney et al., 1988; Frasure-Smith et. al., 1985, 1989, 1993; Williams et al., 1992). These studies suggest that interventions which provide support and/or alleviate depression in MI patients may enhance their psychosocial recovery and decrease morbidity and mortality. To the extent that psychosocial intervention can be shown to impact favorably on survival and recovery in MI patients, the human and financial burden associated with heart disease can be reduced.

However, the studies published to date have methodological weaknesses that limit their ability to conclusively evaluate the effects of psychosocial intervention in the treatment of post-MI patients. Many studies have used very small sample sizes, resulting in a lack of power to detect differences between treatment and control groups. In other cases, flawed randomization procedures, inadequate or unreliable ascertainment of clinical endpoints, differential loss to follow-up between treatment and control groups, and lack of "intent to treat" analyses make interpretation of findings difficult.

The purpose of the Enhancing Recovery in Coronary Heart Disease (ENRICHD) Patients Study is to conduct a multi-center clinical trial to determine the effects of psychosocial intervention, designed to increase social support and alleviate depression, on the combined endpoint of all cause mortality and nonfatal infarction in patients with recently diagnosed acute MI who are at high psychosocial risk, that is, who are depressed and/or have low social support. Secondary medical endpoints include all cause mortality; cardiovascular mortality; recurrent nonfatal MI; revascularization procedures; cardiovascular hospitalizations; and changes in risk factor profiles. Secondary psychosocial endpoints include severity of depression; degree of lack of social support; and health-related quality of life. The pilot phase involved assessment of the feasibility of recruiting and retaining post-MI patients for the trial. On the basis of the pilot phase, the trial continues to accrue sufficient numbers of patients to evaluate the effects of the intervention on mortality and reinfarction.

1.1 Objectives for ENRICHD

1.1.1 Primary Objective

The primary objective of the ENRICHD Patients Study is to evaluate the effects of interventions designed to increase social support and decrease depression in post-MI patients, relative to usual care, on a combined endpoint of all cause mortality and nonfatal infarction.
1.1.2 Secondary Objectives

Additional objectives are to:

(1) document the effects of the intervention relative to usual care on a variety of secondary outcomes of interest, including all cause mortality; cardiovascular mortality; recurrent nonfatal MI; revascularization procedures; cardiovascular hospitalizations; and changes in selected risk factor profiles; presence and severity of depression; degree and type of social support; and health-related quality of life.

(2) evaluate (to the extent possible, given limited statistical power) the effect of the intervention in subgroups defined by gender, minority status, and etiology of psychosocial risk.

(3) conduct exploratory studies where feasible of psychosocial, behavioral and physiologic mechanisms through which the psychosocial intervention used exerts effects on the clinical outcomes of interest.

1.2 Overview of Study Design

ENRICHD is a multi-center, randomized, controlled clinical trial. The study population will consist of 3,000 patients recently hospitalized with acute MI, who are at high psychosocial risk for mortality or re-infarction due to low social support or depression. The trial will evaluate the effect of a psychosocial intervention, in comparison to usual medical care, on the rates of mortality and re-infarction.

1.2.1 Project Schedule

The research plan involves a phased approach: During the first year of the trial (Phase I), an initial group of 400 patients was recruited, randomized and evaluated after six months of intervention. The objectives of Phase I were: (1) to determine the feasibility of recruiting adequate numbers of MI patients at high psychosocial risk to the trial; (2) to assess patient acceptance of and adherence to the intervention being studied; and, (3) to determine whether the intervention can be successfully delivered to the study population. Primary endpoints for Phase I will be measures of: patient recruitment, to include recruitment of women and minorities; patient adherence to protocol; and delivery of the psychosocial intervention and control group procedures, according to protocol.

Phase II involves enrolling 2,600 additional patients to allow a comparison of the effects of the psychosocial intervention with those of the usual care conditions on the endpoint of total mortality plus reinfarction.

