

# 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

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## 2. Chapter 2: Eligibility

### 2.1 Overview of Approach and Goals

The overall approach to recruitment, eligibility determination, baseline assessment and randomization is one of attempting to enroll eligible participants who are at increased risk for morbidity and mortality as quickly and efficiently as possible after an acute MI. This approach was adopted in an effort to begin treatment as quickly as possible in those participants assigned to treatment so that the benefits of treatment might be realized early after the MI, when patients are at the highest risk. It is important that every effort be made to overcome barriers to enrollment and participation of eligible patients so that those who are the most ill or who might face other barriers to participation will not be excluded, except in cases in which barriers to active participation cannot be overcome.

### 2.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are summarized in Table 1. The sequence of screening, eligibility determination, and randomization are summarized in Figure 1. An overview and rationale for each of the inclusion and exclusion criteria are summarized below.

#### 2.2.1 Inclusion Criteria

Patients will be enrolled who meet the following criteria.

##### 2.2.1.1 Hospitalized for MI

Only patients who have been hospitalized for an acute MI at visit (SV1) will be eligible for enrollment in ENRICHD. For ENRICHD, an acute MI will be determined by:

Hospitalized for MI: defined by having characteristic marker proteins to twice the upper limit established within the institution from which the patient is being recruited and at least one of the following:

- (a) symptoms compatible with acute MI; and/or
- (b) characteristic evolutionary electrocardiographic ST-T changes or new Q waves.

**1. Enzyme criteria for MI:** If CKMB is the marker used locally and if (a) values are increased above the upper bound of the reference range as assessed by the site cardiologist and are characteristic of MI that manifest a rising and falling pattern, and (b) acute myocardial infarction has been diagnosed locally, and (c) if symptoms are compatible with acute MI and/or characteristic ECG findings are present as defined in the ENRICHD eligibility criteria.

**2. Patients who under go acute angioplasty:** Patients who present with ST segment elevation and classic signs and symptoms of MI and meet ENRICHD criteria for marker protein elevations



after acute angioplasty are eligible so long as the diagnosis of acute infarction is confirmed by the site cardiologist.

Patients who present with chest pain, ST segment depression, a local diagnosis of acute myocardial infarction, and a three-fold increase in any of the biomarkers of myocardial injury are eligible if the site cardiologist concurs with the diagnosis of acute infarction

These determinations will be possible by chart review in most cases. A few cases may require confirmation by patients' physicians or investigation of results of tests done at referring hospitals. The diagnostic criteria for patients who undergo acute PTCA or have elevations of CK-MB less than twice the upper bound of the reference range used locally should be reviewed by the site cardiologist. Information may be found on:

- a) the ambulance run sheet;
- b) an ER triage sheet;
- c) the emergency room sheet;
- d) the admitting history and physical; and
- e) the physician's or nurse's narrative notes.

Read the chart carefully. Once signs and symptoms of MI are documented in the medical record, similar confirming notes are usually found in other sections of the chart, and may be more extensive. Medical student's notes are usually a very thorough review of the patient's condition.

### **2.2.1.2 Characteristic enzyme increases**

Since elevations in enzyme levels may result from conditions other than cardiac injury, patients who meet enzyme criteria are only eligible if the local physician has determined that the cause for the elevations is an acute MI. Elevations in enzyme levels may be seen, in particular, after an acute intervention (PCTA or CABG); these patients will only be included if the indication for the intervention was acute myocardial intervention.

Enzyme increases that qualify patients as eligible include an increase in cardiac enzyme levels (CK, LDH, Troponin T or I) to twice the upper limit of the normal value for the institution. Only the values of the marker protein used to make the diagnosis has to be reported to the data center.

***CK-MB***

Check first to see if a CK-MB was ordered on each patient. This information should be noted on the ER flow sheet in the MD orders portion, or in the general notes, and specific laboratory values should be available in the laboratory section of the medical record, under the cardiac enzymes section, if it has been ordered and conducted.

To qualify for ENRICHD, the CK-MB must manifest a rising and falling pattern of elevations with at least one value above the upper bound of the reference range. If elevations are more than two-fold the upper bound of the reference range, no consultation is necessary. To ensure accurate diagnosis when values are lower, the case and the values should be discussed with the site cardiologist. In addition, the local physician must have determined that these changes have resulted from an acute myocardial infarction. Normal ranges for institutions are usually found on each lab report for the test being reported. An MB bump (elevation) will appear in patients presenting to the hospital early in the course of an evolving MI.

For patients who present with ST segment depression and undergo acute PTCA, a three-fold elevation of CK-MB is required for diagnosis. For patients who present 24 hours after onset of the MI symptoms, LD or troponins can be used instead of CK-MB to determine an MI has occurred.

**2.2.1.3 LD**

LD (or LDH; Lactic Dehydrogenase) appears in the blood approximately 24 hours after the onset of MI symptoms. In the absence of CK-MB elevation, look for LD elevation.

To qualify for ENRICHD, patients must have an LDH elevation  $\geq 1.5$  times the upper limits of normal for your institution **and** LDH1 > LDH2.

For patients who present with ST segment depression and undergo acute PTCA, a three-fold elevation of LD is required for diagnosis.

**2.2.1.4 Cardiac Troponin T or I**

To qualify for ENRICHD, a patients must have Troponin T or I greater than two times the upper limit of normal at the institution in which the patient is being recruited.

For patients who present with ST segment depression and undergo acute PTCA, a three-fold elevation of Troponin is required for diagnosis.

**2.2.1.5 Signs and symptoms of MI.**

Signs and symptoms of MI include:

- a) Chest pain/chest pressure

- b) Jaw pain
- c) Arm or back pain
- d) Diaphoresis (sweating)
- e) Shortness of breath
- f) Nausea/vomiting
- g) Abdominal discomfort

Chest pain and/or pressure is the most common symptom found in patients of both genders and all race/ethnic groups and ages. Yet, it is not necessarily the most common complaint, and it does not occur in all patients, particularly older patients. In a patient experiencing an MI and reporting chest pain, the pain may get somewhat better and worse over time. Chest pain may be described as burning, tightness, squeezing or pressure, and the pain may be felt in places other than the chest. Left arm pain that may radiate to the jaw, back pain, and even just jaw pain is common. Patients may complain only of severe chest pressure rather than pain - i.e.- “I feel like an elephant is sitting on my chest”.

### **2.2.1.6 Evolutionary electrocardiographic ST-T changes or new Q waves**

ECG changes can be determined in the report of the 12-lead ECG obtained on the patient. These are usually found together in one section of the medical record. Do not confuse rhythm strips with 12-lead ECGs.

Characteristic evolutionary changes include:

- a. Evolving ST or T wave elevations (at least 1 mm in two contiguous leads)
- b. T wave inversion
- c. New Q waves (> 30 msec and 1 mm depth)

Compare several ECGs. If an ECG done prior to this episode is available, compare it with the series from this event. Note the changes. Do not be afraid to ask for assistance with ECG interpretation; this is a skill that comes with time.

### **2.2.2 Depressed and/or socially isolated**

To be eligible for inclusion, patients must meet the criteria for depression, social isolation, or both, as discussed below within 28 days of the onset of acute myocardial infarction. Patients are eligible for randomization as soon as they:

1. meet criteria for depression and/or low social support;
2. satisfy the other inclusion and exclusion criteria; **and**

### 3. complete baseline data collection.

Every effort should be made to enroll patients while they are still in the hospital. For those patients who are discharged prior to completing baseline data collection and who may be eligible, every effort should be made to complete eligibility determination and baseline data collection as soon after discharge as possible, as described in Chapter 4. Specifics concerning the criteria for depression and social isolation are summarized below.

#### **2.2.2.1 Depression**

To meet criteria for depression in ENRICHD, a patient must first meet the modified DSM-IV criteria for a current major or minor depressive disorder or dysthymia (American Psychiatric Association, 1994) (see ENRICHD modified criteria summarized in Table 2). The specific modified DSM-IV criteria are:

- Minor depression symptom criteria,  $1 \leq$  duration week; prior HX Major depression.
- Major depression symptom criteria,  $1 \leq$  duration week; prior HX Major depression.
- Major depression symptom criteria, and duration  $\geq 2$  weeks (regardless of prior history).

The first 7 items on the DISH (Part A) assess the cardinal symptoms of depression (dysphoria and anhedonia). If neither is present, the patient cannot meet the DSM-IV criteria for depression.

#### **2.2.2.2 Psychodiagnostic Interview**

The modified DSM-IV criteria for major or minor depression are summarized in Table 2 and will be determined from psychodiagnostic interview. In order to be eligible for inclusion in ENRICHD, patients must meet these criteria for major or minor depression based on a psychodiagnostic interview to be administered (DISH) at the initial visit (SV1 while hospitalized for an MI; see Figure 1) or re-screening visit (to be conducted post-discharge from 0-14 days from the index MI; see Figure 1) and within 21 days of the index MI. Issues concerning differentiating between medical and depressive symptoms and the standardized psychodiagnostic interview are summarized below.

In order to determine whether a patient meets the modified DSM-IV criteria for major or minor depression (see Table 2), it will be necessary to conduct an interview with a new interview schedule, the Depression Interview and Structured Hamilton; Freedland, 1996), developed specifically to meet the requirements of ENRICHD. It was designed to obtain an accurate DSM-IV diagnosis, an assessment of the longitudinal course of the disorder, and a reliable Hamilton score, in an efficient, integrated interview format that would allow easy phone follow-up. It was also designed to be suitable for use by diverse personnel and to eliminate most of the need for diagnostic overreading.

The DISH (see Appendix A) integrates material from several different sources, including the Hamilton Rating Scale for Depression (Hamilton, 1960); the standardized version of the Hamilton scale developed by NIMH for use in the Early Clinical Drug Evaluation (ECDEU) program; the Structured Interview Guide for the Hamilton Depression Rating Scale (Williams, 1988, 1992); the

National Institute of Mental Health Diagnostic Interview Schedule (Robins, Hezeer Croghan, & Ratcliff, 1981); a modified version of the NIMH Diagnostic Interview Schedule (Carney & Freedland, 1988) that has been used primarily in research on depression in patients with coronary heart disease; and the DSM-IV manual itself.

The DISH consists of several sections (see Appendix A). The Current Depression Symptoms section determines the severity, frequency, and chronicity of all of the DSM-IV criterion symptoms of major and minor depression and dysthymia. It also elicits the information needed to derive the standard (17-item) Hamilton depression severity score for the past week.

The Psychiatric History section provides a brief assessment of the patient's lifetime history of depression, other psychiatric disorders (including disorders that, if present, exclude the patient from participation in the trial), and psychiatric and psychological treatment. It also probes to identify impairment in social, occupational, or other areas of psychosocial functioning. Most of this section will only be administered at baseline.

The Recent History of Depressive Disorder section evaluates whether there have been any changes in depressive symptomatology in the interval between the present and the previous interview. This section will not be administered at baseline but at a later follow-up visit.

The Notification section directs the interviewer to take appropriate steps when it is necessary to notify the patient's physician and/or nurse about severe depression or active suicidality, and to document these steps. This section will be used to assist in determining exclusion from ENRICHD prior to randomization (see discussion of suicidality in section on Exclusion Criteria #7 in this chapter) as well as to implement an appropriate action in the case of patients who become suicidal after enrollment in ENRICHD.

The History and Course Chart is used in conjunction with the Psychiatric History and the Recent History of Depressive Disorder sections to characterize the longitudinal course of the patient's depressive disorder or dysthymia. It is designed to fill in the gaps between the "snapshot" views of the patient's condition that are obtained at each interview.

Finally, the Diagnostic Summary Form provides a standardized format for coding the current diagnosis and the Hamilton depression score. The form is designed to increase the reliability of the diagnostic judgments that are formed on the basis of the interview, and serves as one basis for randomizing patients into the study.

### **2.2.2.3 Differentiation Between Medical and Depressive Symptoms.**

The threshold is very high in DSM-IV for calling something a "medical symptom" (i.e., a symptom of medical illness, medication, or substance abuse rather than of depression):

"Some of the criterion items of a Major Depressive Episode are identical to the characteristic signs and symptoms of general medical conditions (e.g., weight loss with untreated diabetes, fatigue with cancer). Such symptoms should count toward a Major Depressive Episode except

when they are clearly and fully accounted for by a general medical condition. For example, weight loss in a person with ulcerative colitis who has many bowel movements and little food intake should not be counted toward a Major Depressive Episode. On the other hand, when sadness, guilt, insomnia, or weight loss are present in a person with a recent myocardial infarction, each symptom would count toward a Major Depressive Episode because these are not clearly and fully accounted for by the physiological effects of a myocardial infarction” (DSM-IV, pp. 322-323).

The burden is on the interviewer to judge whether any individual symptom exceeds this DSM-IV threshold and to document the medical condition or medication that is believed to account for the symptom. It is not possible to devise rules that would be applicable in every case. For example, weight loss in a post-MI patient may not be due to the direct physiological effects of the myocardial infarction, but it is not uncommon for cardiac patients to be given diuretics to control edema. If a patient’s weight loss is due entirely to diuresis rather than to loss of appetite, it should not count as a depressive symptom. The Manual of Operations, therefore, will include guidelines to assist interviewers in making these judgments, and interviewers are expected to consult with the appropriate medical personnel, when necessary, to reach an informed conclusion about a symptom.

It may be difficult or impossible for an interviewer to judge whether a depressive syndrome is due entirely to the direct physiological effects of an underlying medical condition such as hypothyroidism. For this reason, consultation may be needed with appropriate medical personnel when a co-morbid medical conditions may be masquerading as depression in post-MI patients. Interviewers are expected to attempt to diagnose depression in the presence of these medical conditions, and it will be the responsibility of each clinic to establish procedures to review decisions made by interviewers in diagnosing depression in such circumstances.

#### Beck Depression Inventory:

For those sites in which screening with the DISH is not feasible, the BDI may continue to be used as a screening tool under the original protocol (ver. 5.0 protocol criteria). However, note that for randomization into the study, depressed patients no longer need to have a BDI  $\geq 10$  for entry, as long as patients meet one of the qualifying diagnoses from the DISH.

#### **2.2.2.4 Social Isolation**

To meet criteria for social isolation in ENRICHD, a patient must score 2 or lower on at least two items of the ENRICHD Social Support Instrument (ESSI), excluding item 4 (availability of someone to help you with daily chores). The criteria has been broadened to include a score of 3 or less on two or more 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.

The ESSI is a seven-item scale based on items which have been individually predictive of mortality in cardiac patients and/or came from larger well-validated social support scales. It was developed based on a review of previous scales and items which have predictive validity. A summary of this review suggests that the critical element of most items predictive of poor prognosis is related to

perceptions of social support, emotional support in particular, rather than dimensions of either network structure (e.g. network size, geographical proximity or living arrangements) or subjective feelings of loneliness. The scale was created by identifying items from the following three studies by Williams et al<sup>1</sup>, Gorkin et al<sup>2</sup>, and Berkman et al<sup>3</sup>. The item from CAST<sup>2</sup> was actually an integration of two items from the MOS<sup>4</sup>. In an effort to develop a scale with 6-7 items, we disaggregated those two items and added two other items from the MOS which tap a similar construct. The questions about confidant and marital status are directly from the Williams et al study. The question on emotional support is from the New Haven EPESE. The response categories have been modified so that they follow a consistent format based on the MOS (with the exception of the items about marital status).

### **2.2.3 Exclusion Criteria**

As summarized in the Medical Eligibility Form (see forms in Forms Appendix), patients will be excluded from participation who meet any of the following 10 criteria.

#### **2.2.3.1 Post-procedure MI**

Patients who have had an MI subsequent to a procedure, such as CABG surgery or PTCA, will be excluded from ENRICHD. These patients can be identified by:

- a. admission for a cardiac procedure with MI occurring subsequently; or
- b. an elevation on a CK-MB done during or just after a cardiac procedure.

Refer to interventional cardiac catheterization lab procedure notes for determination of whether the MI was procedure related. Often clues may be found there that the MI occurred during or just after the procedure.

However, patients in whom these procedures are done to treat an acute infarction need not be excluded. Even if enzyme criteria are not met prior to the intervention, these patients are eligible provided the intervention was initiated to treat the acute infarction and enzyme criteria are met subsequent to the procedure.

Patients who have undergone noncardiac surgery (orthopedic, abdominal or vascular) and suffer a subsequent myocardial infarction will be candidates for the study. Only those MIs presumably caused by procedures that affect the coronary arteries will be excluded from the study.

#### **2.2.3.2 Presence of Conditions Likely to Terminate Fatally Within One Year**

Patients with these conditions will be excluded from ENRICHD since they potentially reduce the number of outcomes attributable to the intervention, are likely to compromise patients' ability to participate actively in the intervention as they become more ill, and increase dramatically the difficulty in presenting a standardized psychosocial intervention.

Check the history and physical exam sections of the chart for disease process which severely limit life expectancy. These would include advanced lung or liver cancer, lymphomas, leukemia, advanced

liver disease, active AIDS, severe CHF or COPD, and advanced rheumatologic disease. Patients on the cardiac transplantation list are also excluded. On the other hand, patients with prostate carcinoma, limited breast cancer, skin malignancy, and endstage renal disease receiving dialysis would be candidates for the study.

In the laboratory section of the chart, look for values that may indicate underlying disease process likely to cause death within the year. These could include elevated creatinine, elevated BUN, very low hemoglobin or hematocrit, or very low platelet or white cell counts. Read all lab reports and note any values markedly outside the normal range. Investigate to determine the meaning of such values.

This determination should be based primarily on the judgment of the patient's physician(s). However, the PI at each site (or designee) should be consulted before any patient is excluded on this basis.

### **2.2.3.3 Conditions Likely to Limit the Physical Capacity to Participate Despite Efforts to Overcome Barriers to Participation**

Every effort will be made by ENRICHD staff to overcome barriers to participation (e.g., assisting with transportation). Nonetheless, even when co-morbid conditions do not pose an important threat to life, they may impair functional capacity to an extent that clinical units will not be able to overcome them and limit participation in the study. In these cases where limitations cannot be overcome, patients will be excluded from participation.

This determination should be made on the basis of the patient's judgment, after the study activities have been explained to them and in collaboration with the Clinical Center PI. Efforts should be made to find ways to help patients with physical limitations participate if the patient is interested in the study. For instance, patients with severe COPD could come to a group with an oxygen tank. At the same time realistic considerations about the patients potentially dropping out need to be considered.

Note that physicians may express a concern that the patient may not feel well enough to participate. Health status (except as it may be terminal) is not an exclusion criterion.

### **2.2.3.4 Participation in Concurrent Research Protocols Likely to Conflict with ENRICHD**

In general, patients participating in other research protocols will only be excluded from ENRICHD if participation in the concurrent research protocol poses a significant logistical burden or the other protocol provides a treatment similar or (or conflicting with) the ENRICHD intervention.

Patients who are currently in a research protocol investigating depression or social isolation in post MI patients, such as the testing of antidepressant pharmacologic therapies would be excluded from ENRICHD. However, patients involved in investigations of standard or novel pharmacologic therapies for myocardial infarction such as new thrombolytic therapy agents, new lipid lowering



agents, new beta blockers, new ACE inhibitors, new forms of anti-platelet, or anti-thrombin agents are potentially eligible.

### **2.2.3.5 Major Psychological Co-morbidity**

Patients who have major psychological co-morbidity which either would compromise their participation in ENRICHHD, would result in them being inappropriate for the ENRICHHD treatment, would be likely to require alternative psychosocial treatment during the ENRICHHD study period, or would affect the interpretation of ENRICHHD results will be excluded from participation in ENRICHHD. These psychological conditions include any of the following:

- a. schizophrenia or bipolar disorder evidenced by chart review or psychodiagnostic interview;
- b. dementia evidenced from chart review, psychodiagnostic interview, or by administration of the Short Blessed Dementia Screening Test given by discretion of the interviewer during the psychodiagnostic interview at SV2 (patients who score above the standard cutoff score of 10 will be excluded; see copy of Short Blessed Test in the Forms Appendix );
- c. active substance abuse evidenced by chart review or clinical interview;
- d. other major psychological conditions precluding participation in trial.

Note that these are not absolute contraindications. For instance, a patient with schizophrenia in remission, with adequate interpersonal skills to participate in group, should not de facto be excluded from the social isolation intervention (they may be excluded from the depression arm). These exclusions should be relatively rare.

### **2.2.3.6 Active Suicidal Ideation**

Suicidal ideation is a common symptom of depression, so it is likely to be a common finding among patients screened for eligibility to participate in ENRICHHD. Although interviewers should always be duly concerned about suicidal ideation, they should not assume that it always portends suicidal behavior. Indeed, relatively few cases of attempted or completed suicide have been reported in the literature on depression in medically ill patients. However, major depression has been implicated as a contributing factor in between 40 and 60% of all suicides (Claton, 1985; Murphy, 1986). Furthermore, the incidence of completed suicide is especially high among elderly individuals (National Center for Health Statistics, 1992), and the prevalence of attempted suicide is particularly high among individuals who are separated or divorced (Moscicki et al., 1988). Since ENRICHHD participants will be depressed and/or socially isolated and most will be middle aged or older, a small number of the patients screened for participation will inevitably be at risk for suicide.

In screening a patient for ENRICHHD, the objective of suicide risk assessment is to classify him or her as (1) possibly or definitely at imminent risk of attempting suicide or otherwise harming him/herself (a psychiatric emergency); (2) not at imminent risk, but possibly or definitely at elevated risk of attempting suicide within the next few weeks or months (not an emergency, but a serious situation nevertheless); or (3) not at elevated risk of attempting suicide.

The information upon which to base this classification is to be obtained from the BDI, the DISH, and, when applicable, from collateral sources (the patient's medical chart, caregivers, etc.).

Beck Depression Inventory: Item #9 on the BDI asks the patient about suicidal ideation. Since the BDI is only a questionnaire rather than a more in-depth psychodiagnostic interview, it does not provide sufficient information to judge whether there is any real risk of suicide. Nevertheless, whenever the BDI is administered at baseline, treatment process, or outcome measure, it is to be reviewed in a timely manner to ascertain whether the patient has reported any suicidal ideation.

A score of 1 on BDI Item #9 indicates that the patient has recently had some thoughts about suicide but that he or she "would not carry them out". This suggests (but does not guarantee) that the patient is not at imminent risk, and that his or her longer-term risk is only mildly elevated, if at all. If this is an isolated finding (e.g., no other suicidal features are detected), the designated senior project staff member(s) should be informed, but it is not necessary to notify the patient's physician or to take any other actions unless so directed by the senior project staff.

A score of 2 on BDI Item #9 suggests the presence of suicidal ideation that may be more significant, and a score of 3 is a fairly clear warning sign of suicidal intent. Even if this is an isolated finding (i.e., no other suicidal features are detected), the designated senior project staff member(s) should be informed and the patient's physician(s) should be notified in a timely manner. See Chapter 8 for details on the physician notification procedure.

Depression Interview: Suicidal ideation is assessed as part of the standardized psychodiagnostic interview, but only if the entire interview is administered (i.e., suicidality is not assessed if the screening interview is terminated early due to negative responses to questions about the cardinal symptoms of depression). If the full interview is administered and the patient reports having had any suicidal ideation during the past week, the interviewer is to probe to determine the frequency, chronicity, and content of the ideation.

Following guidelines delineated by Clark and Fawcett (1992), the identification of active thoughts of suicide is to be followed up by determining whether (1) the patient has considered and/or has access to any specific method(s) of suicide; (2) the patient wants to or intends to or is planning to attempt suicide in the near future, and if so, why; (3) the patient has rehearsed or made preparations to carry out the plan; (4) the patient has a past history of suicide attempt(s); and (5) there are any additional circumstances that may add to the risk of attempting or completing suicide (e.g., current alcohol abuse, social isolation, hopelessness, or crisis such as job loss).