1.2.2 Participant Eligibility

All study participants will be recruited during a hospitalization for a verified acute MI. Potential participants will be assessed for psychosocial risk and must meet standardized criteria for depression and/or low perceived social support to be eligible. Every effort will be made to enroll patients as soon after the event as possible; in all cases patients must be randomized within 28 days of onset to be eligible. In order to qualify on the basis of depression, patients must meet modified DSM-IV criteria for major or minor depression. In order to qualify on the basis of low perceived social
support patients must have a score of 2 or less on at least two items, excluding item #4 (help with chores); or a score of 3 or less on two items, excluding items #4 and 7 (help with chores and marital status) and a total score of 18 or less on items 1, 2, 3, 5, and 6 on the ENRICHD Social Support Instrument (ESSI). Details of the medical and psychological inclusion and exclusion criteria are described in Chapter 3.

1.2.3 Intervention

Patients in the psychosocial intervention group will receive interventions tailored to their individual deficits in psychosocial functioning. Treatment will begin with individual counseling, followed by group sessions, both based on cognitive-behavioral therapy. Severely depressed patients will receive standardized pharmacotherapy as indicated.

Patients in both groups will receive health education, to standardize knowledge of cardiovascular disease and its management. Both groups will receive standard medical treatment, as practiced in that institution.

1.2.4 Study Size and Duration

Three thousand patients will be recruited over a 36 month period. Follow-up of all patients will continue until the last patient randomized has completed eighteen months of follow-up. Thus follow-up time will range from a minimum of 1 1/2 to a maximum of 4 1/2 years; assuming uniform recruitment the average follow-up time will be 3 years. Each patient will have follow-up examinations at 6 and 18 months, and annually thereafter. In addition, patients will be contacted by telephone at the 6 month point between annual visits (12 months, 24 months, etc.).

1.3 Study Organization

1.3.1 Participating Units and Primary Functions

The organizations participating in ENRICHD, and their role in the study are described below:

**Clinical Centers:** The Clinical Centers have primary responsibility for patient recruitment, delivery of the interventions, patient retention and follow-up, and data collection. The Clinical Center Investigators and staff collaborate in the development of the study protocol, manual of operations, data collection forms, and training and certification procedures. The participating Clinical Centers, and their Principal Investigators are:

- Duke University  
  James A. Blumenthal, Ph.D.
- Rush-Presbyterian-St. Luke’s Medical Center  
  Lynda H. Powell, Ph.D.
- Stanford University  
  Robert F. DeBusk, M.D.
University of Alabama at Birmingham              James D. Raczynski, Ph.D.
University of Miami                               Neil Schneiderman, Ph.D.
University of Washington                          Pamela Mitchell, Ph.D.
Washington University                             Robert M. Carney, Ph.D.
Yale University                                   Matthew M. Burg, Ph.D.

Coordinating Center: The Coordinating Center has primary responsibility for the statistical design of the study, development of data collection procedures, data management, and statistical analysis. It develops and implements the randomization procedure. The Coordinating Center has primary responsibility for insuring the accuracy and quality of data collection, assists in training and certification of clinical center staff and performs analyses of study data for quality control. The Coordinating Center prepares and distributes reports monitoring study progress and interim analyses for the DSMB. Coordinating Center has administrative / editorial responsibility for developing and updating the study manual of operations and data collection forms. The Coordinating Center provides logistical support for study meetings. The coordinating center is located at the University of North Carolina at Chapel Hill, and the Principal Investigator is James D. Hosking, PhD.

ECG Reading Center: The St. Louis University ECG Core Reading Laboratory is the central evaluation center of Electrocardiograms. The ECG Reading Center is responsible for developing data collection procedures, and data transfer procedures for use by the Clinical Centers. They perform standardized classification of the ECGs, and report the results to the Coordinating Center. Administratively, the Reading Center is a subcontract to the Coordinating Center. The Principal Investigator is Bernard Chaitman, M.D.