If one or more of these features are detected, the interviewer must attempt to determine whether the patient is at imminent risk (i.e., in immediate danger of attempting suicide or otherwise harming him/herself). If the interviewer believes that the risk may be or definitely is imminent, the situation is to be treated as a psychiatric emergency. In such situations, the need to protect the patient overrides both the patient's usual confidentiality rights and the rest of the usual screening procedures. (It is unnecessary to complete the screening process anyway, because patients who are

at imminent risk of suicide are excluded from enrollment in the trial). The interviewer is required to take the following steps:

If the patient is still in the hospital, both the physician and the nurse in charge of the patient's care are to be notified immediately after the interview has been completed. If the patient has been discharged from the hospital, the patient's physician is to be notified as soon as possible. If a suicide attempt is in progress, or if there is a substantial risk that a suicide attempt may be made before the physician would have time to intervene (e.g., the patient has swallowed a bottle of pills or is holding a weapon), the interviewer is required to call 911 immediately to dispatch emergency assistance. The interviewer is also required to notify the designated senior study staff as soon as possible and to discuss whether any other steps are necessary to protect the patient (e.g., notification of family members, caregivers, etc.)

Patients who are not at imminent risk, but who are possibly or definitely at elevated risk of attempting suicide within the next few weeks or months, are eligible to participate in the trial unless excluded on other grounds. If a patient is or may be at elevated risk of attempting suicide within the next few weeks or months, physician notification is mandatory, and it must be completed in a timely manner. Notification of the designated senior project staff member(s) is also mandatory. If the patient is randomized to the Treatment arm of the trial, the findings are to be discussed with his or her psychotherapist (and, if applicable, the project psychiatrist). If the patient is excluded from the trial or is randomized to the Usual Care arm, the designated project staff member should, if necessary, initiate a follow-up contact with the patient's physician to confirm that the patient is being properly evaluated and/or treated.

Patients need not be excluded from participation in the trial simply because of a low-probability, long-term risk of suicide or because of transient or passive suicidal ideation. Furthermore, the interviewer's duty to protect the patient's confidentiality outweighs any potential need to notify the patient's physician or other caregivers. For example, assume that the only evidence of any suicidality obtained from a patient is his statement that, "Once in a while, I wonder what I would do if things got a lot worse than they are now. I might think about killing myself, but I'd never do that. It's just plain wrong, and I couldn't do that to my family anyway." In such a case, the interviewer would have no need, no responsibility, and no right to disclose this information to the patient's physician or other caregivers.

### **2.2.3.7 Unwillingness to Provide Informed Consent**

Patients who are not willing or able to provide written informed consent cannot be randomized in ENRICHD.

### **2.2.3.8 Inability to Complete Screening Visits**

Patients who fail to complete ENRICHD screening visits or who cannot provide complete baseline data will not be randomized in ENRICHD. The inability to respond to a single item on the baseline questionnaires would not exclude a patient. However, patients who fail to complete a number of items should be excluded.

### 2.2.3.9 Inaccessibility for Intervention and/or Follow-up

Despite active efforts to accommodate patients' special needs, those who have extreme difficulty attending therapy sessions and follow-up visits, and are therefore unlikely to be adherent with treatment and follow-up will be excluded from participation in ENRICHD. Establishing exclusion criteria to define accessibility is essentially related to such dimensions as the number of miles which a patient lives from an intervention or assessment site, the time that it takes to travel such distances, frequent business travel, plans to move from the area during the period of study, and not having access to a telephone for contact and follow-up. Nonetheless, differences between clinical centers in such factors as urban vs. rural location and availability of public transportation as well as differences in factors such as patient motivation and resources to overcome accessibility barriers preclude definitive criteria which are applicable to all centers and all patients. Each site will define specific guidelines for determining accessibility, and patients who are judged to have accessibility barriers which are likely to compromise their active participation in ENRICHD will be excluded.

### 2.2.4 Ethnicity and Gender Composition of ENRICHD

One of the major selection criteria for a clinical site for ENRICHD was the ability to recruit women and minorities into the study. Clinical sites were selected to produce an overall study population of 50% women and 50% minorities, and will be monitored by the UNC Coordinating Center throughout the study to assure that our performance matches our expectations. Recruitment of women and minorities is essential at the beginning of the trial. If the overall proportion of women and of minorities appears to be falling significantly short of 50% for each, options and approaches to increasing the recruitment of women and minorities at some or all existing clinical sites will be reevaluated.

## 2.3 References

Beck A.T., Steer, R.A., Garbin, M.G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clinical Psychology Review 8:77-100.

Schaefer, C., Quesenberry, C.P., & Wi, S. (1995). Mortality following conjugal bereavement and the effects of a shared environment. American Journal of Epidemiology 141:1142-1152.

## Table 1. Eligibility Criteria for ENRICHD

### Inclusion Criteria

Hospitalized for MI: defined by having characteristic marker proteins to twice the upper limit established within the institution from which the patient is being recruited and at least one of the following:

- (a) symptoms compatible with acute MI; and/or
- (b) characteristic evolutionary electrocardiographic ST-T changes or new Q waves.

**1. Enzyme criteria for MI:** If CKMB is the marker used locally and if (a) values are increased above the upper bound of the reference range as assessed by the site cardiologist and are characteristic of MI that manifest a rising and falling pattern, and (b) acute myocardial infarction has been diagnosed locally, and (c) if symptoms are compatible with acute MI and/or characteristic ECG findings are present as defined in the ENRICHD eligibility criteria.

**2. Patients who under go acute angioplasty:** Patients who present with ST segment elevation and classic signs and symptoms of MI and meet ENRICHD criteria for marker protein elevations after acute angioplasty are eligible so long as the diagnosis of acute infarction is confirmed by the site cardiologist.

Patients who present with chest pain, ST segment depression, a local diagnosis of acute myocardial infarction, and a three-fold increase in any of the biomarkers of myocardial injury are eligible if the site cardiologist concurs with the diagnosis of acute infarction

### **Depression or social isolation as determined by:**

- a. depressed - major or minor depression based on modified DSM-IV criteria (exclusive of requirement concerning depression being reactive to a physical condition; see Table 2 for modified DSM-IV criteria) during SV2

### and/or

To meet the criteria for social isolation, a patient must score 2 or lower on at least two items of the ENRICHD Social Support Instrument (ESSI), excluding item 4 (availability of someone to help you with daily chores) or (b) a score of 3 or less on two or more items, excluding items #4 and 7 (help with chores and marital status) and (c) a total score of 18 or less on items 1, 2, 3, 5 and 6.

## **Exclusion Criteria**

1. Post-procedure MI (unless the procedure was performed to treat the acute infarction; see section 2.2.2.1)
2. Presence of Conditions Likely to Terminate Fatally Within One Year
3. Conditions Likely to Limit the Physical Capacity to Participate Despite Efforts to Overcome Barriers to Participation
4. Participation in Concurrent Research Protocols Likely to Conflict with ENRICHHD
5. Major Psychological Co-morbidity -- defined by any of the following
  - schizophrenia or bipolar disorder evidenced by chart review or clinical interview
  - dementia evidenced from chart review, clinical interview, or by a Short BLESSED score >10
  - current substance abuse evidenced by chart review or clinical interview
  - other major psychological conditions precluding participation in trial
6. Active Suicidal Ideation
7. Unwillingness to Provide Informed Consent
8. Inability to Complete Screening Visits
9. Inaccessibility for Intervention and/or Follow-up

## Table 2. DSM-IV Criteria for Major and Minor Unipolar Depressive Disorders

Major Depressive Episode: The diagnosis of a current major depressive episode requires that all criteria (“a” through “e”) be met.

- a. **Five or more** of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Those patients who meet these symptom criteria but not the two-week duration criterion and have had a previous episode of major depression, will be considered to have met criteria for major depression and be eligible for randomization if they meet all other eligibility criteria.
  - (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
  - (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
  - (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
  - (4) insomnia or hypersomnia nearly every day
  - (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
  - (6) fatigue or loss of energy nearly every day
  - (7) feelings of worthlessness or excessive or inappropriate guilt nearly every day (not merely self-reproach or guilt about being depressed)
  - (8) diminished ability to think or concentrate or indecisiveness, nearly every day (either by subjective account or as observed by others)
  - (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- b. No evidence of concurrent manic episode is present.
- c. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- d. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a prescribed medication) or a general medical condition (e.g., hypothyroidism).

- e. The symptoms are not better accounted for by acute bereavement. When grief and other depression-like features occur after the loss of a loved one, the diagnosis of major or minor depression is deferred until the symptoms have persisted for longer than 2 months OR until marked morbid preoccupation with worthlessness, suicidal ideation, or severe psychomotor retardation are present for two weeks or longer.

### Minor Depressive Episode

- a. Principal Criteria: The DSM-IV criteria for a current minor depressive episode are essentially identical to those for major depression, except that **at least two but less than five** of the depressive symptoms listed above must have been present during the same two-week period. As in major depression, at least one of the symptoms must be either depressed mood or loss of interest or pleasure. Those patients who meet these symptom criteria but not the two-week duration criterion and have had a previous episode of major depression, will be considered to have met criteria for minor depression and be eligible for randomization if they meet all other eligibility criteria.
- b. Exceptional Criteria
  - (1) Dysthymia: As defined by DSM-IV, dysthymia is a form of chronic, mild depression. Its features are very similar to those of minor depressive disorder, but the depressive symptoms must have persisted for at least two years to warrant a diagnosis of dysthymia. Because of its chronicity, dysthymia may be more difficult to treat than an acute minor depressive episode, and underlying dysthymia is known to complicate the course and treatment of major depressive episodes (a condition that has been labeled as “double depression”). However, little if anything is known about whether dysthymia and minor depression differ with respect to their prognostic implications in cardiac patients. For the purpose of determining eligibility to participate in the trial, no distinction will be made between minor depression and dysthymia.
  - (2) Major Depression in Partial Remission: Unless the interviewer is very familiar with the patient’s recent psychiatric history, it can be difficult to differentially diagnose minor depression and major depression in partial remission. Virtually nothing is known about whether these two conditions have different prognostic implications for post-MI patients. For the purpose of determining eligibility to participate in the trial, no distinction will be made between minor depression and major depression in partial remission.



**Figure 1. Overview of Proposed Screening/Recruitment Visits\***



## 3. Chapter 3: Screening, Recruitment and Enrollment

### 3.1 General Issues and Approach Related to Recruitment and Screening

The overall goal of ENRICHD is to recruit at least 3,000 patients over the three years of recruitment (10/15/96-10/14/99), or at least 125 patients each year for a total of at least 375 patients in each of the eight clinical centers. In order to ensure that the study will provide meaningful data on women and diverse racial/ethnic groups, the overall goal will be to recruit 50% women and 50% minorities.

Recruitment methods for ENRICHD will be implemented by eight clinical units in different parts of the country, each of which will be working in at least several hospitals. In addition to the ethnic and cultural diversity found among the eight clinical units, the variation in hospital procedures, practice conventions, clinical trial experience and conventions, and influence of managed care will be great. Hence, the general approaches to recruitment and the specific methods to be employed in each hospital will need to be adjusted to the variations found among hospitals, regions and ethnic and cultural groups. Despite the variations in approaches and methods found between clinical units and hospitals, the overall approach to recruitment, eligibility determination, baseline assessment and randomization is one of attempting to enroll eligible participants who are at increased risk for morbidity and mortality as quickly and efficiently as possible after an acute MI. This approach was adopted in an effort to begin treatment as quickly as possible in those participants assigned to treatment so that the benefits of treatment might be realized early after the MI, when patients are at the highest risk. It is important that every effort will be made to overcome barriers to enrollment and participation of eligible patients so that those who are the most ill or who might face other barriers to participation will not be excluded except in cases in which barriers to active participation cannot be overcome and so that the overall study's recruitment goals are achieved.

#### 3.1.1 General Issues Related to Recruitment and Screening

Despite the variations that will be inherent in the specific approaches and methods adopted by clinical units and within hospitals, there are a number of broad issues that require consideration for recruitment and screening for ENRICHD. Among these issues are the following:

- I. enrolling patients as quickly and efficiently into ENRICHD, so that they might benefit from the psychosocial intervention during the period soon after having suffered an MI when they are at their greatest risk for mortality and re-infarction

Data suggest that patients who survive a myocardial infarction will suffer their highest risk for mortality within a relatively brief period (3-6 months) after the infarct. Data further suggest that patients with major depression are those who have the highest risk for mortality within three to six months after a myocardial infarction (Frazure-Smith, unpublished data). At the same time, while some benefits from psychosocial interventions, such as with depressed patients, can be seen soon after beginning therapy, skills changes associated with cognitive/behavioral interventions require some period of treatment to effect. Hence, ENRICHD investigators recognized the importance of

enrolling patients quickly so that those randomized to the psychosocial intervention might have sufficient exposure to the intervention to effect changes in their depression/low social support at the time when they are at greatest risk.

To accommodate concerns that participants are enrolled very early so that the intervention can then begin early in an effort to effect change in depression and social support, thereby reducing early mortality risk, ENRICHD has adopted a screening and recruitment plan that will allow enrollment of most patients in-hospital. However, patients in whom it is not possible to complete the baseline assessments in-hospital, may be randomized after completing baseline data collection during a post-discharge follow-up visit.

II. enrolling participants, particularly minority and low-SES participants, while they are still inpatients so that contact could be established between study personnel and these participants while they are still in the hospital in an effort to promote feeling “connected” and involved in the study and adherence and retention

Quick, inpatient enrollment would allow an opportunity for substantial contact between study personnel and participants and actually promote adherence and retention. This was thought to be particularly important for minorities, low-SES populations, and possibly even women.

III. balancing the desirability of enrolling participants quickly, while still ensuring that those who are enrolled have an adequate period and “behavioral run-in” to ensure high protocol adherence and retention

Clinical trials must often balance the desire to enroll participants quickly to meet recruitment goals while not enrolling participants so quickly that an adequate commitment from potential participants has not been obtained, resulting in participants who are less likely to be adherent and be retained. To ensure adequate motivation of potential participants to participate, common procedures often include multiple screening visits or “behavioral run-ins”. Patients who, in the Investigator’s judgment, may not have had adequate time in-hospital to make a solid commitment to participation, may be scheduled for a post-discharge follow-up visit to test compliance prior to randomization.

IV. ensuring that patients can be screened for eligibility both within the hospital as well as after discharge so that those who do not meet eligibility criteria upon initial screening but who meet criteria for depression and low social support soon after discharge would be eligible to participate

ENRICHD investigators recognized that some patients may have been depressed prior to their myocardial infarction, while some patients may become depressed in a reactive manner after their myocardial infarction has occurred. Hence, while some patients might meet duration criteria for major and minor depression while in the hospital for an acute myocardial infarction, others may not meet criteria for as much as two weeks after their hospitalization. After careful consideration, it was decided by ENRICHD investigators that recruitment and eligibility determination for ENRICHD

would allow patients who meet depression criteria either while in the hospital or within the first few weeks (i.e., up to 21 days after their infarct) after discharge to be eligible to participate.

Similar issues arose when examining social support. Since it is common for patients to experience increased social support from family and friends during a hospitalization only to experience a loss of support upon discharge, it was considered that some patients may meet criteria for social support/isolation while still hospitalized while others may not meet criteria until after discharge. Nonetheless, as with the depression criteria, it was thought that those patients who did not meet criteria until after discharge should still be eligible for participation and that screening methods should accommodate procedures to ensure screening both in the hospital and upon a post-discharge screening follow-up evaluation.

- V. ensuring that the recruitment, screening, and eligibility determination in ENRICHD adopted methods to ensure that patients unlikely to meet eligibility for ENRICHD would be excluded from participation early so as to minimize staff time and expense as well as patient burden and facilitate maximizing efficiency

While it was thought to be important to enroll patients who meet depression and/or social support/isolation criteria while they were either an inpatient or within two weeks of discharge to accommodate patients who might not meet eligibility while an inpatient, it was also thought to be desirable to develop a screening algorithm that would not require follow-up of all patients after discharge but only those who are likely to meet study eligibility criteria upon follow-up.

Thus, the screening and recruitment methods were developed to accommodate follow-up of patients who are likely to become depressed or meet criteria for social support/isolation within two weeks of discharge. However, patients will only be eligible for follow-up if they meet one or both of the following criteria upon initial screening in the hospital (SV1): a) meeting the DISH criteria for minor or major depression and/or b) meeting the criteria for ESSI.

- VI. incorporating appropriate methods to address gender and ethnic/cultural issues to ensure proportions of these sub-groups that will be adequate to meet overall study recruitment goals of 50% women and 50% minority representation

Clinical trials have identified barriers to participation for women and minorities. Hence, consideration was given to methods to facilitate and support women and minorities in overcoming barriers to participation. As discussed further below, central to the methods adopted in ENRICHD is the role of a Case Coordinator (CC) who will facilitate developing an adequate “infrastructure” for the patient and who will be trained to maintain personalized contact with participants and address logistical, belief and attitudinal issues that are likely to emerge among these individuals.

### **3.1.2 General Approach to Screening and Recruitment**

Key to addressing the above issues in the approach to screening and recruitment for ENRICHD is ensuring an adequate “infrastructure” to facilitate the recruitment, screening, and later active

participation of all participants based on their individual needs. Particularly in a trial focusing on depressed and/or socially isolated post-MI patients, many of whom will have cardiac symptoms and be exposed to complex medical tests and medical and surgical treatments and many of whom will be minorities and women, it will be important to identify a cadre of health professionals who can assume responsibility for working with hospital staff, the patient's physician(s), and study staff to enroll and retain patients. The Case Coordinator, a nurse with a coronary care or acute medical care background is best situated by training, experience and location to perform these activities.

Since patients will be enrolled soon after acute myocardial infarction from coronary care units or medical intensive care units, an effective liaison between the staffs of these units and the Case Coordinators will be essential. The Case Coordinators will be responsible for identifying potentially eligible patients, describing the study to them, gaining their informed consent to obtain information from the medical record, querying the primary physician to obtain critical information known only to the physician such as whether a bypass surgery is contemplated, and addressing the unique needs of individual participants. The Case Coordinator will ensure that a "relationship" is established with participants to address the individual needs of participants, particularly those often encountered by minorities and women as we describe more fully in Section 3.3 below.

## **3.2 Overview of Screening Visits and Study Eligibility**

An overview of the screening visits is summarized in Figure 1 of Chapter 2. The following sections describe the sequence of screening, recruitment and baseline data collection visits by visit.

### **3.2.1 Pre-Screening (PS)**

The Case Coordinator and individual hospital screening contacts will be responsible for approaching potentially eligible post-MI patients in participating hospitals for whom the patient's physician has provided consent. Depending on local IRB and hospital requirements, chart pre-screening (PS) will occur either before or after obtaining patients' consent to participate. In many cases, clarification of patients' status will have to be obtained from nursing staff and patients' physicians during the prescreening to determine if particular patients are eligible.

### **3.2.2 Screening Visit 1 (SV1)**

In cases in which patient consent is not required prior to chart review, informed consent will be obtained after chart review for eligible participants so that all patients will have provided informed consent prior to SV1. SV1 will consist of administration of the DISH Part A and the ESSI. For both the DISH Part A and ESSI, patients' progression through screening will be determined by their classification according to these two instruments.

*(For those sites in which screening with the DISH is not feasible, the BDI may be continued to be used as a screening tool under the original protocol (vers 5.0 criteria) However, note that for randomization into the study, depressed patients no longer need to have a BDI =  $\geq 10$  for entry.)*

### **3.2.3 Screening Visit 2 (SV2)**

Once a patient meets basic eligibility at screening either at initial screening (SV1) or re-screening after discharge (SV1a), they will be qualify for eligibility determination with the DISH at SV2. SV2 can, at the discretion of the local site, occur immediately after eligibility determination at SV1 or SV1a or at a later visit but must occur within 21 days of patients' myocardial infarctions. Screening at SV2 will consist of administration of the DISH and the BLESSED if determined to be warranted to gain further information concerning patients' cognitive functioning. The DISH will be administered in this manner to all patients who qualify at SV1 or SV1a, even those who meet eligibility based on ESSI score. Patients who do not meet eligibility based on major or minor depression will be eligible for re-screening (SV2a) during a follow-up to SV2. Those patients who meet depression eligibility (i.e., have either major or minor depression according to modified DSM-IV criteria) and/or meet social support/isolation criteria and who meet all other eligibility criteria will proceed to baseline data collection at SV3.

### **3.2.4 Follow-up Screening Visit 2 (SV2a)**

Those patients who have met criteria for screening at SV2, have not been found to meet criteria for major or minor depression, and have met criterion for social support/isolation will be eligible for re-screening to determine depression eligibility at SV2a. SV2a will be scheduled to correspond to a point that might be expected to allow patients to have had symptoms previously endorsed during DISH administration at SV2 for a period of two weeks but must be scheduled within 21 days after patients' myocardial infarctions. Determination of major or minor depression during SV2a will be conducted by querying patients about the duration of symptoms endorsed during the previous DISH administration as a follow-up to the DISH. SV2a may be conducted either via phone or in-person visit at the discretion of the local clinic. Patients who do not have either major or minor depression according to DSM-IV criteria at SV2a will be ineligible to participate further. Patients who meet criteria for major or minor depression and all other eligibility criteria will proceed to SV3.

### **3.2.5 Screening Visit 3 (SV3)**

Patients who meet eligibility criteria at SV2 will then be scheduled for a visit (SV3) during which additional baseline data will be collected. The measures to be collected at this visit are described in the baseline determination section of this MOO. SV3 can, at the discretion of the local site, occur immediately after eligibility determination at SV2 or at a later visit but must occur within 21 days of patients' myocardial infarctions. However, every effort should be made to enroll patients as quickly as possible.

## **3.3 Specific Approaches/Methods to Recruitment**

There are a number of specific approaches and methods to recruitment for ENRICHD that are anticipated to ensure active participation of physicians/hospitals, to promote receptivity of potential patients for ENRICHD, and to address particular logistical, belief and attitudinal issues common

among minorities that may affect participation. These approaches and methods are summarized below.

### **3.3.1 Approaches to Promote Active Participation of Physicians/Hospitals**

A number of strategies will be adopted in ENRICHD to ensure that the providers and hospitals will be likely to support recruitment, adherence and active participation of patients. As discussed in Section 1.2, the role of the CC in developing personal relationships with the providers in the study hospitals, ensuring that the providers are appropriately engaged in recruitment generally and particularly in decisions that are being made concerning individual patients.

Additional approaches to promote the active participation of providers and hospitals are:

- promoting articles, flyers and community talks to disseminate information to the broader community about the risks associated with depression and low social support and awareness of the project

General awareness of the project within the broader community was thought to be important to generate support both from the professional community as well as from potential patients and their families.

- gaining support for the project from relevant professional groups

Support should be sought not only from cardiologists who may be treating patients at the time of enrollment but also from other professionals who may influence the cardiologists and the patients. Among these professional groups are: primary care physicians affiliated with referring hospitals who may have great influence over their patients; cardiac rehabilitation staff who may have substantial contact and influence with patients during their rehabilitation; and inpatient and outpatient nursing staffs who also may influence both patients as well as physicians. Support from these professional groups will be promoted by:

- making personal contacts with the CC and/or local hospital nurse responsible for recruitment; discussions with attending physicians outside study practices
- making professional talks about the ENRICHD project objectives and protocol at the institutions Grand Rounds, Cath Conference, or Medical Staff meetings
- sending out a mailing such as a letter, announcing the project and asking for their support from Dr. Lenfant) and a letter from the Investigator at each center to all attending physicians describing ENRICHD.
- participating in inservice session for hospital personnel in all identified prescreening areas

If outside physicians are familiar with the study, are assured that their patient will be used ONLY for the study and under no circumstances will he be accepted into your PI's practice, you will have



success in gaining permission to approach many of these referred patients. Additionally, your physician will continue to receive referrals from these practices.