The Beck Institute: The Beck Institute collaborates with the ENRICHD Investigators to develop and present training for ENRICHD therapists in the use of individual and group therapy to treat depression and low social support. Training is based on the principles and objectives presented in the ENRICHD protocol and manual of operations. The Institute provides quality assurance of the therapists throughout the trial, through review of audiotapes of therapy sessions and individual and conference calls with therapists and intervention supervisors. Judith S. Beck, Ph.D. is the Project Director. Administratively, the Institute is a subcontract to the Coordinating Center.

1.3.2 Committee Responsibilities and Membership

Data and Safety Monitoring Board: The Data and Safety Monitoring Board (DSMB) is an independent group of experts in the relevant biomedical and behavior fields, biostatistics, and bioethics, appointed by NHLBI. The primary role of the DSMB is to advise the NHLBI on scientific, safety, ethical, and other policy issues relating to the study. The DSMB meets at least twice a year. The NHLBI Project Officer, the Steering Committee Chair and Co-Chair, and the Coordinating Center Principal Investigator also participate in DSMB meetings as non-voting
members. The DSMB will review the protocol prior to study initiation. During the execution of the study, the DSMB monitors study progress and reviews interim analyses of outcome and safety data. As appropriate, the DSMB makes recommendations to the NHLBI and Steering Committee concerning changes in study conduct.

**Steering Committee:** The Steering Committee is composed of the Principal Investigator of each of the Clinical Centers, the Principal Investigator of the Coordinating Center, and the Project Officer. Other members may be appointed by the Project Office on the basis of special expertise. The chairperson of the committee (Dr. Lisa Berkman) and Co-chairperson (Dr. Allan Jaffe) are appointed by the Director of NHLBI. The Steering Committee oversees all aspects of the design, execution, and publication of the study. The Steering Committee meets semi-annually to monitor the progress of the study and review non-endpoints data (endpoints data will be provided only to the DSMB until the trial is completed). The Steering Committee establishes subcommittees to develop and monitor aspects of the study, reporting recommendations to the full committee for approval. The subcommittee Chairs are appointed by NHLBI.

**Executive Committee:** The Executive Committee manages the day-to-day operations of the study between Steering Committee meetings. It develops the agendas for and prepares recommendations for the Steering Committee meetings. Membership consists of the NHLBI Project Officer (Dr. Susan Czajkowski), Steering Committee Chair (Dr. Lisa Berkman) and Co-Chair (Dr. Allan Jaffe), Coordinating Center Principal Investigator (Dr. James Hosking), and a Clinical Center Principal Investigator (Dr. Robert Carney). Ex-officio members may be appointed from the Project Office and the Coordinating Center. The Executive Committee meets by conference call at least monthly.

**Subcommittees:** The Steering Committee establishes subcommittees to develop and monitor various aspects of the study. Subcommittee members can include Investigators and staff of the Clinical Centers, Coordinating Center, and Project Office, as appropriate. Subcommittees develop recommendations and proposals for Steering Committee review and decision. Currently, the following subcommittees have been established:

- Eligibility, Recruitment, Adherence and Retention  
  (Dr. James Raczynski, Chair; Dr. Robert DeBusk, Co-Chair)

- Intervention  
  (Dr. Lynda Powell, Chair)

- Measurement and Endpoints  
  (Dr. Robert DeBusk, Chair; Dr. Gail Ironson, Co-Chair - Psychosocial; Dr. Christopher O'Connor, Co-Chair - Medical)

- Quality Control  
  (Dr. Marie Cowan, Chair; Dr. Matthew Burg, Co-Chair)
• Substudies and Ancillary studies  
  (Dr. Neil Schneiderman, Chair; Dr. Redford Williams, Co-Chair)

• Publications  
  (Dr. James Blumenthal, Chair)

• Psychopharmacology Subcommittee  
  (Dr. C. Barr Taylor, Chair)
1.4 Chapter References