A courtesy, and helpful in gaining cooperation from outside practice physicians, is requesting their participation as Sub-investigators in ENRICHD, and listing them on the 1572.

While the active support of the professional community is seen as very important for ENRICHD, we recognize that a balance must be struck between ensuring that these professionals are supportive but not promoting their efforts to identify and manage depression and/or low social support to the extent that this would affect significantly their management of patients assigned to the usual care group. All of the investigative teams involved in ENRICHD are experienced in dealing with such issues, and we are confident that our efforts can strike an appropriate balance in this regard.

- involvement of HMOs as appropriate

For some sites, we recognize that the active support of HMOs will be important in our efforts to recruit participants. In other sites, given the rapid changes in managed care, the active support of newly-emerging HMOs may become more important over the proposed three years of recruitment for ENRICHD. All of the sites are aware of these issues and either already have solicited the support of HMOs or are prepared to do so when appropriate.

- educating the professional community through a HomePage on WWW.
- ENRICHD home page address is: [www-bios.sph.unc.edu/csc](http://www-bios.sph.unc.edu/csc)

It is our experience that many members of the professional community have become avid purveyors of the WWW. Hence, the ENRICHD HomePage on the WWW. The home page is an effort to educate these providers about ENRICHD to promote their support of recruitment and retention efforts.

### **3.3.2 Approaches to Promote Receptivity of Potential Patients and Families**

- community education to promote receptivity by potential participants and their families

As mentioned in 3.3.1., we anticipate active efforts to promote community education through multiple channels, using the media as well as talks within the community. Educating potential patients and families about the risk associated with depression and/or low social support may be important in promoting their receptivity to enrollment in ENRICHD. However, as with efforts within the professional community, care will need to be taken to ensure that concerns are not raised to the point that patients and families do not significantly alter their approach to seek care or self-manage depression and low social support for those patients assigned to usual care. Thus, we are sensitive to the needs to promote general education about ENRICHD but only in a relatively limited manner.

- developing tools and methods to ensure that potentially eligible post-MI patients and their patients can be educated quickly and efficiently

We recognize that much of the orientation and education of post-MI patients and their families concerning ENRICHD will need to occur while the patients are hospitalized since the community educational efforts to which they may have been exposed prior to the MI will be minimal. While patients and their families will need to be fully informed, we also recognize that hospitalization after a cardiac event is a busy period and little time may be available during the day to meet with patients and their families to inform them as well as to screen them. Hence, ENRICHD will develop brochures and a video tape in an effort to facilitate efficient education and orientation of patients and their families. We have had particular success with the use of video tapes and anticipate that this will be a very useful method for ENRICHD since most hospital rooms are now equipped with VCRs. We also anticipate that our recruitment and screening will largely need to occur during evening hours and plan our staffing patterns accordingly.

- incorporating motivational interviewing methods to promote patients to identify and clarify their own, personal reasons for participating in ENRICHD

Within the past few years, several of the ENRICHD investigators have had particular success in teaching recruitment staff to incorporate motivational interviewing methods into their discussions with patients. Motivational interviewing was originally developed by Miller and colleagues as a method of systematically identifying personal reasons for reducing alcohol consumption among problem drinkers (refs) but has more recently been applied in efforts to promote recruitment, adherence and retention within clinical trials. Thus, we will train the CCs and local hospital recruitment nurses to use motivational interviewing methods in an effort to promote recruitment and active participation.

- enlist support of health care providers (physicians and nurses) to lend credibility and provide potential patients with encouragement and support for participation

Physicians and nurses provide a highly credible source of information for most patients, particularly when they are hospitalized during an acute event. Consequently, there is great value in enlisting the support of health care providers in encouraging and supporting their patients to participate in ENRICHD. Health care providers should be enlisted in the recruitment process, encouraging them to mention ENRICHD to potentially eligible patients and to encourage patients to participate even before patients are approached by ENRICHD staff. For patients who seem reluctant to participate when they are approached, active efforts should be made to discuss the patient's participation with his/her nurse and physician, and these health care providers should be enlisted in efforts to fully inform patients of the potential benefits of enrolling in the trial.

### **3.3.3 Approaches to Address Particular Issues Among Minorities**

ENRICHD will enroll 50% women and 50% minorities in the total sample. In order to achieve that objective, we plan to implement a number of recruitment strategies specifically designed to assist

women and minority patients in participating in the study. Since both these patient groups have often been under represented in previous clinical trials of the management of MI, we will use a set of generic recruitment strategies aimed at facilitating participation by both patient groups. The issues that we have identified and will address that are of particular importance for women, minority and low-SES participants can be categorized into logistical, belief and attitudinal issues. Important issues that will be addressed are further considered below.

- logistical issues such as transportation, child care, timing of visits, etc

As mentioned in Section 4.1.2, the role of the Case Coordinator will be critical in assisting intervention patients to meet individual needs. The Case Coordinators will be particularly sensitive to issues concerning transportation, meals, child care and other family obligations, timing of counseling sessions etc. In some cases, this will require liaison with social workers and other health professionals. In other cases, it will involve the Case Coordinator serving as an advocate for participants within the site activities to ensure that methods to overcome child care and session timing concerns are addressed at the local level.

- cultural diversity and sensitivity of staff

Recruitment efforts often suffer from a lack in diversity and sensitivity in study personnel, leading to poor recruitment results in certain subsets of patients. Obviously, this issue is not limited to female and minority patients, and may apply generally to the heterogeneous mix of patients that will be targeted for this trial. We will, therefore, endeavor to hire appropriate personnel aimed at maximizing the diversity of the staff. This will allow us to, where possible, match staff to patients in terms of gender and ethnicity. In addition, we will make sure that we have bilingual staff, particularly at the sites that plan to recruit Spanish-speaking patients.

In addition, we will require that all staff receive adequate training to ensure cultural sensitivity. Sensitivity on the part of the staff is not only important regarding the mixed gender and ethnicity composition of the study sample, but also regarding the age and specific psychosocial characteristics of the patients targeted in this trial. For example, given the recruitment objective of 50% women, we will likely enroll a substantial number of older and potentially quite frail patients, who might need special assistance during recruitment. Equally important is the fact that the ENRICHD trial is aimed at socially isolated and depressed patients, and we will therefore instruct recruitment staff regarding the nature of these conditions, and train them how to be sensitive to these conditions while trying to enroll them in the study. Severely depressed patients may form a particular challenge during recruitment, and recruitment staff will undergo special training to help them develop the skills to enroll these patients in adequate numbers.

- literacy and language issues

In a study which attempts to enroll bilingual people, mono-lingual non-English speaking people, and low-SES persons, literacy and language issues are extremely important. Populations for ENRICHD in which language is a concern is largely limited to Hispanic populations. While there is clearly

variation in language across different segments of the Hispanic population, diversity in our target recruitment population is sufficiently limited so as to make it possible to use a single translation of text material. Those centers recruiting non-English speaking participants will have sufficient recruitment, screening, clinical and intervention staff who are fluent in Spanish to address communication concerns. We will also ensure that appropriate text materials are used. Spanish language versions of all ENRICHD questionnaires are available.

Literacy is an issue that will likely be encountered by all of the ENRICHD centers. To address these issues, written materials to be provided to participants were developed at an 8th-grade reading level. However, we have also found that it is essential that appropriate options be available to participants for assistance in reading in completing assessment and intervention materials. For assessment materials, all of the ENRICHD centers have used procedures to ensure that clinic staff are available and ask participants whether they would like questionnaires and materials read to them. In our experience, asking in this manner in a straight-forward and non-judgmental manner is often sufficient to minimize the embarrassment of participants and awkwardness of the situation.

To address literacy concerns with materials that are sent home, we have often found that participants will have family members or friends who can assist in reading. Particularly for a study such as ENRICHD, focusing on the treatment of depressed and/or socially isolated persons, efforts to involve significant others in this manner might be seen as having therapeutic benefit in addition to ensuring that the content of materials can be conveyed. Any record keeping by participants assigned to the intervention can also adequately be dealt with by having significant others record the information or providing tape recorders for the recording of information. The Case Coordinator and therapists will work individually with patients to ensure that appropriate measures are being used to deal with any literacy issues.

- complex belief and attitudinal issues

Low-SES and minority participants often report beliefs and attitudes that serve as barriers to participation in trials such as ENRICHD. We have found it effective, nonetheless, to acknowledge these common beliefs and attitudes from the outset, thereby allowing open discussion between the staff member and the participant. Common among these belief and attitudinal barriers are: fear of large institutional settings; fear/distrust of "research" and/or academic institutions; concern/unfamiliarity with randomization methods; and concerns about treatment continuity of care and primary care. Training of therapists, Case Coordinators and other staff will ensure that ENRICHD project staff are familiar with these issues and prepared to openly discuss these matters with participants. Within the overall context of a supportive environment, open discussion in this manner is often sufficient to minimize these concerns.

Belief and attitude barriers to participation will also be addressed through soliciting the support and endorsement of key influentials who are women and who are minorities. Comments by these individuals will be incorporated in video and print materials to be used in ENRICHD.

### **3.4 Tracking Systems/Screening Logs to Monitor Recruitment**

We have found accrual tracking systems to be essential for examining issues related to comparability of enrolled versus not enrolled patients and for conducting efficient recruitment. These data can be used to facilitate recruitment by allowing quick determinations to be made not only of recruitment progress but also to characterize rates at which participants are showing for visits, reasons for ineligibility, and recruitment methods that prompted participants to volunteer; these data can then be used to refine recruitment methods and procedures for a more efficient recruitment over time. In a study which seeks to recruit proportions of particular groups, such as in ENRICHHD for the enrollment of women and minorities, adequate data are also useful for tailoring recruitment methods over time in an attempt to meet goals for these groups. Additionally, these data will be essential to our ability to describe individuals who were not eligible for randomization, characterizing their demographic characteristics and specific reasons for ineligibility, as well as individuals who choose not to participate. Hence, the Coordinating Center will develop an accrual tracking system, incorporating variables seen as useful by the Clinical Units. Variables that will be included are:

- overall yields by screening visits (consent, show and eligibility determination rates)
- responses and yields by recruitment method/hospitals
- key baseline socio-demographic and medical variables from those not randomized and those not willing to provide consent for screening

### **3.5 Identification of Potentially Eligible Participants**

#### **3.5.1 Potential Sources of Post MI Patients**

Patients can be identified at a number of different locations, including: the hospital's daily patient census, the Emergency Room, the Coronary Care Unit of Intensive Care Unit, the telemetry floors, the medical floors, the Cardiac Catheterization Lab or the Interventional Cardiac Cath Lab, and on Laboratory Printouts. It is extremely important to consider all units in your institution where you might locate possible ENRICHHD patients, so that no post MI patient fail to be screened. The hospital census may identify patients with acute MIs; if so it is a good place to start screening, but if you only look there you may miss many potential patients. In many hospitals, ICUs and ERs keep logs of patients that would identify those with acute MIs. These lists should be used to identify additional patients to be screened. Patients referred in to a tertiary center from outside physicians may come into your institution after their MI, only for an angioplasty or other intervention. These patients would not be noted on your hospital census as MI patients. Other patients may initially be admitted to your institution with a diagnosis of unstable angina, or rule out MI, but go on later to rule in for MI. All areas listed above are units where you might locate post MI patients. Consider your own institution for additional areas to screen. By making contact with staff in these areas before ENRICHHD begins, and providing inservice training about ENRICHHD, you may receive patient referrals from them and will minimize the chances of missing potential patients. Another

approach to identifying potential ENRICHD patients is to make arrangements to receive your institution's laboratory printout of patients with abnormal biomarkers.

### **3.5.2 Personal Contacts Will Assist in the Identification of Post-MI Patients**

Contacts from a variety of hospital areas can prove to be efficient sources of promising leads, such as:

- a) The ER Head Nurse can provide you the ER admit sheet on a daily basis. The Head Nurses in the Cardiac Care Unit or other unit may do the same
- b) Floor Nurses can let you know which patient is still too ill to discuss the study, or whether a patient is incompetent.
- c) Nursing staff can provide information on when the patient may be discharged, and what time of the day might be best to approach this patient.

Talk to anyone in your institution who may be of help in the identification and screening of MI patients. Making friendly contacts in all hospital areas identified can save you time because these people can provide data directly to you on patients currently in house post MI, or with a diagnosis that may become an MI. They may also provide information on patients admitted for a cardiac procedure, such as a PTCA. This can gain you needed information without time consuming and extensive leg work on your part.

### **3.5.3 Who Can Give You Permission To Approach Patients About ENRICHD?**

This will vary by institution and situation, but may include: a) attending physicians; b) emergency room physicians; and/or c) private physicians from outside practices. Approaching patients that don't "belong" to the physician you work for can cause multiple problems, unless you receive prior permission from that patient's referral physician. In large institutions with many referrals from outside general practice MDs, or internists, recruiting these patients without the knowledge and permission of their physician may be viewed in a hostile manner. In some cases the referring physician may be participating in another trial and plan to enroll that patient, once he/she is discharged from your institution. Your enrolling the patient in ENRICHD would often prevent that enrollment from happening, and result in animosity from the referral MD. Outside referral physicians are often very conscious that patients they refer to a specialist may continue to seek care from the specialist rather than returning to the referral physician for ongoing care. Both for reasons of common courtesy and for continued referrals from these physicians, it is important that the outside physician know about the ENRICHD protocol and give permission for his/her patients to be screened and approached about the study. Receiving blanket approval from attending physicians to approach their patients is suggested wherever feasible. This is more likely to occur if they know you will be sensitive to their lines of referral. When you screen patients from physicians who gave blanket approval (particularly those who do not regularly make rounds of their hospitalized patients), notify them (by mail) that the patient has been approached. This is not only a courtesy, but also a

way to help keep the patient in ENRICHD. If their physician knows the patient is in ENRICHD, and discusses the study in a positive way, the chance of dropout will be reduced.

### **3.5.4 Organization and Management of the Screening Process**

The organization and management of the screening process will differ from site to site depending on the characteristics of the hospitals, the qualifications of the screening staff, and the preferences of investigators and staff. However, it is important to determine clearly who has responsibility for each step in the screening, eligibility determination, baseline data collection, and randomization process. Perhaps the best way to determine responsibilities by screening visits (SV0, SV1, SV1a, etc.), since these visits cluster comparable or compatible activities together. While it may be determined that a single individual has responsibility for more than one screening visit and that screening visits may occur sequentially without the patient even realizing that a new step in the screening process has been entered, alternatives to this approach are possible, depending on local circumstances, that break up the screening visits by time and by responsible staff member.

Variations in the screening process will also occur based on institution size and type, staff member's work schedules and workloads, screening frequency desired, and availability of charts for screening. If your institution is a large tertiary center, with many admissions each day, and patients located in many areas, through prescreening make take a significant amount of time each day. At large centers, it may be necessary to have more than one person prescreening patients for ENRICHD to be certain that all MI patients in your institution are covered. This need will vary, dependent on the number of patients available for screening, and the Coordinator's other responsibilities and work schedule. Obtaining medical records and auditing for inclusion/exclusion criteria on each identified MI patient may be a time consuming task. Chart auditing is an easy skill to teach; if Coordinator hours are at a premium, consider hiring a student part time to complete chart audits on identified post MI patients. At some large research centers, a Coordinator may be able to screen simultaneously for multiple trials with similar patients needs. At smaller hospitals, with fewer patients, one Coordinator screening on a daily (weekdays) basis should easily be able to prescreen every MI patient.

In most cases, prescreening should be done each weekday. Without daily screening, patients may be located several days post MI, resulting in the patient being discharged before an approach for ENRICHD is possible. Hospital stays for uncomplicated AMI are becoming shorter and shorter. For this reason, it's recommended that Friday prescreening be done in the afternoon, and Monday's, in the early morning. To help determine the average amount of time uncomplicated patients will remain in your institution, and therefore their availability for screening, find out the procedures done on post MI, patients at your hospital. For example, in our institution cardiac catheterization is routine prior to patient discharge, but not in every institution. A catheterization may add another partial day to a patient's hospital stay. Each patient is unique, but by determining standard practice patterns in your institution, you will get a feel for the amount of time available to find patients and screen them for study eligibility prior to their discharge. Ease of chart access for audits may vary by time of day and your institution's practices. Determine an optimum time for review in your institution by questioning staff on the various units.

### 3.5.5 Organization of the chart review process

Prior to examining any charts or approaching any patients, permission should be obtained from the hospital administration, unit staff, and/or individual physicians according to local hospital procedures and policies and local IRB requirements. Note: IRB requirements may require patient informed consent prior to chart review. Also, IRB requirements or local procedures and policies may require physician approval before chart review. If either of these situations is the case, then consent and/or physician approval must be obtained before looking at any charts.

Screening of ENRICHHD pilot study patients should then proceed as follows. Once patients are identified, determine which unit has the largest group of MI patients. Proceed with chart auditing on that unit first.

- a) Obtain medical records on all identified MI patients located on the unit.
- b) Organize the records by patient's date of hospital admission.
- c) Start audit with the record of the patient admitted first.
- d) Begin audit by reviewing chart information easiest to locate with respect to inclusion / exclusion criteria; compare to determine if patient fits study criteria.
- e) Look first at the admitting history and physical exam to determine underlying medical conditions.
- f) If the first patient reviewed fits criteria, and is close to discharge, consider whether there will be time to approach the patient later, or whether he/she may be discharged imminently.
- g) If time allows, continue reviewing charts until all MI patients on that unit have been prescreened for ENRICHHD. Then approach the patient who seems closest to discharge first.

To avoid reviewing the entire record on patients who may not qualify, review first for concomitant medical conditions that may limit life expectancy or the patient's ability to benefit from the study, or patients with known physical or mental limitations that might interfere with full study participation. Be sure to review MD narrative/progress notes for clues as to when the patient will be discharged. Better yet, ask the physician or the nurse caring for the patient.

### 3.5.6 Rescreening Promising Candidates

Keep a list of patients whose charts were screened who were excluded for conditions that might change prior to discharge. Examples of such exclusions include:

- a. High values of lab safety parameters, or low values of cardiac enzymes
- b. Patient too ill / unstable for current approach



- c. Patient currently on prohibited medications

Plan to re-screen chart for changes in patient condition prior to discharge:

- a. Note date of planned re-screen on patient list
- b. Continue re-screening until patient is eligible or definitively ineligible for ENRICHD enrollment

## **3.6 Conducting the Screening and Baseline Interviews**

### **3.6.1 Planning the Approach to the Patient**

Once the patient is prescreened, and appears eligible for ENRICHD, plan carefully a time to approach him/her. Your visit needs to take place between the patient's tests and procedures to get to them at a time they are not tired, and they can focus their attention on you.

Try to get a rough idea of the customary tests and procedures in your institution/community for post MI patients, and their usual sequence. With this knowledge, and careful attention to what stage the patient has reached, you can attempt to time your visit optimally.

- a. Approach early in the hospitalization may be preferable; there is less chance of missing patient.
- b. Each institution differs in timing of patient procedures; determine procedure schedule for particular patient.
- c. Allow sufficient time to complete introduction, brief explanation, consent and interview in one visit.
- d. Patients More Frequently Have Visitors Afternoons, Evenings and Weekends.
- e. Late evening, after visitor hours, may be appropriate, as may late night or very early morning.
- f. Day of discharge is the worst day for patient approach; patient is focused on leaving hospital.

### **3.6.2 Conducting the Initial Patient Contact**

**Smile and take it slowly; be empathetic and patient.**

- a. Introduce yourself; tell where you're from and what you're doing
- b. Mention the patient's doctor suggested (or approved) your contact
- c. Ask if patient has a few minutes to talk to you. If patient is "too tired", ask about a better time

**Be courteous**

- a. If visitors are present, introduce yourself; say you'd like to talk to the patient
- b. Don't run visitors off; instead, ask when you can return, perhaps while visitors get a meal
- c. Assure patient's privacy
  - 1) If staff are present in room, wait to get into personal information until they leave
  - 2) Some hospital rooms are small and not private. Curtains provide only the appearance of privacy. Modulate your voice level appropriately.
- d. Allow some time to get to know the patient. Take the time to let her talk to you awhile about what is on her mind before you begin talking about ENRICHD

**3.6.3 Gaining Acceptance**

A sample "Overview and Consent Script is provided in Appendix 4.1. This may be modified to meet local requirements and circumstances. General principals in obtaining consent include:

- a. Be Positive About the Study: **Your Attitude Counts**
- b. Briefly explain the study; save specifics for later
  - 1) Emphasize all MI patients are being approached for this study which is being run nationally at many large medical centers
  - 2) Use non-medical terminology and simple explanations whenever possible
  - 3) Explain that earlier research suggests a post MI patient's mood and his/her interactions with the people around him may effect his cardiac outcome

4. Identify the patients' role in ENRICHD

- c. Assure patient confidentiality of any information collected
  - 1) Explain that the patients name will not be on any of the study materials, that patients are identified by study number and initials instead
  - 2) Explain who has access to the information
    - Patient must be told that others besides yourself will see the information, but they will be people connected with the study, or people who work auditing studies or for the FDA

- d. Assure patient of lack of pain or discomfort in interview participation
- e. Thank the patient for agreeing to participate

Make certain the patient understands that he/she was not specially singled out to participate in this study due to something he/she did or said, instead that ALL patients admitted to your institution with a heart attack are being considered for ENRICHD participation.

Talk honestly about the role the patient plays in research studies, and in ENRICHD. Explain honestly that although the patient may gain nothing from participation, information learned from his participation and that of the other patients may lead to improvements in the care of people having heart attacks in the future.

Make certain that patients understand that the information they give you on a questionnaire or in an interview is as confidential as their medical record. Some people other than yourself will see it, but the patient's name will not be attached to the information in any way, even if information is written up about the study later.

Many patients are concerned about additional pain or discomfort; assure the patient that this interview is "talking only", no discomfort. In fairness to the patient, they need to know that if they qualify and go on to full study participation, they will have blood drawn at a later date.

### **3.6.4 Approaching Patients who can't be interviewed in-hospital**

General principles with patients who have been discharged include:

- a. Initial face to face contact while the patient is hospitalized is preferable to a telephone introduction
- b. If patient's remaining time in the hospital is very short, make your introduction brief
- c. State that you'd like to call the patient when he settles in at home to talk with him further
- d. Mention the conversation will concern the patient's mood after his heart attack
  - 2. Tell the patient his doctor either suggested or OK'ed your contacting the patient
- d. Request permission to telephone in a day or two; ask what time is best
- e. Make phone call as scheduled; follow guidance provided for in hospital approach

### 3.6.5 General Issues in Interviewing Patients

There are a number of general issues to which interviewers must adhere in interviewing patients. These include the following:

- Sensitivity to patient burden. Consent must be obtained from patients' physicians before approaching patients to participate in the pilot study. Patients who are too ill, easily fatigued, or who would be overly burdened by participation will not be approached for recruitment. The screening and baseline measures (for patients who participate in completing the baseline measures) will be administered at separate times, rather than in one session, in order to avoid patient fatigue. Interviewers must be sensitive to signs of fatigue or other indications that patients are uncomfortable, such as yawning, difficulty concentrating, agitation, etc. If interviewers note signs of fatigue or discomfort, they will discontinue or postpone the assessment should it become onerous to patients. At the first signs of fatigue or discomfort, interviewers will discuss with patients the option of interrupting or terminating the assessment. In addition, when beginning each measure, interviewers will check with patients to make sure that they wish to continue.
- Literacy/data collection method. Some of the data collection for the pilot requires that it be collected in an interview format, while some of it can either be completed by self-administered questionnaire or by interview depending on patient preference. Although not the only factor that will determine patient preference for interview format, literacy will be one of these factors for at least some patients. While some individuals are comfortable in admitting that they are low in literacy, this is uncomfortable for many patients. It is essential to be sensitive to these, as well as other, potential patient concerns. The best manner in which to handle issues of patient preference is typically to ask all patients for their preference, such as by asking them: "I have some questionnaires which you can complete either on your own, or I can read them to you if you like; what would you prefer?"
- Confidentiality of information. All information obtained from chart review, discussions with patients' physicians or other medical care staff, and from the patients themselves is confidential. Procedures have been developed centrally to ensure the confidentiality of information, such as ensuring that patient information is not identified with patient names and that analyses are conducted and reported by group rather than by individual patient. However, each site will also develop and enact procedures to ensure the confidentiality of information. This will be particularly challenging with interview information that is collected from patients. Interviewers must ensure that confidentiality is not violated in the collection of information as a result of family members, other patients, or non-ENRICHD staff being able to hear or see patients' responses. The methods to do this will vary from setting to setting but will require either conducting the interviews in patients' rooms when no one other than ENRICHD staff are present and no one can over-hear the interview (e.g., the door must be closed) or in another room in which confidentiality can be assured.
- Presence of family members or friends. There are concerns about confidentiality from conducting interviews with family or friends present, and this is to be avoided. However,

some patients may state a preference for having family members or friends present during the interview and hence may waive their right to confidentiality of their data from these persons. Even in these cases, though, it is best to conduct the interviews in private, because the patient may feel more freely answer questions truthfully in private than in the presence of family or friends. Hence, even when patients express a preference for others to be present, it is best to discourage this by saying something such as: “We have found that it is best to conduct these interviews in private. The interview won’t take long, and perhaps your [family or friend] can excuse us for this time. Alternatively, I can return at another time so that we can complete the interview.”

- Completion of self-administered questionnaires. Some of the questionnaires can be completed by patients if they so desire. However, even when patients are completing the questionnaires on their own, interviewers should remain in the room with the patient for two reasons: 1) to answer any questions that might arise; and 2) to ensure that no one comes into the room and attempts to assist patients in completing the questionnaires. We are interested in patients’ responses to the questionnaires, not in responses that may be influenced by others. Hence, interviewers should remain in the room at all times when patients are completing questionnaires.
- Detection of patients at suicidal risk. Since the psychodiagnostic interview addresses diagnosis of depression and suicidal risk, issues concerning how detection of these conditions must be addressed. These issues are addressed more thoroughly in DISH Manual (see appendix). However, protocols for determining how the detection of depression and low social support are to be handled at each hospital must be determined and followed and is the responsibility of each clinical unit.
- Benefits to patients. ENRICHD has great potential for determining the benefit of psychosocial treatment of depressed and/or socially isolated post-MI patients on the development of new MIs and deaths. In addition, the information gained from the study will also be of direct benefit to the participants. If patients are found to be depressed via the diagnostic interview, this information will be provided to their primary care physician so that appropriate referrals can be made for treatment. Since depression is not an uncommon phenomenon during the post-MI period, yet is rarely if ever routinely assessed in post-MI patients, timely diagnosis and referral represent a direct benefit for these patients which may not be realized under typical hospital procedures.

## **3.7 Eligibility Determination and Randomization**

### **3.7.1 Eligibility Determination**

For each eligible patient screened, the following procedures should be followed prior to calling the ENRICHD Coordinating Center to randomize the patient:

- Enter the patient information on the ENRICHD administrative form - Screening Log (SLA)
- Complete the Medical Eligibility form (MEA)
- Complete Social Support Inventory screen scoring (ESSI)
- Complete the DISH (see detailed instructions in Appendix; Appendix 4.2 contains a sample script for introducing the DISH)
- Complete the Randomization Worksheet (RAN)

If the patient meets all medical inclusion and exclusion criteria, proceed with randomization into the ENRICHD study, and meets DSM IV criteria for major depression, or meets the low social support criterion score.

If the patient meets all medical inclusion and exclusion criteria, but the decision is made not to randomize the patient into the ENRICHD study at this time because of failure to reach a threshold score on the psychosocial screen, re-evaluate the patient within 2 weeks for a change in symptoms of depression or low social support.

### **3.7.2 Randomization Procedures**

Complete the following procedures to randomize an ENRICHD patient:

1. With the completed Randomization Worksheet in hand, place a telephone call to the data coordinating center, 1-800-472-2595. The ENRICHD coordinating center Telephone Randomization System (TRS) will prompt you for your user ID and Personal Identification Number (PIN) to verify that you are an authorized user.
2. Next, information from the Randomization Worksheet will be used to answer a series of qualifying questions. The TRS computer will prompt you for the patient ID, BDI, and ESSI scores and the DIS, and Dysthymia scores from the DISH.
3. After confirming that the patient meets either the depression or low social support criteria, TRS will provide the patient's treatment assignment and randomization ID number. TS will also FAX the randomization information for the patient to your ENRICHD field center case manager office for confirmation.
4. Record the treatment assignment and treatment number on the randomization form worksheet.
5. Appendix 4.3 contains a sample script for informing the patient about their treatment assignment.
6. Once the phone call is completed, schedule the appointment with the ENRICHD therapist for patients assigned to the intervention group. For the usual care patients, take this opportunity to

schedule the first follow-up visit 6 months from today (within a visit scheduling window of 3 weeks).

### **Appendix 3.1. Sample Overview and Consent Script.**

**"Hello Mr./Mrs. Jones. How are you feeling? (How are you doing? How are things going for you?) I'm Jane Doe from the \_\_\_\_\_ Department. I work with a group of doctors who are studying new ways to help people recover from a heart attack and I would like to describe this study to you. Dr. \_\_\_\_\_ has agreed for me to talk to you about this.**

(This statement can and should be made stronger when true, e.g., Your doctor knows about this program and believes that it would be a good opportunity for you).

**"The project I am about to describe is a research study funded by the National Institutes of Health in Washington, D.C. It involves identifying people who have just had a heart attack who may be having problems with feeling down or depressed or feeling stressed, or who might not be getting as much support from other people in their lives.**

**The scientists who have put this new program together have spent many years interviewing heart patients. They have found that prolonged sadness or depression or feeling isolated (apart from) from others are common problems for heart patients that make it more difficult (harder) for them to recover.**

**I would like to ask you some questions that will help me decide if this program fits you. If the program might help you, I would like to then do a longer interview. If after the interview it appears that (looks like, seems like) you might be depressed (be feeling down or sad) or that you might need more social support, then I will invite you to be in our study. There is no cost for your participation in this study.**

**Do you have any questions at this point?**

(Pay attention to the subject's non-verbal behavior which may give you some information as to their interest. Some people will be ready to go over the consent at this point, others may be backing out.)



**"If you would like to take part in this project, there is a 50-50 chance that you could receive the new program to help you with these difficulties (problems). Even if you aren't assigned to receive the new treatment, we will want to check in with you every six months to see how you are doing. You will be free to seek treatment on your own if you wish. In either case, your medical care and any other treatments will continue under the direction of your usual doctor (internist, cardiologist, clinic doctor, etc.). Can I answer some questions for you?**

**Let's go over the consent form together."**

## **Appendix 3.2. Sample Script for Introducing the DISH.**

**"Now I would like to ask you some questions about how you have been feeling and how your mood has been. Some of the questions may seem a little unusual or may not apply to you, but they are all about attitudes and feelings that patients may experience. Answering these questions should take less than an hour. While we would like you to answer each question to the best of your ability, you are free to choose not to answer any question or questions that you do not want to answer. Do you have any questions at this point?"**

(Note: It is best to remind patients that they can refuse to answer any questions the first time that the problem occurs. Sometimes telling them this gives them enough reassurance to go ahead and answer. We often explain the importance of, or reasons for, asking questions when we get to that point. How to help patients with this will be covered in the interview training.)

### **Appendix 3.3. Sample Randomization Information Script.**

**"Mr./Mrs. Jones. Hello. I am from the ENRICHD PROJECT (etc.). (Personalize call here, e.g., How are you doing, etc.) I have had a chance to call the Coordinating Center to get your group assignment. You have been randomized to the \_\_\_\_\_ group.**

**"This means (usual care) that you will continue to be treated by your doctor over the course of the study and will receive phone calls from the project staff about every six months. You will be asked to come to the clinic at 6 and 12 months from now, and then every year for the next \_\_\_\_ years for a short visit to discuss your recovery. Your blood pressure and weight will be measured, and you will be asked to complete a few questionnaires by interview. Your continued participation in the project is very important to the project. You will help ensure that we are able to obtain the best information we can about patients' recovery from a heart attack. Do you have any questions?"**

**"This means (intervention) that you will be followed by the staff of the ENRICHD program, and will be receiving individual counseling by a counselor over the next few weeks, and you will then graduate to a group program where you will be able to share experiences with other patients who have had a heart attack and have similar concerns as you do. You may be prescribed anti-depressant medication if**

**you are very depressed or don't improve with this counseling. These counseling sessions may last up to six months. You will also be telephoned by the ENRICHD staff and will be asked to come to the clinic for a short visit every six months. You will be asked about your recovery, your blood pressure and weight will be measured, and you will be asked to complete a few questionnaires by interview. Your continued participation in the project is very important and will help ensure that we are able to obtain the best information we can about patients' recovery from a heart attack. Do you have any questions?"**

### **Appendix 3.4. Educational Component Script.**

**"Mr./Mrs. Jones as part of the ENRICHD Program I want to provide you with some important information about your recovery now that you have had a heart attack. The (American Heart Association) has developed a program for people like yourself to help you with some of the adjustments you need to make in your lifestyle. These changes include such things as modifying your eating habits to lower your cholesterol, beginning a regular program of exercise based on what your doctor says is safe for you, and quitting smoking if you smoked prior to coming into the hospital. This workbook is yours to keep--to read and to review over the next few weeks. It has answers to many of the questions that you may have once you get home and back to work. The workbook gives you factual information and also contains some self-assessments that let you test how well you are doing. Most of the important information you need to know is presented in the first part of each section of the workbook. We hope you will take the time to read each section and use the information to give you ideas to help you make changes in your lifestyle. You may also want to share this workbook with other family members who are interested in your recovery."**

## 4. Chapter 4: Randomizing Participants

### 4.1 Introduction

The treatment group a participant is assigned to is determined by a telephone call to the ENRICHD Coordinating Center. Assignments are made by a computer algorithm run at the Coordinating Center. Because the assignment for each participant is determined through a chance process, this procedure is called “randomization.” However, controlled, documented, and accurate execution of this process is absolutely essential to the scientific validity of the trial. If you have any uncertainty about whether a patient is eligible to be randomized or about the procedure to follow, contact your clinical center supervisor or the Coordinating Center before proceeding.

Before patients can be enrolled from a hospital, NHLBI must have received written assurance from the hospital. No treatment assignments can be made for a hospital until NHLBI notifies the Coordinating Center that the information is complete.

Each Clinical Center Staff member must be trained and certified in the use of the system before being authorized to randomize participants. Upon certification, you will receive a four digit “PIN”, which must be used in addition to your ENRICHD staff ID number in order to access the system.

#### 4.1.1 Overview

The ENRICHD Telephone Randomization System (TRS) allows authorized users at ENRICHD clinical centers to make a telephone call to the Coordinating Center, respond to a series of questions using the telephone keypad and receive a treatment assignment for a specified patient. Written confirmation of the assignment will be faxed to the clinical center.

The TRS runs on a computer located at the Coordinating Center and is intended to be available 24 hours a day. In case of a system failure, designated Coordinating Center personnel will perform randomizations manually.

## 4.2 Using the Telephone Randomization System

### 4.2.1 Interacting with the System

The system uses pre-recorded speech samples to generate all instructions and prompts. The user responds to questions and provides information by pressing keys on the telephone keypad. The numeric keys are used for most choices. The pound key (#) is used to confirm a response or to indicate the end of a multi-digit response. The star (\*) key is used to indicate a prior response is incorrect and should be ignored. The system always indicates what keys should be used to respond to a question.

As you become familiar with the sequence of prompts, you can interrupt a prompt at any time by responding with the appropriate key.

### 4.2.2 Steps in the Telephone Randomization Process

- 1) Complete the Randomization Worksheet for the participant.

The System will prompt you to enter most of the information from this sheet. It also provides a place for you to record the treatment assignment provided and a treatment ID number used to verify that the treatment was assigned following the standard ENRICHD process.

- 2) Call the TRS at 800-472-2595

You must use a touchtone telephone when calling the Telephone Randomization System. The telephone number is 800-472-2595. The system can process two simultaneous calls. Most phone calls will require less than 5 minutes to complete. Since an average of three randomizations per day are expected, more than two simultaneous calls are extremely unlikely.

The system should answer the call on the second or third ring. If the line is busy, call back a few minutes later. If the line continues to be busy or if the line rings with no answer, call the Coordinating Center for assistance (see section 4.4, getting help).

The system will produce an introductory message.

- 3) Enter your ENRICHD Staff ID number.

The system will prompt you to enter your three-digit Staff ID number, followed by the # key. Each user from a center will have his own ID. Please use your own ID. Contact the Coordinating Center for additional IDs when new users are certified to use the system.

The entered staff ID number is spoken by the system, you are prompted to confirm or correct.

Press the pound key (#) if the value is correct. If you have made a mistake, press the star key (\*). If you press the star key you are asked again to enter your ID. This sequence will repeat until you press the pound key to confirm your entry.

4) Enter your Personal Identification Number (PIN).

The system will prompt you to enter your 4-digit PIN, followed by the # key. Each user from a center will have his own PIN.

The entered PIN is spoken by the system, and you are prompted to confirm or correct.

Press the pound key (#) if the value is correct. If you have made a mistake, press the star key (\*). If you press the star key you are asked to reenter your PIN. This sequence will repeat until you press the pound key to confirm your entry.

5) The ID and password are checked against a list of valid IDs and passwords.

If the ID and password are valid, the center for which the user may randomize patients is spoken. You are allowed to randomize patients from your center only.

If the ID or password is invalid, you are asked to enter and confirm the invalid value or values again. You are given three chances to enter a valid ID and password. If you fail to do so, the call is terminated. Check your assigned Staff ID number and PIN with your clinical center supervisor. If you used the correct numbers, contact the Coordinating Center for assistance.

To discourage attempts by unauthorized persons to access the system, the number of unsuccessful attempts at use over time is monitored. If the frequency exceeds a limit, the system is made completely unavailable for a period of time. Users calling during this time-out period hear a message that the system is currently unavailable. Contact the Coordinating Center for assistance.

6) Enter and verify the Eligibility ID for the participant.

The eligibility ID is the combination of the 2-digit center code and the 7 digit Patient ID number. Press the pound key after all 9 digits have been entered.

The eligibility ID entered is spoken.

To insure accurate entry, you are asked to reenter the eligibility ID.



In order to confirm the eligibility ID, two consecutive entries must match. If your two entries are not identical, you will be prompted to try again. You are given three chances to enter two consecutive matching values, or the call is terminated.

7) The eligibility ID is checked for validity:

- the center must be the one for which the user is authorized to enter patients
- the hospital number must be valid for the center and authorized to enter patients
- the patient number must be a valid ENRICHD patient number
- the patient number must not already have been randomized.

8) Enter and verify the last 4 digits of the patient's social security number.

As with the eligibility ID, you will be prompted to enter the number twice, to insure it is accurate.

If a participant does not have a social security number, or refuses to provide it, contact the Coordinating Center to receive a substitute code.

9) Enter the information from items 2-9 on the Randomization Worksheet.

These responses are entered only once. They are not confirmed by re-entry.

10) The system checks the responses and determines whether the patient meets the eligibility requirements.

If the patient is eligible, the system speaks the randomization ID and treatment assignment to the user. This information is repeated. Record the treatment assignment and treatment number on items 10 and 11 of the Randomization Worksheet. This information will also be faxed to a designated number at your center.

If the patient is not eligible, the user is informed and given the chance to randomize another patient or hang up to exit the system.

11) The system prompts you to randomize the next patient, or hang up to end the session.

### **4.3 Getting Help**

If you encounter difficulty using the system, contact your clinical center supervisor. If your supervisor is unable to resolve the problem, contact any of these ENRICHD staff:

Marston Youngblood: 919/962-3083

James Schaefer: 919/962-3052

Jim Hosking: 919/962-3085

If you are not successful in reaching anyone, contact the Coordinating Center at 919/962-6971. Ask to speak to someone who can provide assistance concerning ENRICHD randomization.

## 5. Chapter 5: Medical Measures and Endpoints Follow-up Data Collection Procedures

### 5.1 Introduction to Screening, Eligibility, and Baseline Medical Forms

The Medical Eligibility form (MEA) will be used for screening all patients admitted to hospital for acute MI. Information to be collected includes basic demographic information (age, race sex) plus the detailed inclusion and exclusion criteria defined for the study. For patients who are eligible by meeting the medical criteria, a Medical History form (MHA), and Baseline Examination form (BEA) are also complete. The MHA and BEA are intended to be completed as fully as possible from patient chart review prior to conducting the interview portion of the forms.

### 5.2 Medical Eligibility Form -- Screening, Inclusive/Exclusive criteria- MEA Version C

#### A) Demographics.

- 1a.) Age- record the patient age in years as noted in the chart.
- 1b.) Sex- note gender from chart or other screening log sources.
- 1c.) Race- record using the standard NIH ethnic group guidelines (see section 5.3).

#### B) Acute MI criteria.

The criteria for myocardial infarction, which is the criteria for the inclusion in the study, is outlined in section 3.3.1 of the protocol and is newly restated below.

- 2) Acute myocardial infarction must have one of the following characteristic enzyme profiles:
  - a. Cardiac enzymes are 2 times the upper limit of normal or greater for either peak CK, troponin or LDH. The CKMB level will take priority over CK alone or troponin if more than one assay is performed.
  - b. Include patients as meeting the criteria for the diagnosis of acute myocardial infarction if:
    - (a) MBCK values are increased above the upper bound of the reference range as assessed by the site cardiologist even if they are not two-fold greater than the upper limit of normal, provided a rising and falling pattern is manifested, and (b) acute myocardial infarction has been diagnosed locally, and if symptoms compatible with acute MI and/or characteristic ECG findings are present as defined in the ENRICHD eligibility criteria.
  - c. Acute angioplasty. (a) Include patients who present with ST segment elevation and classic signs and symptoms of MI if these patients meet ENRICHD criteria for marker protein elevations even if an acute angioplasty had been done so long as the diagnosis of

- acute infarction is confirmed by the site cardiologist; (b) NOT include patients with ST segment elevation if no elevations of marker proteins occur; (c) Include patients who present with chest pain, ST segment depression, a local diagnosis of acute myocardial infarction, if a three-fold increase in any of the biomarkers of myocardial injury is present and if the site cardiologist concurs with the diagnosis of acute infarction; (d) NOT include patients with less severe elevations. In the situation where ST segment depression is present, it is more difficult to know whether acute infarction has occurred from the initial history, physical and electrocardiogram or whether or not elevations could be due to the acute interventional procedure. However, recently, criteria have been proposed to diagnose acute myocardial infarction during the periprocedural time period if a three-fold increase in any of the marker proteins occurs.
- 3) The characteristic evolutionary electrocardiographic ST changes or new Q-wave are defined in section 3.1 of the protocol.
  - 4) The symptoms compatible with myocardial infarction will include those of chest pain, burning, tightness, squeezing, or pressure in chest which may radiate to arm, neck, or jaw lasting 20 minutes or greater or unrelieved by three nitroglycerin tablets which may be accompanied by nausea, vomiting or angina equivalent including shortness of breath, syncope, or excessive fatigue.

**C) Medical exclusive criteria for patients with documented MI.**

- 5) Patients who have a condition in which the probability of death is greater than 20% at one year will be excluded from the study. This would include cancer such as lung cancer, lymphomas, leukemia, advanced liver disease, and advanced rheumatologic disease. On the other hand, patients with prostate carcinoma, limited breast cancer, skin malignancy, and endstage renal disease receiving dialysis would be candidates for the study. If there is a question regarding the potential eligibility of the patient, this should be directed towards the project clinician at the Coordinating Center.
- 6) Severe cardiac complications are present such that the patient cannot either physically withstand assessment for eligibility, or communicate because of current condition (e.g. on a ventilator).
- 7) Conditions likely to limit physical capacity. Every effort should be made to include these patients in the study. However, it is likely that some of these patients will not be candidates because they are bedridden, or have physical limitations such that they could not be brought to the clinic by any support system or other methods and thus would result in exclusion from the study. Otherwise, we would encourage all patients, even those with important physical limitations option to participate.
- 8) Patient is not fluent in either English, or Spanish and either cannot comprehend the study instruments, or able to participate in therapy due to language barrier.

- 9) Major psychiatric comorbid illness present, except depression. Patients with current illnesses such as dementia, schizophrenia, active suicidal ideation, alcoholism can present problems for long term follow-up and adherence to therapy.
- 10) Patients who are in current research protocols involved in the investigation of the depressed or socially isolated post MI patients including the testing of antidepressant pharmacologic therapies would be excluded from this study. However, all patients involved in investigations of standard or novel pharmacologic therapies for myocardial infarction such as new thrombolytic therapy agents, new lipid lowering agents, new beta blockers, new ACE inhibitors, new forms of anti-platelet, or anti-thrombin.
- 11) Patient refuses consent-- self explanatory.
- 12) Physician refusal for patient to participate. Self explanatory.
- 13). Patients cannot have a post procedural MI. This includes procedures such as CABG, and PTCA. These procedures are associated with enzymes leaks that have a different outcome than patients with de novo myocardial infarction. Patients who have undergone noncardiac surgery (orthopedic, abdominal or vascular) and suffer a subsequent myocardial infarction will be candidates for the study. Thus, only those procedures that affect the coronary arteries will be excluded from the study.
- 14) Patient able to complete screening visits. If the patient is not able to complete all of the medical and psychological screening, then they are not eligible for the study.
- 15) Patient accessible for follow-up visits. If the patient is not accessible either by telephone, or in person for collection of follow-up data they are ineligible.
- 16) Death before randomization, self explanatory.
- 17) Screening window of 28 days elapsed before the entire baseline assessment of patient could be completed. The limit on age of the index MI intended to limit the eligibility of patients to the more recent, acute, phase following the qualifying event.
- 18) Patient is currently taking antidepressant medications less than 14 days. Short duration antidepressant use is still an exclusion. However, patients can be rescreened within the 28 day window and if the depression diagnosis evaluated at that time is meets DISH criteria, then the patient could be included in the trial.
- 19) Patient assessed as having good social support and nondepressed by ESSI and DISH is self evident, and is used as a screening aid in recording the outcome of assessment.

### **5.3 Medical History Form**

**A) Demographics** - The questions in this section are intended to be based on patient interview. Response cards will be used for the sensitive questions of race and income.

- 1) Birth Date of the patient may be present in the chart, but confirmation should be obtained to get as consistent and accurate information.
- 2) Gender of the patient should be self-explanatory.
- 3) Racial group of the patient will be recorded using ethnic categories defined by NHLBI guidelines. Hand or show the patient the queue card listing the 5 racial groups and have them select the group with which they identify that is consistent with the guidelines.

A synopsis of those guidelines follows: **Black** refers to a person having origins in any of the Black racial groups of Africa. In the United States this definition includes native-born Black Americans, Africans, West Indians, and Haitians. **Hispanic** refers to people born in North, Central, and South America, and in the Caribbean whose language is Spanish or Portuguese, and people born in Brazil, French Guyana, British Guyana, and Dutch Guyana although they are part of South America. The most common Hispanic groups in the U.S. are Mexican Americans, Puerto Ricans, and Cubans. **Native American** refers to a person having origins in any of the original peoples of North America and who maintains cultural identification through community recognition or tribal affiliation in one of the tribes residing in the lower 48 states. NHLBI classifies Native Hawaiians as Native Americans in addition to American Indians, Alaska Eskimos, and Aleuts. **Pacific Islander** refers to a person having origin in any of the peoples of the Pacific Islands (except Hawaii). **Asian** refers to a person having origin in any of the peoples of the Far East, Southeast Asia, and the Indian subcontinent.

- 4) Marital Status and living arrangement is self explanatory.
- 5) Highest grade of regular schooling completed is self explanatory.
- 6) Employment Status refers to being employed for wages, full or part-time basis.
- 7) Income for the past year should be presented to the patient as a category selected from the queue card. Mark the letter associated with the total household income range selected either on an annual basis, or the monthly equivalent which is in parentheses.

**B) Risk factors - comorbid illness.** These data items will generally be present in the patient chart. In general, a failure to mention the presence of a problem means the problem did not exist. However, asking the patient is always recommended for confirmation.

- 8) Hypertension is defined as a history of or currently diagnosed hypertension either treated or untreated, usually with blood pressure measurements of a systolic blood pressure measurement of 140 mmHg and/or a diastolic blood pressure 90 mmHg. There should be evidence of a diagnosis of hypertension either in the chart or from the patient; a random blood pressure measurement above these thresholds is not adequate.

- 9) Diabetes Mellitus - A history of diagnosis of diabetes mellitus. Check yes for insulin treated, if insulin given currently or has been given anytime prior to index myocardial infarction.
- 10) Smoking history - Check yes if patient smokes now or has ever smoked regularly. Indicate whether the patient is a current smoker or has quit smoking. If he/she has quit, give the year he/she last smoked. Provide the number of years smoked and average number of cigarettes per day. The definition of a current smoker is anyone who has smoked or taken a puff of a tobacco product within the month prior to hospitalization.
- 11) Hypercholesterolemia - A prior diagnosis of hypercholesterolemia treated or untreated or a history of or currently documented serum cholesterol > 200 mg/dl or a LDL cholesterol > 130 mg/dl.
- 12) Estrogen use - Check yes if patient has taken Estrogen within two years of index MI either as an oral contraceptive or hormone replacement therapy. Also indicate if Estrogen is currently being used by patient. Provide the age of menopause onset.
- 13) Family history of heart disease - Definite MI or sudden death before 55 years of age in the father or other 1<sup>o</sup> relative, or before 65 years of age in mother or other female 1<sup>o</sup> relative.
- 14) Renal insufficiency - Only patients with creatinine > 1.8 mg/dl should be defined as having renal insufficiency.
- 15) Malignancy - The presence of a malignant neoplasm should be noted in the chart. If not, and the patient is unsure please check with the attending physician since a severe malignancy could exclude the patient from ENRICHD.
- 16) Pulmonary disease - a history of or diagnosis of pulmonary disease such as asthma, COPD, pulmonary fibrosis or other diagnosis.
- 17) Rheumatologic disease - A history of or diagnosis of rheumatologic diseases such as arthritis, or other collagen - vascular diseases. Joint aches and pains do not qualify as true rheumatologic disease.
- 18) History of thyroid disease - history of hypothyroidism or hyperthyroidism, diseases such as thyroiditis, goiter, myxedema, or exophthalmos.
- 19) Depression - Patients on medication for depression prior to index myocardial infarction. Patients on antidepressants for other reason will have the drug reflected in their medications but should not be included here.
- 20) Liver cirrhosis - Patients with advanced liver disease with an expected survival that is reduced.
- 21) Other comorbid illnesses - Provide other clinically important comorbid illnesses using standard diagnostic medical terminology when possible.

### **C) History of Cardiovascular Diseases / Procedures**

- 22) History of a definite myocardial infarction - prior to current symptom episode - Record number of previous MIs, and the date of the most recent. Check type (Q-wave, non Q-wave) if known, and check location of most recent MI (anterior, inferior etc.) if it is known.
- 23-26) Previous angina, prior stroke, CABG, PTCA - A history occurring **prior** to index MI. PTCA includes all percutaneous interventions. Record number of prior CABG or PTCA and date of the most recent procedures.
- 27) CHF, NYHA Class: a condition classifiable on a NYHA scale. Check the worse classification during the six weeks prior to the six week MI. Asking for physician help if clarification is needed is recommended.
- a) NYHA Class I - Patients with cardiac disease, but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
  - b) NYHA Class II - Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
  - c) NYHA Class III - Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnea, or anginal pain.
  - d) NYHA Class IV - Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
- 28) Previous history of atrial fibrillation- A history of atrial fibrillation occurring prior to the index MI.
- 29) Previous times when the patients were resuscitated from cardiac arrest prior to index MI. Record date of prior event from chart if available.
- 30) Peripheral vascular disease- A history of prior PVD characterized by symptoms such as claudication, gangrene, or a record of surgical procedures or angioplasty to restore blood flow to the extremities.

### **D) Current Medications**



31-49) Check the patient chart just prior to, or immediately after discharge, and record the medications currently prescribed for the patient. Use the medications dictionary that groups drugs by class for recording on the form.

#### **5.4 Baseline Examination Form**

The Baseline Examination form is completed primarily from a review of the patient's chart associated with hospitalization for the index MI event that qualifies that person for enrollment into the trial. A limited physical examination is performed, noting vital signs along with ascertainment of specific signs and symptoms of heart failure. However, when questions arise, they should be directed to the attending physician or one of the ENRICHD medical investigators.

##### **A. INDEX MYOCARDIAL INFARCTION:**

- 1) Hospital Admission Date: record the date associated with admission of the index event.
- 2) Hospital Discharge Date: once the patient has been discharged for the index event, complete this item.
- 3) Index MI date-indicate the confirmation date of the myocardial infarction based upon enzyme elevation and physician documentation in History and Physical (H&P). On occasion, it is difficult to determine the exact onset of a heart attack. Often the major event is preceded by multiple small events. If there is confusion about the date of the index MI, choose the date and time that the patient came to the hospital.
- 4) Infarct Type: Q waves- A development of new Q waves in 2 or 3 leads in anterior, inferior or lateral regions. The easiest way to preserve these data would be to xerox the recording. In the absence of that, indicating whether the infarction is Q-wave or non Q-wave. should be entered. If help is needed, the attending physician or ENRICHD cardiologist should be consulted.
- 5) Infarct Location-Anterior: loss of R waves or development of QS complexes in leads V1-3, Inferior: development of new Q waves in leads II, III, or AVF. Other: Lateral, defined as development of new Q waves in leads I, AVL, or 2 of 3 leads of V4-6.
- 6-7) Ejection fraction-% left ventricular ejection fraction: If the ejection fraction has been measured, the number should be indicated in number 6 and the method in number 7. If no ejection fraction measurement is available, but a catheterization, echocardiogram or radionuclide imaging study has been done and it is indicated whether or not the diminution in ejection fraction is severe, moderate, mild or if the ejection fraction is normal, it should be indicated in 7A. If such tests have been done but no report indicates the severity of LV dysfunction, one of the ENRICHD investigators should be asked to investigate whether an estimation can be obtained..

- 8) Killip class - At the time of index MI should be recorded in the chart; if not delineated in the chart, determinants are listed in the bottom of the form and can be used to determine the appropriate class.

## **B. TREATMENT OF INDEX MI**

Simply check those procedures which have been done during the patient's hospitalization for acute myocardial infarction. These may not necessarily be those that occurred in the intensive care unit but should include the entire hospitalization. Note the dates for cardiac catheterization and CAGB if performed.

- 9) IV thrombolytic therapy-enter use of any thrombolytic agent such as streptokinase as a yes or no answer.
- 10) PTCA-indicate percutaneous transluminal coronary angioplasty (PTCA), stent or atherectomy and the hours that procedure occurred after admission to hospital. Note elapsed time since admission for performance of procedure.
- 11) IABP-enter use of aortic balloon pump during early course of recovery as a yes or no answer.
- 12) Swan Ganz-Self Explanatory.
- 13) Defibrillation-Indicate use of defibrillator for ventricular tachycardia or fibrillation during hospitalization course as a yes or no answer.
- 14) Temporary Pacemaker-Self Explanatory.
- 15) Intubation-Indicate whether intubation was performed at any time during hospitalization as a yes or no answer.
- 16) CPR-Cardiopulmonary resuscitation-Indicate whether CPR was performed at any time during hospitalization as a yes or no answer.
- 17) Cardiac Catheterization-Indicate whether cardiac catheterization was performed during hospitalization for index myocardial infarction and date of catheterization.
- 18) CABG- Coronary Artery Bypass Graft performed associated with the index MI. Record date the procedure was performed.

## **C. ENZYME LEVEL/LABORATORY/UPPER LIMIT OF NORMAL**

Laboratory values should be recorded from the chart. Values that are not available cannot be included. If values are available from a referring hospital, it would be optimal to obtain those laboratory values for completeness of the baseline data.

- 19-22) Peak CK-Characteristic elevation of creatinine kinase (CK) and creatinine kinase MB fraction above upper limits of normal for each hospital laboratory.
- 23-26) LDH-characteristics highest elevation of lactic acid dehydrogenase isoenzymes: recording of LDH 1 and 2 and hospital upper limits of normal.
- 27-28) Troponin T or I - characteristic elevation of the markers troponin T or I.
- 29) Creatinine-Self Explanatory.
- 30) Total cholesterol- Document earliest recorded measurement of lipoproteins at time of myocardial infarction.

## **D. MI COMPLICATIONS**

Complications during hospitalization should be indicated in the boxes for questions 31-41.

Questions with interpretation of these data should be checked with the attending physician or ENRICHD cardiologist.

- 31) Congestive Heart Failure-Syndrome of heart failure manifested by dyspnea, rales, jugular venous distention, gallop rhythm, or evidence of cardiomegaly or pulmonary vascular redistribution on chest X-ray.
- 32) Pulmonary Edema-Defined as either pulmonary vascular redistribution or frank pulmonary edema as noted by the radiologists interpretation on chest X-ray.
- 33) Respiratory Failure-as defined by H&P or intubation during early course of recovery.
- 34) Sustained Ventricular Tachycardia/Ventricular Fibrillation-episodes of either rhythm of greater than 30 seconds duration.
- 35) Advanced Heart Block (2<sup>o</sup> or 3<sup>o</sup>) - Mobitz 1-classical Wenchebach with increasing prolongation of the PR interval with a dropped beat Mobitz 2-a dropped sinus beat without prolongation of PR interval 3<sup>o</sup> heart block-dissociation of the arterial and ventricular rhythms.
- 36) Cardiogenic Shock-Persistent hypotension and tachycardial despite treatment with intravenous fluids and inotropic agents.
- 37) Ventricular Septal Defect-Positive only if presence is documented by a diagnostic test such as an angiogram, right heart cath, echo-doppler, or radionuclide study.
- 38) Severe Mitral Regurgitation-Holosystolic murmur at the cardiac apex as indicated by physical exam, catheterization or non-invasive study such as echo.
- 39) Supraventricular Arrhythmias-Characteristic widening of QRS complexes associated with RBBB or LBBB.
- 40) HR<45 beats/minute-Self Explanatory.
- 41) Stroke - Documented evidence of a cerebrovascular accident.

**E. PHYSICAL EXAM AT BASELINE**

The majority of these data can be garnered from the chart or by a nurse. All except for number 49, the presence of an abnormal cardiac sound can easily be obtained by well qualified nursing personnel. If there is difficulty appreciating whether an S3 gallop is present, one of the physicians caring for the patient or one of the ENRICHD investigators should be asked to do an examination.

At this time a baseline electrocardiogram should be obtained for comparison with future electrocardiograms to be taken during follow up. This ECG may be taken by the ENRICHD staff (see section 5.5 that follows for protocol for obtaining electrocardiograms) which would permit the best comparison to be made. However, if the ENRICHD team is unable to obtain an electrocardiogram themselves, a xerox copy of one taken several days after the index event could be scanned into a mini computer or copied to preserve the data for transmission to the data center and ECG core laboratory.

- 42) Date of Examination-- record date the patient physical exam was performed.
- 43) Height (in inches or in meters)-- stated height can be used if measurement impractical.
- 44) Weight (in pounds or kilograms) -- weigh patient without shoes, heavy clothing.
- 45-46) Systolic and Diastolic blood pressure-Measurement of blood pressure should be recorded in sitting position using a mercury sphygmomanometer, with appropriate cuff width for pts arm. After 5 minutes of rest, 1st measurement and 2nd measurements should be taken at least 2 minutes apart using same arm for measurement.
- 47) Heart Rate- Measured for 15 seconds and recorded in beats per minute.
- 48) Pulmonary Rales-The presence of a rales more than bibasilar with or without elevated neck pains or a third heart sound gallop.
- 49) S3 Gallop-Low pitched sound heard at apex in the left decubitus position.

## 5.5 ENRICHD ECG Procedures

### Introduction

At baseline after randomization preferably and after follow-up at 6, 18, and 30 months, a standard supine 12-lead resting ECG should be recorded.

#### 5.5.1 Electrode Position Measuring and Marking

Because it is essential for the study to be able to compare baseline ECG data with subsequent records, a uniform procedure for electrode placement and skin preparation is required. The method and procedure for standardizing electrode locations are outlined below.

The participant, chest bared, is instructed to lie on the recording bed with arms relaxed at the sides. The individual is asked to avoid movements which may cause errors in marking the electrode locations, but encouraged to converse with the technician. Prior experience with electrocardiograms is discussed, as is the purpose of the ECG recording. The participant should be told this is a research ECG to be used for analysis.

For best electrode/skin interface, place the electrodes on the skin at least 2-3 minutes before taking the ECG.

A good felt tip pen is used to mark the six chest electrode positions. Wipe the general area of the following 10 electrode sites with a sterile alcohol prep to remove skin oil and perspiration. It is extremely important that care be taken to locate these positions accurately. Therefore, the procedure given below must be meticulously followed. Electrode positions in women with large, pendulous breasts must be determined in relation to the anatomic points described below - as for all participants. The electrodes must then be placed on top of the breast (in the correct position).

#### Limb Leads

Locate electrode LL on the left ankle (inside).

Locate electrode RL on the right ankle (inside).

Locate electrode LA on the left wrist (inside).

Locate electrode RA on the right wrist (inside).

Figure 1. Electrode and Leadwire Placement

**Electrode V1**

Locate electrode V1 in the fourth intercostal space at the right sternal border. This should be at the same level as V2 and immediately to the right of the sternum.

**Electrode V2**

Locate the sternal angle and second left rib between the index and middle fingers of your right hand. Count down to the fourth rib and identify the fourth intercostal space below it. Locate V2 in the fourth intercostal space immediately to the left of the sternal border.

**Electrode V3**

Using a flexible ruler, mark the location of electrode V3 midway between the locations of V2 and V4.

**Electrode V4**

Electrode V4 is located using the E-V6 Halfpoint Method (3). Using a medical tape measure (American Hospital Supply, Cat. No. 30940), measure the distance between the E point and the V6 marking. The tape should be resting lightly on the skin, not pressing into the flesh. The E and V6 marks should clearly be seen above the tape. Without moving the tape, mark the location of electrode V4 midway between E and V6.

**Electrode V5**

Using a flexible ruler, mark the location of electrode V5 midway between the locations of V4 and V6.

**Anterior 5th Interspace Marker (E Point)**

Identify the fifth rib and fifth intercostal space below V2 by counting down ribs as described for V2. Follow this space horizontally to the midsternal line and mark this point. This is the "E" point.

**Electrode V6**

With the chest square held lightly against the body (see Figure 2) locate the V6 electrode at the same level as the E point in the midaxillary line (straight down from the center of the armpit). If breast tissue is over the V6 area, mark the V6 location on the breast.

Do not attempt to move the breast in order to mark V6 on the chest wall.

Figure 2. Location of V6 Electrode Using the Dal-Square

### **5.5.2 Skin Preparation**

Prepare the skin for applying electrodes by wiping with alcohol, then briskly with a gauze pad. If technical problems are observed due to poor electrode contact, it is necessary to do further preparation as described below:

1. With the participant's consent, remove any excess hair from each electrode site on the chest and legs using an electric shaver.



2. At each electrode location in turn, the outer horny layer of the epidermis is removed by gentle dermal abrasion with a piece of 6-0 (220) sandpaper. Only three passes (in the form of an asterisk) at each site using light pressure are required.

If the skin preparation has removed the felt pen marking at any of the electrode sites, these are accurately re-established by carefully repeating the procedure described in Electrode Position Measuring and Marking. It is important that the electrode sites be marked using the exact technique described.

### **5.5.3 Application of Electrodes**

Disposable electrodes or suction cups may be used. When placing each electrode, massage it in a small circular motion to maximize the pre-gel contact with the skin but avoid overlap of gel from one electrode to the next.

Center the four limb electrodes on the inside of the wrist or ankle with the tab for the clip pointing toward the head. Center the six chest electrodes on the chest markings with the tabs pointing down. Do not let the electrodes overlap or touch each other if possible.

Clip the appropriate leadwire to each electrode (Figure 1). Do not pull or jerk tangled wires. To untangle wires, disconnect lead wires from electrodes.

### **Recording the 12-lead ECG**

Hit the record button on your ECG machine. Make sure that a standard 10 mm pulse is recorded as a standard.

### **5.5.4 Self-Evaluation of Technical Performance**

This section allows technicians to monitor their own ECG technique. It is intended to help technicians who are having difficulty meeting the quality standards set by the ECG Reading Center. These data are not intended to be collected by the study.

The technician examines the ECG tracing to estimate the noise level and baseline drift. Based on the requirements of the Minnesota Code, acceptable and unacceptable levels of noise and baseline drift have been established. These levels are scored using the following table:

<u>Quality Grade</u>	Noise <u>(mm)</u>	Overall <u>Drift (mm)</u>	Beat-to-beat <u>Drift (mm)</u>
1	< .25	< 1	< 1
2	< .50	< 2	< 1.5
3	< 1	< 3	< 2
4	< 2	< 4	< 3
5	$\geq 2$	$\geq 4$	$\geq 3$

The grade levels given in this table are related to the ability of the analysis program to achieve the required accuracy. Quality Grade 5 is unacceptable. ECGs of Quality Grade 5 must be deleted from the machine's memory and retaken immediately.

1. First, the tracing is examined for obvious errors such as right arm/left arm and other common lead misplacements (see Figure 3, negative p-waves in I indicate lead switch). These ECGs must be deleted from the machine's memory and retaken immediately.

Figure 3. Right Arm/Left Arm Lead Switch

2. The Quality Grade for noise is obtained by measuring the noise level as vertical peak-to-peak values in terms of number of small paper divisions (smallest grid squares). Note that recording sensitivity is 1 mv per centimeter, (one small paper division = 1 mm = 0.1 mv). A noise level of more than 2 small paper divisions ( $> 0.2$  mv peak to peak) is unacceptable (Figure 4).
3. The Quality Grade for overall drift is obtained by searching each of the 12-leads for the maximum and minimum baseline levels within that lead (as determined by the PR and/or TP segments) over the 10 second recording and measuring the vertical distance between them. A distance of more than 4 small paper divisions is unacceptable (Figure 5).
4. The Quality Grade for beat-to-beat drift is determined by searching for the pair of successive QRS complexes having the largest amplitude difference (vertical distance) between successive PR segments. A difference of more than 3 small paper divisions ( $> 0.3$  mv) indicates an unacceptable record (Figure 6).

Improvement in technical quality will indeed result if the prescribed procedure for electrode position marking, electrode and skin preparation, electrode replacement and equipment use are carefully followed. Baseline drift problems, which are essentially caused by poor electrode-skin contact are particularly easy to remedy, as is 60-cycle interference.

Sixty-cycle interference is characterized by perfectly regular fine oscillations occurring at the rate of sixty per second (Figure 7).

Electrical equipment of any kind may be the source of AC interference on an ECG in all leads or only certain ones. Check quality of skin preparation and electrode contact. Check leadwires and resecure attachment of the alligator clip to the electrode. Make sure participant does not touch any metal part of the bed or other equipment. Proximity to a wall with hidden wiring or a partially broken cable may also cause this problem.

Muscle Tremor causes irregular oscillations of low amplitude and varying rapidity superimposed upon the ECG waveform (Figure 8). Muscle tremor is the involuntary muscle activity of a participant whose state is tense, apprehensive, or uncomfortable. This is why a clear explanation of the electrocardiogram test and reassurance are necessary for the participant. The participant is asked if the temperature of the room is too low for her/him and is covered with a blanket if so.

### **5.5.5 Original Hard Copy Record**

The original 12-lead ECG record is copied and the copy filed at the field center. The original is sent to the coordinating center. Make sure the patient's ID number is on each.

Figure 4. Unacceptable Noise Level

Figure 5. Unacceptable Overall Baseline Drift

Figure 6. Unacceptable Beat-to-Beat Baseline Drift

Figure 7. Sixty-Cycle Interference

Figure 8. Artifact Caused by Muscle Tremor

## 5.6 Follow-up and End Points Data Collection

Since the primary objective of the ENRICHD Study is to evaluate the effects of psychosocial intervention, relative to usual care, on the combined endpoint of all-cause mortality and reinfarction in recently diagnosed acute MI patients who are depressed and/or have low social support, medical information must be collected uniformly on all patients who experience suspected end points during the course of the trial to evaluate outcomes. Secondary objectives include evaluation of the effects of the intervention on a number of medical endpoints of interest which also must be supported by the underlying data. This chapter describes the forms used to document those endpoints, and the procedures that the Events Classification Committee will follow in review of reported events. Clinical center staff need to be alert to detection of potential primary and secondary endpoints, either through direct patient contact at a follow-up visit, or via secondary sources (newspapers, electronic media, etc.) on an ongoing basis for the duration of the trial.

### 5.6.1 Primary Endpoint

The primary endpoint of this study is the first occurrence of a nonfatal myocardial infarction or mortality for any reason (“all cause”).

### 5.6.2 Secondary Medical Endpoints

The secondary medical endpoints in this study are:

1. All cause mortality (death of the patient from any cause)
2. Cardiovascular mortality (due to sudden death, fatal MI, or intractable heart failure death)
3. Recurrent nonfatal myocardial infarction (occurrence of another nonfatal MI since baseline)
4. Revascularization procedures (PTCA, CABG, cardiac transplantation)
5. Cardiovascular hospitalizations (a hospitalization having a discharge ICD-9 code of 401, 404, 411-414, 428 or 429 is a cardiovascular hospitalization)
6. HCFA quality of care process indicators (minimum standards that are felt to be an important component of the management of acute MI patients, such as the use of aspirin or thrombolytic therapy in appropriate patients)
7. Risk factor profile change (blood pressure change, self-report of compliance with medical regimens, and smoking status)

(See Appendix F of the ENRICHD protocol which contains specific definitions for the primary and secondary medical endpoints outlined above.)

## 5.7 Event Reporting and Submission of Events

The documentation for potential endpoint events that will be collected will be the occurrence of death, suspected MI, other cardiovascular events, and revascularization. Reporting of events to the Coordinating Center can occur directly as the result of information collected during routine follow-up visits and phone calls, in which the patients will be asked if any of these events have occurred since they were last contacted. The information will be recorded on a follow-up form along with the date, name of the hospital, and care physician. Once a suspected event is detected by the clinical center, complete Notification of Event (NOE) form to alert the Coordinating Center that a potential event has been detected, and that more detailed information is to follow pending a chart review and collection of supporting documentation surrounding the event. The NOE form lists the specific information required to be sent to the Coordinating Center for compilation into a case file for the Event Classification Committee to review. Detailed information concerning a hospital admission is to be recorded on a separate Hospitalization and Secondary Events forms (HOS) along with a copy of the discharge summary and determination by the PI or ENRICHD cardiologist. In the event of a patient death, obtain a copy of the official death certificate and complete a Death Certificate form (DCI) along with a copy of the discharge summary and determination by the PI or ENRICHD cardiologist. Reports of non-fatal events can also be initiated by the patient notifying the clinical center directly of a hospitalization, and will constitute a back-up method of notification. Specific instructions for completion of the end points related forms are detailed in section 5.8 of this chapter.

## 5.8 Endpoint Classification Committee

Standardized, treatment-masked classification of all-cause mortality and nonfatal MI as the primary endpoint and the individual components of the endpoint including cardiovascular mortality, non-cardiovascular mortality, fatal and nonfatal MI, and mode of death will be performed by an Events Classification Committee. The committee will be chaired by a cardiologist and consist of eight cardiologists as members with at least one representative from each clinical center. The committee will meet on a six month basis to adjudicate all deaths and potential MIs. Each suspected event will be reviewed by two cardiologists who are not affiliated with the clinical center from which the patient was recruited. Each reviewer will be provided with summary and original materials to support determination of end points. Information will be provided from hospital records, including enzyme measurements, and accompanying ECG strips. In the event of death, relevant records will be obtained from hospital, or primary care physician, and a copy of the death certificate will be abstracted. The Coordinating Center will blind all supporting end points information submitted to it so that no indication of treatment assignment remains. Full agreement on the primary and secondary events by both reviewers must be reached in order to classify an event. In case of a disagreement by the reviewers, a third independent reviewer will adjudicate the end points determination. The judgment of the adjudicator is final in event classification. The decisions of the committee will be facilitated by development of case law guidelines for standardized classification of end points.

## 5.9 Collection of End Points Measurements

Medical measurements for the determination of end points are recorded by the clinical center on the Notification of Admission, Hospitalization and Secondary Events, and Death certificate forms (see section 5.8.1). The Events Classification Committee will record the results of their determination on the Clinical Events ECG (ECG), and Clinical Events Review (CER) forms during a semi-annual meeting (see section 5.8.2). Detailed explanation for completion of the two groups of end points data collection forms follows. For all suspected events, and without specific request from the Coordinating Center, each clinic will forward the copies of ECGs and ECG reports clearly labeled by patient ID number along with supporting HOS and/or DCT forms abstracted from hospital records, death certificates, or coroner's reports.

### **5.9.1 Follow-up, Notification of Event, Hospitalization, and Death Reporting Forms**

Data collection forms associated with routine follow-up of the patient for monitoring any change in health status over the course of the trial are the Follow-up Examination (FUX), Notification of Event (NOE), Hospitalization and Secondary Events (HOS), and Death Certificate forms (DCT). The scheduled collection of information in clinic during a follow-up examination is at 6 months and 18 months after randomization, and annually after that period (30, 42, 54 months post-randomization).

The remainder of the forms are event driven, only completed upon the basis of patient self report of hospitalization, or based on reports from the patient's physician.

#### **5.9.1.1 Instructions for Completing the Follow-up Examination Form (FUX Version A)**

This Follow-up Examination form is to be completed during routine scheduled follow-up of the ENRICHD patient. Responses to questions 1,2, and 17-21 flag circumstances where a suspected end point may have been reached. Instances of suspected endpoints include whenever a hospital admission or specific cardiac related procedure occurs.

**Center:** use 2 digit ENRICHD center ID number

**Patient ID:** use 7 digit patient ID number

**Patient Initials:** first middle and last initials (enter "X" if patient has no middle initial)

**Visit Code:** use boxes provided to identify visit number

**Date:** use 2 digit codes for month, day and year

**Staff ID number:** use your assigned ENRICHD 3 digit staff ID#)

#### **Health Status and Risk Factor Changes**

- 1) Hospitalization: Has the patient been hospitalized since the last visit? If, Yes, first complete a preliminary notification of event form, and then complete Hospitalization Form, and include send supporting end points review information to the coordinating center. Last visit is the last ENRICHD contact including scheduled phone contacts which are given visit numbers.



- 2) Serious Illness: ER - Has the patient been to the emergency room since the last ENRICHD Visit, but did not require hospitalization?
- 3) Angina: Since the last ENRICHD Visit, has the patient had angina; if so, characterize in questions 3a, 3b, 3c. Be aware that all chest pain is not angina and that ischemic symptoms or anginal equivalents need not be typical but may be shortness of breath or fatigue, especially in older patients. Specific questions should be handled locally by the ENRICHD physician.
- 4) Cigarette Smoking: Any self report by the patient of smoking within the last week. Obtain confirmation from the patient's confidant.
- 5) Drinking: If the patient reports any alcohol intake within the last week, check yes. If yes, ask the patient how many drinks they had? Enter the average number of drinks consumed. If the patient does not report any alcohol intake during the week check the corresponding box. Any self report of alcohol consumption within the last week should be noted. Obtain confirmation from the patient's confidant about the alcohol consumption.
- 6) Fatigue: Early onset with minimal physical exertion, or at rest.
- 7) SOB: Any report of shortness of breath either at rest or with minimal physical effort.
- 8) Orthopnea or PND: Report if patient is having difficulty breathing at night (this is usually episodic and called PND, paroxysmal nocturnal dyspnea), or sleep using pillows to elevate themselves while sleeping at night (this need is known as orthopnea).
- 9) Hours employed for wages: Probe to see if the patient has returned to work and is earning a wage. If retired at baseline, or on disability, confirm employment status. Record average number of hours worked per week. Record 0, if not presently working or retired.
- 10) Participation cardiac rehabilitation: Answer yes if during the period since the last visit, has the patient participated in a supervised cardiac rehabilitation programs.
- 11) Regular exercise: Record self report of patient exercising regularly on a weekly or daily basis, not monthly.
- 12) Counseling, psychotherapy, or stress management: Answer yes if patient is engaging in any of these activities and is professionally supervised. Counseling and therapy includes therapy through the ENRICHD intervention.
- 13) Diet modification: Ask the patient if he/she is presently following any kind of dietary modification. If so, was the diet modification plan made on the advice of a doctor or health care worker? Record any modification of the patients diet to follow the AHA active partnership guidelines, and the change is effected, not if only contemplated.

- 14) Cognitive strategies: Record self report of patient practicing CBT strategies to counter depression or low social support. Is the patient involved in any routine that is designed to help them feel better about her/himself. The question is posed in terms of problem solving to avoid complex terms possibly unfamiliar to patients in usual care or the intervention arm.
- 15) Medications for anxiety or depression: Ask the question, “Are you taking any medication for anxiety or depression?” If yes, ask the patient when they started to take the medication? Enter the name of the medication, dose, and if use is current at time of the visit. Please note that medicine being recorded should be for anxiety or depression. Any other medications that are taken for other reasons should not be included.
- 16) Depression: Ask if patient is feeling low, or depressed. This is by patient report only; it is not a clinical diagnosis to be made by the ENRICHD staff. Probe to determine duration of this reported episode if reported.

Any of the following procedures in questions 17-21 should alert you that a suspected event may have occurred, and a hospitalization form will need to be completed with supporting documentation from the patient’s medical records.

- 17) CABG: Coronary artery bypass graft.
- 18) IV Thrombolytic Therapy: IV therapy administering tPA or streptokinase for example to improve coronary circulation.
- 19) PTCA: Balloon angioplasty of any coronary arteries.
- 20) Coronary Angiogram: Use of this diagnostic imaging procedure may indicate worsening condition of patient, or associated with a related surgical intervention.
- 21) Vascular Stent: Placement of this device during an interventional procedure may also indicate worsening condition of patient.
- 22) Other Cardiovascular procedure: Any other reported cardiovascular procedure.
- 22-27) Physical Exam: Repeat of the physical exam given at baseline visit. Height, weight, BP, heart rate, heart sounds recorded using the same procedures described earlier under the baseline examination.
- 28) Killip Class: Determination of Killip class based on the exam as described in the baseline section of the manual of operations.
- 29) NYHA CHF Class: Determination of CHF severity, using 1-4 scale and 0 if no signs, and not on medication for heart failure as described at baseline. This NYHA Classification refers to the patient’s typical status over the last two weeks prior to hospitalization (or to the acute episode that lead to hospitalization).

**Class 1 No limitation:** Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations, e.g., can walk one level mile without symptoms.

**Class II Slight limitation of physical activity:** Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina, e.g., walking two level blocks or one flight of stairs causes symptoms.

**Class III Marked limitation of physical activity:** Although the patient is comfortable at rest, less than ordinary activity will lead to symptoms, e.g., walking from the living room to the bedroom causes symptoms.

**Class IV Inability to carry on any physical activity without discomfort:** Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

30-50) Medications: Use of medications within the last two weeks. Encourage patient to bring pill bottles into clinic so that actual drug names can be verified instead of relying on patient recall. This should also include over the counter medications (which may include ASA which is being taken for prescription, but is purchased over the counter).

<b>5.9.1.2 Instructions for Completing the Notification of Event Form (NOE, Version A)</b>
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This form is to be completed whenever a suspected end point has been reached when hospital admission or death occurs. This form should be completed, entered on the computerized Data Management System (DMS), and also faxed to the coordinating center which will then notify the End Point Clinical Event Review Committee chairman.

**Center:** use 2 digit ENRICHD center ID number

**Patient ID:** use 7 digit patient ID number

**Patient Initials:** first middle and last initials

**Visit Code:** use boxes provided to identify visit number

**Sequence Number:** use boxes provided to identify sequential event number

**Date:** use 2 digit codes for month, day and year

**Staff ID number:** use your ENRICHD 3 digit staff ID#)

- 1) Complete date of event using 2 digit code for month, day and year.
- 2) Indicate whether the event is fatal cardiac, fatal non-cardiac, or a non-fatal event.
- 3) For hospitalized events, enter the most appropriate class of suspected event based on available information.
- 4) Check appropriate boxes for **ancillary documents** to be forwarded to Clinical Event Review Committee via the Coordinating Center.

### 5.9.1.3 Instructions for Completing the Notification of Event Form (NOE, Version B)

The same procedures for the Version B Notification of Event form apply whenever a suspected end point has been detected by clinical center personnel (hospital admission or patient death). This form is to be completed whenever a suspected end point has been reached when hospital admission or death occurs. This form should be completed, entered on the computerized Data Management System (DMS), and also faxed to the coordinating center which will then notify the End Point Clinical Event Review Committee chairman. The effective date for use of this form begins August, 1997.

**Center:** use 2 digit ENRICHD center ID number

**Patient ID:** use 7 digit patient ID number

**Patient Initials:** first middle and last initials

**Visit Code:** use boxes provided to identify visit number

**Sequence Number:** use boxes provided to identify sequential event number

**Date:** use 2 digit codes for month, day and year

**Staff ID number:** use your ENRICHD 3 digit staff ID#)

- 1) Complete **date of event** using 2 digit numeric codes for month, day and year.
- 2) Indicate whether the event is (a) fatal cardiac/fatal non-cardiac, or (b) a non-fatal event of either cardiac or non cardiac nature. If the case is not totally clear-cut, assume that the event is cardiac so that it can be reviewed.
- 3) For hospitalized events, check all suspected events based on available information.
- 4) Enter responses in appropriate boxes for **ancillary documents** to be forwarded to Clinical Event Review Committee via the Coordinating Center. If documents are not available to review for this event enter code letter "N", or if not applicable enter "A". Send complete information about event to the Coordinating Center once sufficient documents become available to answer responses on the Hospitalization and Death Certificate forms. Should information about an event (e.g., missing enzymes or hard to located ECG's) suddenly become available, update the NOE hardcopy and change the electronic version as well. Forward the updated documents to the Coordinating Center for inclusion in the patient event file.

### 5.9.1.4 Instructions for Completing Death Certificate Forms (DCT Version A)

In the case of a patient death, cardiac arrest records, related hospitalization and discharges summaries should be appended to the death forms. In addition, records from the ambulance, paramedics or emergency medical technician should be obtained and forwarded along with the death form to the Coordinating Center. If the death occurred in hospital, a Hospitalization form should also be completed. If death occurs outside the hospital, a Notification of Event (NOE) should accompany the Death Certificate (DCT) form.

**Center:** use 2 digit ENRICHD center ID number

**Patient ID:** use 7 digit patient ID number

**Patient Initials:** first middle and last initials

**Visit Code:** use boxes provided to identify visit number

**Date:** use 2 digit codes for month, day and year

**Staff ID number:** use your ENRICHD 3 digit staff ID#)

#### Information from Death Certificate

- 1) **Death certificate number:** This should be obtained from the State death certificate.
- 2) **Social security number:** This should be obtained from the death certificate and matched to the to the social security number obtained from the initial enrollment form. The coordinating center should be notified of any discrepancies between the two.
- 3) **Date of birth:** Use 2 digit code for month, day and year
- 4) **Date of death:** Use 2 digit code for month, day and year
- 5) **Age at death:** Use age at last birthday in years
- 6) **Time of death:** Use 24 hr format
- 7) **Where did the decedent die?** ENRICHD affiliated hospitals can be identified from directory of affiliated hospital (where does the list exist in the manual). The address of place of death is listed on the death certificate; should include apartment number,street, number, city, state and zip code.

- 8) If **decedent died in hospital** circle place of death within the hospital:
- A** = dead on Arrival                      **E** = if died after admission into ER  
**I** = if died as an Inpatient                      **N** = None of the above  
**R** = if not Recorded
- 9) **Name and location of hospital:** Should include full name, city location and state.
- 10) **If this were a coroner nurse or medical examiner's case** check "yes" or "no". If no, go to item 12.
- 11) Please list a **name of the coroner's or medical examiner's complete address including street number, city, state and zip code.** If the answer to number 10 is yes.
- 12) Indicate by "yes" or "no" whether or not **an autopsy was performed.**
- 13) Physician's belief of the **cause of death** record most appropriate code from group below:
- |                                |                                 |                     |
|--------------------------------|---------------------------------|---------------------|
| <b>A</b> = MI                  | <b>E</b> = Vascular non-cardiac | <b>I</b> = Suicide  |
| <b>B</b> = Sudden Death        | <b>F</b> = Unobserved           | <b>J</b> = Accident |
| <b>C</b> = Intractable failure | <b>G</b> = Non-Cardiovascular   | <b>K</b> = Other    |
| <b>D</b> = Stroke              | <b>H</b> = Malignancy           |                     |
- 14) Please use **ICD9 codes for underlying cause of death.**
- 15) **II other listed ICD9 codes** on the death certificate should be included.
- 16) **Transcribed directly from the death certificate the immediate cause of death and two other diagnosis that may be listed as due consequences of the immediate cause of death.**
- 17) **Transcribe other significant conditions as they were recorded on the death certificate.**
- 18) **Name and address of certifying physician.**
- 19) Check off whether **emergency medical services (Paramedical services) report is enclosed.**
- 20) Check off whether the copy of the **death certificate is enclosed** with the form.

**5.9.1.5 Instructions for Completing Hospitalization and Secondary Events Form (HOS, Version A)**

The follow up hospitalization form should be completed at the end of hospitalization and in the case of death a copy of the death certificate should be obtained. These should be forwarded to the coordinating center. Ancillary documents to be included in the case of a hospitalization include copies of all ECGs, a complete record of all cardiac enzyme determination including CKMB, LDH1, LDH2 values, and troponin I or T values where available.

Discharge summaries, emergency room notes, procedural reports such as coronary angiograms or echocardiograms and operative procedural note in the case of angioplasty or coronary artery bypass graft should be appended to the hospitalization form. In the case of a death, cardiac arrest records, related hospitalization and discharges summaries should be appended to the death forms. In addition, records from the ambulance, paramedics or emergency medical technician should be obtained and forwarded along with the death form.

**Center:** use 2 digit ENRICHD center ID number

**Patient ID:** use 7 digit patient ID number

**Patient Initials:** first middle and last initials

**Visit Code:** use boxes provided to identify visit number

**Sequence Number:** use boxes provided to identify event number, beginning with 01

**Date:** use 2 digit codes for month, day and year

**Staff ID number:** use your ENRICHD 3 digit staff ID#)

#### **A. DISCHARGE DIAGNOSIS**

- 1) **Name and location of hospital:** use complete hospital name, city and state
- 2) **ENRICHD-affiliated hospital:** please refer to ENRICHD-affiliated hospital list to determine if this hospital is in an affiliated hospital, if so enter lower case “a” in the given box, if not enter “b”.
- 3) **Medical record number:** please use the medical record number of the admitting hospital
- 4) **Indicate whether the hospital chart has been located** by checking the appropriate box
- 5) **Date of hospital arrival:** use 2 digit code for month, day and year
- 6) **Time of arrival at hospital:** use emergency room time of admission, except for patients who are directly admitted. Use 24 hour format.
- 7) **Date of discharge:** use 2 digit codes for month, day and year
- 8) **Please complete the disposition of the patient on discharge** and fill in the appropriate letter in the given box.
- 9) **Record causes of death** as they appear on the discharge summary. This does not pertain to death certificate causes of death
- 10) **For patients transferred** from another hospital record the entire hospital name, city and state for the referring hospital



- 11) **Discharge Diagnosis:** for the **boxes designated by the letters “A thru E”**, fill in the hospital discharge codes as they appear on the front page of the discharge summary. The actual discharge diagnosis should be written as they appear the lines designated by the **letters “F thru J”**; these should correspond directly to the codes that are listed in the boxes designated to “A thru E”.
- 12) **CHD refers to Coronary Heart Disease.** It will include diagnoses such as acute myocardial infarction, non Q wave myocardial infarction, stable angina pectoris and unstable angina. It may also include diagnosis of ventricular or supraventricular arrhythmia and heart failure. As best as you can determine, estimate the time from the onset of the presenting complaint to arrival at this hospital.
- 13) **CHD events** will include recurrent angina pectoris, subsequent myocardial infarction, sudden cardiac death, and heart failure. Indicates as follows:
- A** - indicate the date of the CHD event
  - B** - whether it occurred following a surgical procedure  
*(if yes, complete items C & D)*
  - C and D** - indicate the date and time of surgery
  - E** - list the type of surgery
- 14) Ascertain the presence of pain is consistent with angina pectoris occurring any time within 72 hours prior to arrival or during the hospitalization. If this is answered “yes”, list as follows:
- A** - the date of onset of pain using 2 digit code
  - B** - whether the pain was in the chest
  - C** - whether nitrates were used to treat the episode
  - D** - whether the nitrate is effective and
  - E** - whether the physicians indicated in the medical record as to whether this was felt to be of non cardiac origin
- 15) Indicate the actual level of **cardiac enzymes drawn within 1st 24 hours** of arrival, or after a **suspected** event and indicate the appropriate unit as follows:
- A** - peak CK would refer to the highest value of CK reported in the first 24 hours after arrival
  - B** - CK ULN refers to the upper limited normal for that laboratory item
  - C** - peak CKMB would be the highest absolute CKMB for the first 24 hours after admission, also indicate if reported as CKMB index and indicate the appropriate units
  - D** - CKMB ULN represent the upper limit of normal for your laboratory
  - E** - the peak LDH value in units per liter

- F** - the upper limit of normal for LDH for your laboratory
- G** - LDH1- please use the peak value within the first 24 hours of arrival, indicate units
- H** - LDH2 -use the peak value within the first 24 hours, indicate the appropriate units
- I** - if Troponin T is used in your hospital please indicate the peak value in milligrams per ml.
- J** - if Troponin I is used in your hospital please indicate the peak value in nanograms per Liter.
- K** - indicates the date of enzyme determination during day one

16.) **Diagnostic Cardiac Enzymes occurring after 1st 24 hours of Arrival, or after a suspected in hospital CHD event:** these items should be completed as in item 15. The highest values on day 3 or after an in-hospital CHD event should be used.

17) This should be completed as in **item 15** and using the highest value obtained on the last day after arrival or after an in-hospital CHD event again, the highest values should be used.

18) Indicate the **first codable ECG** after arrival or in-hospital CHD event:

- A** - whether or not a **codable ECG** is available for this hospitalization
- B** - indicate the date of the first ECG
- C** - indicate whether there are other codable ECGs for this hospitalization

19) Indicate whether or not a **third day codable ECG** is available after arrival or after in-hospital CHD event:

- A** - indicate the date of the third ECG
- B** - indicate whether there are any other codable ECGs hospitalization

20) Indicate the date of the **last codable ECG** after arrival or after in-hospital CHD event.

21) Indicate the number of ECGs sent for end points coding.

**5.9.1.6 Instructions for Completing Hospitalization and Secondary Events Form (HOS, Version B)**

The effective date for use of the version B Hospitalization and Secondary Events forms is July 1997. The same circumstances and supporting documentation surrounding a suspected event apply in the use of the HOS version B form. Additional response areas appear to capture information about the original and up to two transfer for an event.

**Center:** use 2 digit ENRICHD center ID number

**Patient ID:** use 7 digit patient ID number

**Patient Initials:** first middle and last initials

**Visit Code:** use boxes provided to identify visit number

**Sequence Number:** use boxes provided to identify event number, beginning with 01

**Date:** use 2 digit codes for month, day and year

**Staff ID number:** use your ENRICHD 3 digit staff ID#)

**A. DISCHARGE DIAGNOSIS**

- 1) **Number of hospitalizations related to event:** use 1 digit code, enter 1 if no transfer.
- 2) **Name and location of first hospital:** use complete hospital name, city and state for the first (or only) hospital in the treatment series.
- 3) **ENRICHD-affiliated hospital:** please refer to ENRICHD-affiliated hospital list to determine if this hospital is in an affiliated hospital, if so enter lower case **“a”** in the given box, if not enter **“b”**.
- 4) **Medical record number:** please use the medical record number of the admitting hospital
- 5) **Indicate whether the hospital chart has been located** by checking the appropriate box
- 6) **Date of hospital arrival:** use 2 digit code for month, day and year.
- 7) **Time of arrival at first hospital:** use emergency room time for admission, except for patients who are directly admitted. Use 24 hour format.
- 8) **Date of discharge at first hospital:** use 2 digit codes for month, day and year.
- 9-15) Documentation of second hospital in treatment series: skip if no transfers; otherwise, complete as in questions 2 through 8 above.
- 16-22) Documentation of third hospital in treatment series: skip if not applicable; otherwise, complete as in questions 9 through 15, and 2 through 8 above.
- 23) Please complete the disposition of the patient on final hospital discharge and fill in the appropriate letter in the given box.
- 24) Record causes of death as they appear on the discharge summary. This does not pertain to death certificate causes of death.
- 25) **Discharge Diagnosis:** for the **boxes designated by the letters “A thru J”**, fill in the hospital discharge codes as they appear on the front page of the discharge summary. The actual discharge diagnosis should be written as they appear using the lines designated **besides**

**the corresponding ICD-9 code.** The diagnoses must correspond directly to the codes that are listed in the boxes labeled A thru J

- 26) **CHD refers to Coronary Heart Disease.** It will include diagnoses such as acute myocardial infarction, non Q wave myocardial infarction, stable angina pectoris and unstable angina. It **may also include** diagnosis of ventricular or supraventricular arrhythmia and heart failure. As best as you can determine, estimate the time from the onset of the presenting complaint to arrival at this hospital.
- 27) **CHD events** will include recurrent angina pectoris, subsequent myocardial infarction, sudden cardiac death, and heart failure. Indicates as follows:
- A** - indicate the date of the CHD event
  - B** - whether it occurred following a surgical procedure  
*(if yes, complete items C & D)*
  - C and D** - indicate the date and time of surgery
  - E** - list the type of surgery
- 28) Indicate if pain is consistent with angina occurred any time within 72 hours prior to arrival or during the hospitalization.
- 29) Indicate the actual level of **cardiac enzymes drawn within 1st 24 hours** of arrival, or after a **suspected** event and indicate the appropriate unit as follows:
- A** - peak CK would refer to the highest value of CK reported in the first 24 hours after arrival
  - B** - CK ULN refers to the upper limited normal for that laboratory item
  - C** - peak CKMB would be the highest absolute CKMB for the first 24 hours after admission, also indicate if reported as CKMB index and indicate the appropriate units
  - D** - CKMB ULN represent the upper limit of normal for your laboratory
  - E** - the peak LDH value in units per liter
  - F** - the upper limit of normal for LDH for your laboratory
  - G** - LDH1- please use the peak value within the first 24 hours of arrival, indicate units
  - H** - LDH2 -use the peak value within the first 24 hours, indicate the appropriate units
  - I** - if Troponin T is used in your hospital please indicate the peak value in milligrams per ml.

- J** - if Troponin I is used in your hospital please indicate the peak value in nanograms per Liter.
- K** - indicates the date of enzyme determination during day one

30) **Diagnostic Cardiac Enzymes occurring after 1st 24 hours of Arrival, or later than 24 hours after a suspected in hospital CHD event:** these items should be completed as in item 29. The highest values on day 3 or after an in-hospital CHD event should be used.

31) This should be completed as in **item 29** and using the highest value obtained on the last day after arrival or after an in-hospital CHD event again, the highest values should be used.  
*Skip if no further enzymes drawn prior to 48 hour or peak enzyme values after day 3.*

32) Indicate the **first , i.e., legible codable ECG** after arrival or in-hospital CHD event:

- A** - whether or not a **codable ECG** is available for this hospitalization
- B** - indicate the date of the first ECG
- C** - indicate whether there are other codable ECGs for this hospitalization

33) Indicate whether or not a **third day codable ECG** is available after arrival or after in-hospital CHD event:

- A** - indicate the date of the third day ECG
- B** - indicate whether there are any other codable ECGs hospitalization

34) Indicate the date of the **last codable ECG** after arrival or after in-hospital CHD event.

35) Indicate the number of ECGs sent for endpoints coding.

36-46) **Medications prescribed at discharge:** check medication prescribed for patient at time of discharge for this hospitalization.

## 5.9.2 End Points Classification Forms

The Clinical Event Review (CER) and Clinical ECG Interpretation (ECG) forms are completed by members of the Events Classification Committee during review of information compiled to document suspected events. A blinded events review packet will be compiled for each designated reviewer to use during the semi-annual subcommittee meeting by the Coordinating Center.

### 5.9.2.1 Instructions on Completing *Page 1 of 2* ENRICHD Clinical Event Review and End Point Assignment Form

*This form is to be completed by the blinded reviewers after each individual event review.*

- 1) **Center:** Use 2 digit ID number
- 2) **Patient ID:** Use 7 digit patient ID number
- 3) **Patient initials:** Use first, middle and last initials.
- 4) **Visit:** Use the 2 boxes provided to identify visit number.
- 5) **Date form completed:** Use 2 digit codes for month, day and year.
- 6) **Staff ID:** Provide 2 or 3 digit ENRICHD staff ID number
- 7) The primary end point of non-fatal myocardial infarction or death should be completed by checking off the appropriate box. Non fatal myocardial infarction should be further differentiated among unrecognized, symptomatic or hospitalized infarction. More than one box may be applicable.
- 8) In the case of death the appropriate box should be checked and differentiation between noncardiovascular and cardiovascular death should be made. Cardiovascular deaths are to be distinguished among sudden cardiac deaths, death due to MI, death due to heart failure, or other cardiac deaths using definitions provided in the operation manual. Date of death should be completed using 2 digit codes for month, day and year. The time of death should be provided in military time.

#### **5.9.2.2 Instructions for Completing Page 2 of 2 ENRICHD Clinical Event Review End Point Assignment Form**

- 1-6) Identification and date of form should be performed as page one.
- 7) The observation of a secondary end point should be designated by an appropriate check in the boxes provided and the date should be provided using two digit codes for month, day and year.

#### **5.9.2.3 Instructions for ENRICHD Clinical Event Review ECG Interpretation**

- 1-6) Identification and date of form should be performed as page one.
- 7) **Baseline:** If this is a baseline ECG at enrollment please indicate by checking the appropriate box.
- 8) If this is a suspect **new clinical event** after randomization please check the appropriate box.
- 9) **Date:** This refers to the date the event occurred, use 2 digit numbers for month, day and year.

- 10) **Old Q waves:** Indicate the presence of old Q waves used by checking the “yes” box. Please check the appropriate leads in which the old Q was observed.
- 11) **New Q waves:** New Q waves as defined by modified Minnesota code criteria should be designated by checking the “yes” box. The leads in which they occur should be checked in the appropriated box.
- 12) **ST segment elevation > 1mm:** Refers to ST segment elevation in excess of 1mm occurring approximately 80 msec after the J point. If present designate by checking off the “yes” box and check off the leads where the ST segment elevation was observed.
- 13) **ST depression segment > 1mm:** If present please designate by checking off the “yes” box and check off the leads where the ST segment depression was observed.
- 14) **Final interpretation:** Please indicate whether the ECG diagnostic of either old MI or new MI by using the appropriate yes box.

**Appendix A: ENRICHD Medical Measures Data Collection**

<b>Name of Form</b>	<b>Form Mnemonic</b>	<b>Time Point</b>	<b>Visit Number</b>
Tracking	TRK	Screening	01
CAGE	CAG	Screening	01
Medical Eligibility	MEA	Screening	01
Medical History	MHA	Baseline	02
Baseline Examination (with ECG)	BEA	Baseline	02
Randomization Worksheet	RAN	Baseline	02
Telephone Contact	TCF	Follow-up	3, 9, 24, 36
Follow up Examination with ECG (6, 18, 30, 42 & 54 mo)	FUX	Follow-up	4, 7, 9, 10,13
Notification of Event	NOE	Follow-up	per event
Hospitalization and Secondary Events	HOS	Follow-up	per event
Death Certificate	DCT	Follow-up	per event

**Follow-up Visit Collection Schedule**

Month:	3	6	9	12	18	24	30	36	42	48	54
Visit #:	03	04	05	06	07	08	09	10	11	12	13

**Clinic Visit Post Randomization**

Month:	6	19	30	42	54
Visit #:	04	07	09	10	13



**Phone Contacts Post-Randomization**

Month:	3	9	12	24	36	48
Visit #:	03	05	06	08	10	12

## 6. Chapter 6: Psychosocial Measurement

### 6.1 Introduction and Overview

The primary objective of ENRICHD is to reduce mortality and recurrent MI by ameliorating depression and increasing social support in post-MI patients. Thus, evaluation of the effects of the psychosocial intervention on the presence and severity of depression, and on degree and **type** of social support, are major secondary objectives of ENRICHD. Other secondary goals are the evaluation of the effects of the intervention on health-related quality of life (HQL) and on other psychosocial factors, such as perceived stress and self-efficacy. This chapter describes the procedures to be used to measure the psychosocial endpoints in ENRICHD at three separate timepoints: at screening/baseline, at the 6-month follow-up, and at the 18-month follow-up.

### 6.2 Schedule of assessment

Chapter 2 of this manual provides a flow chart depicting the screening and recruitment process to be used in ENRICHD. As shown in the chart, patients' initial psychosocial eligibility for ENRICHD is determined in hospital via administration of the DISH Part A and ENRICHD Social Support Instrument (ESSI). While self-administration may be the most common mode of assessment, often these instruments may need to be administered by an interviewer. If patients meet DSM-IV criteria for major or minor depression, or are determined to have low social support via their scores on the ESSI (see Chapter 2 for details on how to determine psychosocial eligibility using these instruments), they are administered a battery of psychosocial measures, preferably while still in-hospital, and then randomized to either psychosocial treatment or usual care. The psychosocial measures administered at baseline, along with the BDI, ESSI and DISH Part B, are administered again at 6 months post-randomization, and a subset of these measures are administered at 18 months post-randomization. The following table outlines the specific psychosocial measures used in ENRICHD, their schedule of administration, and other relevant descriptive information.

**6.3 Table:**

The table below summarizes the revised schedule for collection of Psychosocial Data

Instrument	Content	Baseline	Follow-Up Months		
			6	12	18
Modified DIS + Hamilton (DISH)	Depression	A <sup>1</sup>	A		-
Beck Depression Inventory (BDI)	Depression	A	A	A	A
ENRICHD Social Support Instrument (ESSI)	Social Support	A	A	A	A
Longitudinal Course Chart (LCS)	(Derived from the DISH)n			A	
ISEL subscale	Tangible Support	S (400)	S (400)		-
Perceived Social Support Scale (PSSS)	Social Support	A	A		-
Social Network Questionnaire (SNQ)	Social Networks	S (800)	S (800)		-
MOS SF36 (HQL)	Health Quality of Life	-	S (800)		-
Life Satisfaction (LSS)	Life Satisfaction and Meaning	-	S (800)		-
Perceived Stress Scale (PSS)	Perceived Stress	S (400)	S (400)		-
Self-Efficacy (SEM)	ENRICHD Intervention	S (400)	S (400)		-

<sup>1</sup>A: all participants

S: subsample of participants (first 400/800 randomized)

-: not collected

## **6.4 Mode of assessment**

The DISH is the only psychosocial measure used in ENRICHD that is always interview-administered. The other psychosocial measures are intended to be self-administered by patients, but can be interview-administered when the need arises. Section 6.11. of this chapter provides guidelines for determining when instruments should be interview versus self-administered, and the Forms Appendix provides instructions for transforming each self-administered measure into an interview.

## **6.5 Location of assessment**

### **6.5.1 Screening**

The measures administered during screening and baseline are intended to be administered in-hospital. In cases where eligibility is not completely determined prior to discharge, the screening instruments can be administered via telephone (see Chapter 3 for details).

### **6.5.2 Baseline**

Although it is intended that the baseline assessment take place in-hospital, this will prove unfeasible for some patients. When the baseline assessment is not conducted in-hospital, patients should be scheduled for assessment prior to discharge where possible, or telephoned as soon as possible after discharge and scheduled for a baseline visit. If it does not take place in hospital, the baseline visit can take place in a clinic or other setting (e.g., research offices), or in the patient's home, if necessary.

### **6.5.3 Follow-up**

Follow-up visits will typically take place in the hospital or clinic (scheduling of these visits may be done to coincide with the patients' regular hospital or clinic visit, where possible). If it is infeasible for the patient to travel to the hospital or clinic for a follow-up visit, home visits can be scheduled.

## **6.6 Screening**

Following determination of medical eligibility, the patient is approached in hospital by the Case Coordinator or other ENRICHD staff member and administered the DISH Part A and ESSI.

### **6.6.1 Beck Depression Inventory (BDI)**

The 21-item BDI is used in ENRICHD to evaluate baseline status and outcomes, and to assess progress during treatment and to monitor patients for relapse (use of the BDI to assess treatment progress and relapse is described in Chapter 10). The BDI is intended to be a self-administered instrument, with each item consisting of four answers without a question. This format makes it difficult to administer as an interview; however, a standard list of questions have been developed so that the BDI can be administered orally by telephone or in person to patients who require that it be interview-administered (e.g., those with poor vision, poor reading ability, etc.). Details on interview administration of psychosocial measures appear in Section 6.11, and instructions on transforming the BDI into an interview appears in the Forms Appendix.

Each item on the BDI is rated on a 0-3 scale. To score the BDI, the items are added so that the total ranges from 0 to 63. (Item #19 (weight loss) is an exception to this rule: if the patient endorses item 19a (dieting to lose weight), Item 19 counts as a zero regardless of how the patient responded to it.)

### **6.6.2 ENRICHD Social Support Instrument (ESSI)**

The ESSI is a 7-item scale which primarily measures functional social support and, in particular, emotional support. It was developed using individual items from previous studies of post-MI and CAD patients that have been shown to predict cardiac events and death. The ESSI is used as a screening tool to determine patients' eligibility for ENRICHD based on low social support, and to assess changes in patients' social support following treatment (at 6 and 18 months post-randomization).

The ESSI is administered with the DISH Part A during hospitalization as the first screening measure to determine patient eligibility. *Patients who score 2 or lower on at least two items of the ENRICHD Social Support Instrument (excluding item 4) or (b) a score of 3 or less on two or more 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 within 14 days of the onset of acute myocardial infarction are considered to meet the psychosocial eligibility criteria for ENRICHD based on low social support, and should be scheduled for a baseline assessment session, preferably while still in hospital.* The ESSI is designed to be self-administered; however, should there be a need for it to be administered orally, the Forms Appendix provides procedures to be used to administer the ESSI as an interview.

### **6.6.3 DSM-IV Depression Interview and Structured Hamilton (DISH)**

The DISH is a structured psychodiagnostic interview that was developed specifically for ENRICHD. It is based on the modified versions of the National Institute of Mental Health Diagnostic Interview Schedule (DIS) that have been used in some of the most important studies of depression in post-MI and other cardiac populations, and on a structured version of the Hamilton Rating Scale for Depression (HAM-D) that was developed by Dr. Janet Williams. The DISH was developed to eliminate the redundancy between certain items on the modified DIS and the HAM-D in order to make the interview more time efficient and less burdensome for the patients and interviewers.

The DISH is used to (1) diagnose current major and minor depressive episodes and dysthymia according to the American Psychiatric Association's DSM-IV criteria; (2) characterize the pattern and duration of depressive symptoms, both in absolute terms and in relation to the MI and other stressors; (3) measure the severity of the depressive disorder on the Hamilton Scale; and (4) document the patient's psychiatric history, including prior episodes of depression, other psychopathology, and previous treatment for depression or other psychiatric disorders. The Hamilton scale is almost universally used in clinical trials of treatments for depression and will also serve important clinical purposes in this trial (e.g., to determine whether the patient may need concurrent antidepressant therapy). The DISH requires about 20 minutes to administer to the average nondepressed patient, and between 30 and 45 minutes for most depressed patients.

The DISH Part B is administered to patients who are determined to meet DSM-IV criteria for either major or minor depression or dysthymia using the DISH Part A are considered eligible for participation in ENRICHD, and should be scheduled for baseline assessment and randomization (see Chapter 3 for further details concerning the DISH and use of depression criteria for enrollment in ENRICHD).

The DISH is also used to assess depression at 6 months post-randomization. In most respects, the interview is conducted the same way at each of these timepoints, but there are a few exceptions to this rule. For example, when the DISH is being used to determine patient eligibility, the interviewer will know after asking the first 6 questions whether the patient has lost interest in his/her favorite activities or whether he or she has been feeling dysphoric (sad) most of the time lately. If neither of these symptoms are present, the patient cannot meet the DSM-IV criteria for major or minor depression, and therefore, the interview can be abbreviated.

At this point, only if the patient has received a score of 2 or lower on at least two items of the ENRICHD Social Support Instrument (excluding item 4) or (b) a score of 3 or less on two or more 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 ESSI will he or she be eligible for participation in ENRICHD.

The Psychiatric History section of the DISH should only be administered during screening/baseline, and not at subsequent timepoints. The opposite is true for the Longitudinal Course Chart, since it is to be administered only at follow-up and not at screening/baseline.

The DISH is called a "structured" interview because it requires every interviewer in the project to ask the same set of questions in the same order. Previous research has shown that structured interviews are much more reliable, thorough, and accurate than unstructured, open-ended clinical interviews. However, clinical interviews that are too rigidly structured can be insensitive to the unique and unexpected responses of individual patients. Consequently, although the DISH is designed to be a structured interview, it is designed to be as flexible as possible.

Problems can arise when structured clinical interviews are conducted in an excessively rigid, rote, or detached manner. These approaches can cause the interviewer to miss important information and to irritate or alienate the patient. When administering a structured clinical interview like the DISH, the questions must be asked in a sensitive manner, and the interviewer should aim to sound like he or she is conversing with and truly interested in the patient as a unique individual, rather than merely reading aloud from a script, or rushing through the interview as fast as possible just to get it over with. Furthermore, the interviewer must listen carefully to -- and think carefully about -- the patient's responses, and try to clarify the ones that are vague, confusing or contradictory, or that suggest the patient did not fully understand the question. Consequently, although the DISH is a structured interview, interviewers often have to improvise when asking clarifying questions on the DISH.

This more flexible approach to interviewing is different than the approach to be taken when the self-administered questionnaires used in ENRICHD need to be interview-administered. In the case of the

DISH, a clinical interview, flexibility and improvising to better clarify patients' answers are important parts of conducting the interview. In the case of the other psychosocial measures, which are intended to be administered as self-administered items but may need to be transformed into interviews when patients have literacy or visual problems, questions should be asked in a more standardized, neutral way to ensure objectivity and eliminate bias. Because the procedures used for administering the DISH are somewhat complex and involve judgment and flexibility on the part of the interviewer, guidelines for administering the DISH are described in detail in the Forms Appendix (General Instructions for the DISH) and (Interview Techniques to be used in Administration of the DISH). Guidelines for transforming the other psychosocial measures into interviews, when needed, appear in Section -- and in the Forms Appendix for each measure.

#### **6.6.4 Short Blessed Test (SBT)**

The SBT is a short mental status test that should be administered during screening when the Case Coordinator or ENRICHD staff member has sufficient reason to believe that the patient may be too cognitively impaired to participate in ENRICHD. Guidelines for when to administer the SBT and how to score this test are given in the Forms Appendix.

### **6.7 Baseline**

If the patient is determined to be eligible to participate in ENRICHD, a baseline assessment should be scheduled while the patient is hospitalized or as soon as possible after discharge. The psychosocial measures to be administered during the baseline visit include the following:

#### **6.7.1 Perceived Social Support Scale (PSSS)**

This measure is a 12-item scale incorporating subscales which measure the degree of perceived support the patient receives from family, friends and significant others.

#### **6.7.2 New Haven EPESE Social Network Questionnaire (SNQ)**

The EPESE SNQ will be used to measure the structure of the patients' social networks. This 19-item questionnaire covers size, frequency of visual and non-visual contact, geographic proximity of close relatives and friends, marital status and religious and group membership.

#### **6.7.3 Selected items from the Interpersonal Support Evaluation List (ISEL)**

Ten items selected from the ISEL measure tangible support, or the extent to which the patient has someone in his or her life to call on for help with practical, financial and other tangible assistance, when needed.

#### **6.7.4 Perceived Stress Scale (PSS)**

The PSS is a 10-item scale that measures the degree to which situations in patients' lives are perceived as stressful (unpredictable, uncontrollable, overwhelming).

### **6.7.5 Self-efficacy Measure (SEM)**

Self-efficacy refers to the confidence in one's ability to behave in such a way as to produce a desirable outcome (Bandura, 1977). The SEM is a 10-item scale developed to reflect the intervention's expected effects on patients' self-efficacy related to the targets of depression and social support.

These measures appear in self-administered form, with guidelines for administering the measures as interviews in the Forms Appendix.

## **6.8 Follow-up**

Six-months following randomization patients should be contacted by the Case Coordinator or other ENRICHD staff member and scheduled for a 6-month follow-up visit. This visit will include assessment of medical status (see Chapter 5 for details on medical aspects of this visit), and administration of the psychosocial measures used in screening (ESSI, DISH) and those administered at the baseline visit (BDI, PSSS). The PSS, and SEM and SNQ, are administered only on a subsample of patients (the first 400/800 patients randomized to ENRICHD). The 10-item ISEL is administered only on a subsample of patients -- the first 400 patients randomized to ENRICHD. In addition to these measures the six-month follow-up will include the LOL, LSS, and selected items from the MOS SF-36 (HQL), also administered to subsample of patients.

### **6.8.1 Selected Medical Outcome Study Short-Form 36 items (MOS SF-36)**

The MOS SF-36 is a generic, standardized survey instrument for the assessment of health-related quality of life (HQL). Selected subscales from the SF-36 to be used in ENRICHD include the physical functioning, role limitations and social functioning subscales; individual items from the SF-36 assess health perceptions, pain and aspects of emotional functioning not captured in the depression measures, such as vitality.

### **6.8.2 Life Satisfaction Scale (LSS)**

The LSS is an 8-item scale measuring satisfaction with life and meaning in life which was derived from studies of long-term survivors of AIDS, and includes items from Ironson's Purpose in Life measure and Neugarten's Life Satisfaction measure, administered to a subsample of randomized patients.

### **6.8.3 Ladder of Life (LOL)**

The LOL, developed by Cantril (1965) uses a 1-10 scale ladder technique to assess patients' overall satisfaction with their lives now, their satisfaction with their lives in the past, and their perceptions of how satisfied they will be in the future.

Eighteen-months following randomization, patients will be scheduled for another follow-up medical and psychosocial assessment; however, the psychosocial measures administered at this visit involve a subset of the measures administered earlier: the BDI, ESSI, and MOS SF-36 items.



#### **6.8.4 Procedures to maximize blindness of interviewers**

As a rule, the procedures for administering the psychosocial measures at follow-up are identical to those used at the baseline assessment. However, in order to minimize possible bias on the part of the interviewer, it is important that the assessor who does the psychosocial assessment at follow-up is kept blind to the randomization status of the study participant and to whether they were depressed or not at entry into the trial (i.e., the assessor should not know whether the study participant was in the intervention or usual care group, nor their original depression diagnosis). (In the case of the DISH, there are certain exceptions to this rule, which are discussed in the following section on "Special procedures for BDI and DISH as follow-up measures.")

To maximize blindness of interviewers to the patient's treatment assignment at follow-up psychosocial assessment, the following procedures are recommended:

- (1) Randomization is done by a person different than the one who will be doing follow-up assessments;
- (2) Randomization group assignment is not communicated to the follow-up assessor;
- (3) Follow-up assessment may not be done by the therapist or other individual who has knowledge of treatment assignment;
- (4) An ENRICHD staff person (NOT the person doing follow-up assessments) should ideally contact the patient prior to follow-up to schedule the follow-up visits. This person should instruct the patient at that time: "DO NOT SAY ANYTHING TO THE INTERVIEWER/ASSESSOR ABOUT WHETHER YOU ARE ASSIGNED TO THE THERAPY PART OF THIS STUDY OR THE USUAL CARE PART."
- (5) Participants should be reminded at the start of the assessment session not to divulge which part of the study (treatment versus usual care) they are in.
- (6) Assessors should note whether the participant gave them any information indicating which group they were assigned to on the evaluation form.

#### **6.8.5 Procedures when suicidal features are present**

When the BDI and the DISH are administered as follow-up measures, the interviewer may determine that suicidal features are present. If so, the assessment, classification and notification procedures discussed in Chapter 2 and Chapter 8 are to be followed. In addition, if the patient is in the treatment arm of the study, his/her therapist and if applicable, the study psychiatrist should be notified (since the interviewer will ideally be blinded to treatment assignment, the Principal Investigator or another individual at the clinical site who has broad oversight and access to treatment assignment should provide follow-up information to the therapist/psychiatrist).

### 6.8.6 Procedures for using the DISH at follow-up

When the DISH is administered as part of the 6-month follow-up assessment, the interviewer should be blinded to treatment assignment, and to whether or not the patient was depressed when he or she was recruited to participate (see section on blinding of interviewer, above). However, this only applies to the Current Depression Symptoms portion of the DISH through 49). During the remaining portion of the interview, you will have to be unblinded in order to complete Item #48, the History and Course Chart, and the Diagnostic Summary Form. In order to complete the Longitudinal Course Chart and Diagnostic Summary Form, you will have to be unblinded to the patient's status at baseline and to what has happened to him/her between then and now.

When preparing to conduct a follow-up interview, you should be given a photocopy of the Diagnostic Summary Form (DSF) from the previous interview (i.e., the screening interview DSF if preparing for the 6-month interview; and the 6-month interview DSF if preparing for the 18-month interview.) This should be given to you in a sealed envelope so that you will be able to remain blinded to the patient's previous assessment until you reach Item #48 on the Longitudinal Course Chart, which concerns the patient's diagnosis from the previous interview. Open the envelope and record the previous diagnosis when you reach Item #48.

The principal objective of the 6-month DISH interviews is to determine the patient's current diagnosis and the current severity of depression. In order to arrive at the current diagnosis, you have to know what the patient's diagnosis was at baseline, and you have to try, under admittedly difficult circumstances, to determine the course of the patient's depressive disorder (if he or she was indeed depressed) since the previous assessments.

A simple example is that you cannot determine whether the patient meets the criteria for major depression in full remission (code #9 on the Diagnostic Summary Form) unless you know that the patient had major depression to begin with, and that the patient has been free of depressive symptoms for at least two months. To make this example a little more complicated, it is possible for a patient to have had only minor depression at baseline, but to have deteriorated over the next few months such that he or she developed major depression. In this case, you would know from reviewing the baseline findings that the patient had minor depression at baseline, and you would know from interviewing the patient about current symptoms that he or she doesn't have any, but you would not know what happened during the months in between.

Unfortunately, you cannot ask the therapist to tell you what happened during these months for patients in the Treatment arm, and there is no therapist to ask in any case for patients in the Usual Care arm. The patient is your only source of information, and you will have to try to retrospectively reconstruct the interim course of the patient's depressive disorder (if one was present). There is no specific structure to follow for this portion of the interview, since you will have to adapt your questions to fit the individual patient.

It is unlikely that you will be able to specify the interim course of the disorder to a high degree of accuracy, even in the best of cases. In some cases, it will be very difficult to obtain a very clear picture of the course. In the more difficult cases, you are simply expected to make a reasonable attempt to document the course, and to discontinue whenever you reach the point at which further efforts on your part are unlikely to yield any useful information.

One other difficulty you may encounter in administering the DISH during follow-up is that the Hamilton scale was designed to measure the severity of depression in depressed patients. Some of the patients you will be assessing will not have had a depressive disorder at baseline, and others will have depressive disorders that are in full remission. In these cases, it is important to bear in mind that the Hamilton items are about depression and associated psychopathology, not about anything else. For example, at least two Hamilton items ask about gastrointestinal distress. One is meant to determine whether the patient doesn't feel like eating; the other is meant to determine whether he or she is feeling nervous. Neither item is designed to detect GI disorders or other GI symptoms that have nothing to do with depression.

## **6.9 Procedures for Administration of Psychosocial Measures (other than the DISH)**

With the exception of the DISH, all of the psychosocial measures described in this chapter are intended to be used as self-administered questionnaires. In some instances, as discussed below, these measures may need to be administered via interview. Regardless of whether they are self-administered or interview-administered, the procedures to be used in administering standardized psychosocial instruments such as those outlined in Table 1 (except for the DISH) are very different than the procedures to be used with the DISH, which is a clinical interview. This section outlines the specific procedures to be used for all psychosocial measurement other than DISH administration.

### **6.9.1 Demeanor and Manner of administration**

As with administration of the DISH, administration of all other psychosocial measures requires establishment of a positive rapport with the patient. It is important that the Case Coordinator or other ENRICHD staff member maintain a professional and friendly manner at every contact with the patient. However, unlike the DISH, which depends upon the interviewer's flexibility and ability to improvise in order to clarify patient responses, a critical aspect of the ENRICHD staff members' demeanor when administering the psychosocial measures is neutrality and objectivity, and assessors should never improvise when clarifying questions or probing for responses. This more neutral, standardized manner helps ensure that the ENRICHD staff member's presence does not influence the patient's perception of or response to a question. For example, when introducing the questionnaire or answering questions, the assessor should be careful to avoid any statements that could influence the patient's responses.

The assessor should also convey a sense of impartiality, and should be gracious and adaptable to all patients regardless of whether or not their dress, appearance, style of speech or personal preferences are consistent with the interviewer's values and preferences. The patient should be confident in the

interviewer and feel that his or her responses are important. The demeanor of the assessor should be casual, yet professional. This requires a thorough familiarity with the questionnaire and procedures prior to administering the first questionnaire to a patient.

Finally, the assessor should be pleasant and friendly, with a sympathetic and understanding attitude. The respondent should be made to feel that there are no correct answers, that what he or she thinks is really what counts, and that his/her opinion can never be wrong. However, the interviewer should avoid long explanations of the study and should not invent or improvise explanations of the study or of specific questions. He or she should use the standard responses and introductory material provided below. Similarly, the assessor should never try to justify or defend what he or she is doing; should not try to explain procedures or question wording; should never suggest an answer; never agree or disagree with an answer; and should never interpret the meaning of a question. If the patient does not understand a question, just repeat the question slowly, exactly as written.

### **6.9.2 Introducing the Self-Administered items**

The following script should be used verbatim when introducing the self-administered items:

"WE WOULD LIKE TO BETTER UNDERSTAND HOW YOU FEEL AND HOW OTHER PERSONS IN THIS STUDY FEEL AND HOW YOU ARE DOING. TO HELP US BETTER UNDERSTAND THESE THINGS ABOUT YOU, PLEASE COMPLETE THIS QUESTIONNAIRE ABOUT YOUR HEALTH AND HEALTH-RELATED INFORMATION.

WE WOULD LIKE YOU TO FILL OUT THE QUESTIONNAIRE. BE SURE TO READ THE INSTRUCTIONS CAREFULLY. REMEMBER, THIS IS NOT A TEST AND THERE ARE NO RIGHT OR WRONG ANSWERS. CHOOSE THE RESPONSE THAT BEST REPRESENTS THE WAY YOU FEEL. YOUR RESPONSES TO THESE QUESTIONS ARE COMPLETELY CONFIDENTIAL -- YOU ARE IDENTIFIED ONLY BY A CODE NUMBER, NOT YOUR NAME. I WILL BRIEFLY LOOK OVER THE QUESTIONNAIRE WHEN YOU ARE DONE JUST TO MAKE SURE THAT ALL THE ITEMS HAVE BEEN COMPLETED.

YOU SHOULD ANSWER THESE QUESTIONS BY YOURSELF. SPOUSES, OR OTHER FAMILY MEMBERS, OR VISITORS, SHOULD NOT ASSIST YOU IN COMPLETING THE QUESTIONNAIRE.

PLEASE FILL OUT THE QUESTIONNAIRE NOW. I WILL BE NEARBY IN CASE YOU WANT TO ASK ME ANY QUESTIONS. RETURN THE QUESTIONNAIRE TO ME WHEN YOU HAVE COMPLETED IT.

### **6.9.3 Administering and Completing the Self-administered items**

Provide a firm writing surface such as a clipboard or table top. Provide a pencil.

If administration is in the hospital or in the home, special attention should be paid to maintaining the privacy of the participant to the extent possible. If feasible, administration should be in a private setting or room. If administration is in a clinic or office setting, or in the hospital, if the patient is mobile and capable of filling out the questionnaire in a private area of the hospital rather than his or her room, you should assist the patient in finding a comfortable, quiet place to complete the questionnaire. If this place is not in the immediate clinic area, it is important that you take responsibility in making sure the patient is returned to familiar surroundings once the questionnaire is completed. If the patient is completing the questionnaire while waiting for a procedure or the doctor, it is your responsibility to monitor the time for the patient or assist in making arrangements for a short delay. The patient should not have to be worrying about a missed appointment while they are completing the questionnaire.

The patient should complete the questionnaire without the help of a spouse or friend, and you should discourage others from staying with the patient while they are completing the questionnaire. This may not always be possible, however, you should reinforce the value of the patient's response.

The assessor should make it clear to the patient that he or she is easily available if the patient has any difficulty with the questions. The assessor should stay in the room while the first page or so of the questionnaire is being filled out, and should say something like: "I'll wait with you while you get started to be sure it is clear to you what is being done." When the subject finishes the first page, the assessor should indicate how he or she can be located should any questions arise. It is advisable for the assessor to periodically check back in with the patient while he or she is taking the questionnaire to ensure there are no problems or questions.

#### **6.9.4 Respondent questions and problems**

The assessor should be very familiar with all questions and their meaning. In response to requests for clarification, re-read the question exactly as it appears, stressing by your voice intonation references to time, place, and question intent -- for facts or feelings. Do not ad-lib an explanation of the question. It is important to stay with the literal expression of the questions since this is the best way to assure standardization of psychosocial assessment across centers.

Always take the blame for problems with the questionnaire. If the respondent complains of particular wording or redundancy or length of the questionnaire, say you don't know why it was done as it was, but it is important for the respondent to answer as best they can.

Appendix 6-A to this chapter contains a list of answers to common questions and problems you may encounter. Should you encounter difficulties with questionnaire wording or procedures that you have serious concerns about or cannot otherwise resolve yourself, check with your Principal Investigator or another person on-site who is responsible for supervising the study, or with a Coordinating Center or Project Office representative.

### 6.9.5 Closing and Review of questionnaire

When the patient returns the questionnaire, the assessor should ask the patient if any of the questions were not clear. Then the assessor should check over the questionnaire for completeness of responses. Among the things to note: Are the answers clearly marked? Are any answers left out or double-marked? Is there a systematic response bias (i.e., patient responds yes to everything)? This review should be done immediately while the patient is in the room so any problems can be addressed right away. If the questionnaire is not complete, ask the respondent whether he/she had any difficulty completing it. Where the patient had difficulty with an item, use the methods described below to clarify the question or probe for a response. If the patient indicates the omission was purposeful, simply record this on the Evaluation form and continue reviewing the questionnaire (it is within the patient's right to decline to answer any particular question). If the incomplete answer or omission was not purposeful (e.g., an inadvertently missed page or item), ask the patient if he or she would complete the unanswered questions. If there are ambiguous responses, such as double markings or unclear erasures, ask for clarification.

Finally, thank the respondent using the following exit script:

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS SURVEY. IT IS POSSIBLE YOU WILL BE ASKED TO COMPLETE THE QUESTIONNAIRE AGAIN AT A LATER DATE.

Complete the "Reviewer Evaluation Form" (form to be developed) following each psychosocial assessment, taking care to note whether the questionnaire was self- or interview administered, noting any difficulties the patient had with the questionnaire or other irregularities (e.g., lack of privacy/spouse present, interruptions to questionnaire administration).

### 6.10 Interview administration of psychosocial measures

While the self-administered questionnaire is designed for ease of administration, for a variety of reasons you can anticipate that a number of respondents will have difficulty completing this task by themselves. Approximately 6% of the American population (with a range of from 2 - 13% across individual states) is formally considered functionally illiterate, having completed fewer than four years of schooling. This rate is probably a gross underestimate of individuals who are likely to have difficulty in completing our self-administered questionnaire because of problems in reading fluency and comprehension. In addition, a number of respondents will have vision problems or difficulty in writing responses. We do not want to lose these respondents, and it is important to provide them the opportunity to get our help in completing the questionnaire.

It is important to provide the opportunity for help in a positive manner, taking care not to convey any negative judgment or feelings. When handing the questionnaire to the respondent, the assessor should say to the respondent "we have found that some people prefer to have the questions read to them. Would you like me to read these questions to you, or would you prefer to fill out the questionnaire yourself?" If the patient is not sure, you might suggest he or she take a minute to look over the

questions to help decide what they prefer. You should be aware of any indications that patients might have trouble reading the questions, such as: less than an eighth grade education; trouble with the informed consent; trouble with seeing the words clearly; a puzzled look or very slow progress on the first page of the questionnaire. Some of the problems you may encounter that would encourage interview-administration of the forms include: vision problems (lighting, patient forgot glasses, or does not have their glasses in the hospital), hearing problems, paralysis, tremor, numbness or insensitivity in their fingers, inability to write legibly, or trouble sustaining the attention needed for the task.

Another potential difficulty which may interfere with self-administration is pain and fatigue. Having more than one session may be necessary. Keeping on track may reduce overall time. Finding small windows of opportunity (when they are not in pain or fatigue) may also be helpful.

If you identify any of the above signs of low literacy, visual or other difficulties filling out the questionnaire, or if the patient indicates he or she prefers to have the questionnaire read, an interview format should be used instead of the self-administered format. All of the self-administered questionnaires can be turned into interviews, if needed. The Forms Appendix contains specific instructions for administering each psychosocial measure as an interview. In addition, the following general guidelines for using an interview format with the self-administered questionnaires should be followed (these guidelines are relevant for all psychosocial measures EXCEPT THE DISH):

- (1) The questions should be read verbatim, not improvised or changed in any way.
- (2) The interviewer should provide neither verbal nor non-verbal responses that can influence the patient's responses. For example, an assessor should not show surprise, pleasure or disapproval to any answer. Even apparently innocuous behaviors like nodding, smiling or sighing will influence the patient's responses to questions. The interviewer's role in administering the psychosocial measures other than the DISH is to obtain as unbiased and uninfluenced a response to the questions as possible.
- (3) Although it is essential that the questions be read verbatim, the interviewer should not sound like an automaton. The interviewer should be thoroughly familiar with the measures, and know the questions so well that it never sounds as if he or she is reading them formally. The interviewer should use a natural, conversational style, but at the same time, he or she should "stay on track" and politely, but firmly, lead the patient through the questionnaire.
- (4) Never add to or subtract words from a question. Read the question exactly as written, and as evenly as possible, without giving unusual inflection to any particular words -- do not give emphasis to any one part of the question or to any response alternative.
- (5) Never change the sequence of questions -- read them in the exact order written -- and never try to ask questions from memory.

- (6) Do not rush the patient -- let him or her understand the question fully, and don't show impatience. Do not record a "don't know" answer too quickly -- people may say "I don't know" when stalling for time to arrange their thoughts. The phrase merely may be an introduction to a meaningful answer, so give the patient a little time to think.
- (7) Never patronize patients who do not speak English fluently, and never react to answers or do anything that suggests to the patient that an answer is right or wrong.
- (8) Never let another person answer for the patient.

### 6.11 Probing for Responses

The psychosocial measures used in ENRICHD (with the exception of the DISH) have been designed to minimize open-ended responses. However, even with closed-response categories, probing is sometimes required. Probing is a critical technique to master as it is an easy place to fall prey to directing responses or altering the meaning of a question. Thus, probes must be as uniform as possible within and across centers.

If the patient provides an inappropriate response to a question (e.g. uses the wrong response category), repeat the question and the response categories. For example, if the interviewer asks a question that requires a patient to provide his or her degree of agreement and instead, the patient says "that's true," the interviewer responds "would you say you strongly agree, agree, etc."

If a patient provides an ambiguous response to a question, then the interviewer must obtain a clarification without directing the response. The following can be used:

- ⇒ (1) pausing -- sometimes just waiting expectantly, or giving the respondent time to think may be helpful;
- ⇒ (2) rereading the question focuses the respondent on the questionnaire task, especially if there is distraction or possible misunderstanding. Say "I'm going to reread the question," then reread the question exactly as written, do not paraphrase.
- ⇒ (3) when necessary, you may ask for more information in a neutral way: "can you tell me more?"
- ⇒ (4) stress generality -- "usually," "mainly," "overall," which answer comes closest?"
- ⇒ (5) stress subjectivity -- "your opinion," "your best estimation," "your recollection."
- ⇒ (6) when zeroing in, keep it neutral (e.g., "can you remember who?" not "was it your son?") -- don't suggest any specific response.



**Appendix A:** Table 1. ENRICHD Data Collection Schedule, Revised March 1998

Psychosocial Measures	Baseline	3 mo	6 mo	9 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo
Enrichd Social Support Instrument (ESSI)	All		All		All	All		All		All		All
Beck Depression Inventory (BDI)	All		All		All	All		All		All		All
Depression Interview and Structured Hamilton (DISH)	All		All									
Longitudinal Course Chart (LCS)					All							
Perceived Social Support Scale (PSSS)	All		All									
Health Quality of Life (HQL)			800									
Ladder of life (LOL)			800									
Life Satisfaction Scale (LSS)			800									
Social Network Questionnaire (SNQ)	800		800									
Perceived Stress Scale (PSS)	400		400									
Self-efficacy Scale (SEM)	400		400									
Interpersonal Support Evaluation List (ISEL)	400		400									
Telephone contact: identification of potential events, contact information update		All		All			All		All		All	

Screened: all patients screened All: All randomized patients

400/800: First 400/800 patients randomized



## 7. Chapter 7: Adherence, Retention and Drop-Out Recovery

### 7.1 Overview

Adherence, retention, and recovery of possible drop-outs from the study are essential to the scientific credibility of the study. Without sufficient adherence to the intervention, sufficient changes in depression and/or social isolation may not be obtained among participants to judge the impact of decreasing depression and/or social isolation upon morbidity and mortality. Without sufficient retention of participants in the arms of the study, the generalizability of the study's findings to the usual depressed and/or socially isolated post-MI patient may not be possible. Additionally, differential retention between the intervention and usual care arms of the study may severely bias the interpretation of the efficacy of the interventions. Thus, it is essential that methods be systematically implemented to promote adherence and retention and recover as many participants who drop out as possible.

ENRICHD will adopt a variety of approaches to promote adherence and retention during the study, and to aid in drop-out recovery. The first set of strategies consists of commonly used methods of assisting participants in adhering to the study protocol, and will be described as general adherence strategies in Section 1. that follows. In addition, we will use motivational interview methods from the moment of recruitment in order to reinforce adherence during the study as previously described in Chapter 3, and further discussed in Section 7.2. below. Finally, we will describe strategies aimed specifically at recovering drop-outs, either due to a failure to return to follow-up assessments or failure to return to intervention sessions (Section 7.3. below).

### 7.2 Approaches to Adherence

Three general strategies will be used to facilitate adherence to the intervention follow-up assessments, and to retain study subjects throughout follow-up. These strategies include logistical assistance, reminders, and involvement by family and/or friends and are discussed further below.

- logistical assistance/support

As previously discussed in Chapter 3, the Case Coordinator (CC) will ensure that participants have sufficient logistical assistance to attend first screening visits and then intervention and assessment sessions once they are randomized. Issues that we anticipate commonly being addressed with patients include providing assistance with transportation, offering meals during return visits to the hospital, and arranging for child-care and other family obligations. The CC will also try to schedule visits at times least likely to interfere with other social or work activities.

- reminders

We also plan to provide all study participants with calendars indicating intervention and/or assessment sessions, and to send them reminders in advance of follow-up assessments. A newsletter will also be developed and sent to both intervention and usual care participants in order to

encourage continued involvement in the study. Appropriate care will be taken to ensure, however, that the newsletter content does not address issues related to either depression or social isolation.

- eliciting support from family/friends

Lack of support is a common barrier to participation for all participants, but may be a particularly common issue among low-SES participants, minorities and women. This may be especially the case with a study which focuses on psychosocial issues where there may be less cultural acceptance of these factors than among more affluent or non-minority groups. We will thus plan to inform family and/or friends of participants during the recruitment phase and to solicit their support and involvement (see Chapter 3). Fortunately, a focus of intervention will be on developing skills to increase social support which should be sufficient for those participants assigned to the active intervention to deal with these issues that may affect participation. For those participants assigned to usual care, however, it will be essential for the CC to facilitate participants addressing social support barriers to participation without actually providing them with much support. For these usual care participants, issues concerning social support barriers to participation will be addressed through developed text materials to be sent to participants and newsletter articles.

### **7.3 Motivational Interviewing Methods**

Motivational interviewing is an approach to assessment and intervention based on Stages of Change Theory which is designed to augment an individual's motivation to change behavior. This approach to health-promotion interventions emphasizes the use of individualized risk appraisal, identification of potential risk-reduction strategies, techniques to increase self-efficacy for behavior change, and strategies to prevent relapse and promote retention. It incorporates several strategies to facilitate transition from one stage to the next, thereby preparing an individual to initiate and/or maintain a recommended behavior. Objective feedback is provided and ambivalence about behavior change explored, with specific attention to eliciting an individual's personal goals and self-motivational statements, formulating personal goals in behavioral terms and problem-solving barriers to change. Reflective listening skills are particularly effective as a method of interaction with patients in eliciting and clarifying their personal goals and self-motivational statements. Motivational interviewing seeks to evaluate the discrepancy between participants' stated goals and their current behaviors in a style that increases motivation for change.

Motivational interviewing methods will be incorporated in the earliest stages of recruitment as previously described in Chapter 4, Section 4.3.2. However, these methods will be extended throughout activities of ENRICHD to encompass interactions of participants with CCs, interview and clinic follow-up staff. Our experience has been that these methods, when used consistently across contacts, are extremely effective in promoting active participation.

Training in motivational interviewing methods will be incorporated into the national training for study staff. Additionally, the supervising psychologist at each site will ensure the training of all staff in motivational interviewing methods to supplement the national training, and staff experience with motivational interviewing methods will be reviewed during staff meetings and supplemented with role-playing as needed to train staff on an on-going basis to use these methods effectively.

## 7.4 Drop-out Recovery

Drop-out recovery methods have been demonstrated in clinical trials to re-engage participants who have become inactive when applied systematically (Probstfield, Russell, Insull, & Yusuf, 1990). While not originally conceptualized in this manner, this approach incorporates the use of good reflective-listening and directive skills to elicit barriers to participation from subjects. This information is then used to problem-solve with participants for methods to overcome the identified participation barriers. Finally, an essential component of drop-out recovery is the application of motivational interviewing methods in an attempt to further elicit and clarify participants' personal reason for continued participation.

The general approach to drop-out recovery will involve contact by the CC in an attempt to: 1) identify barriers to participation; 2) problem-solve for solutions to overcome identified barriers; and 3) apply motivational interviewing methods as discussed above. These efforts will be discussed and reviewed during Case Management Review sessions by the CCs, therapists, and behavioral investigators. If the CC is not successful in re-engaging the participant, then contact will be initiated by a therapist or investigative team member at the discretion of the Case Management Team. Often, contact by a new member of the staff results in new perspectives and is to be encouraged in drop-out recovery.

In general, drop-out may be seen from clinic follow-up visits for all enrolled participants. It is common, though, for participants assigned to active intervention to see drop-outs selectively from either clinic follow-up or intervention sessions; some intervention participants will, of course, drop out from both intervention and clinic follow-up. Drop-out recovery of intervention participants thus requires close coordination and sharing of information between intervention and clinic staffs.

### 7.4.1 Specific Methods for Drop-Out Recovery

The approach to drop-out recovery will involve the following steps: 1) contact the patient; 2) identify reasons for withdrawal; 3) negotiate solutions to overcome barriers; and 4) apply motivational interview methods. Motivational interviewing methods are discussed in Section 7.3 above. The other steps are discussed below.

#### 7.4.1.1 Contact the patient:

Attempt to contact patient - When a patient has missed one intervention session without advanced warning, then the therapist will inform the CC, who will try to contact the patient. The CC will first attempt to contact the patient directly by phone. If patient has an unlisted telephone number, then an attempt should be made to contact the proxy of the patient. The proxy may be asked to have the patient contact study staff, or to find out whether patient is still in the area and his/her vital status. The CC may also send a letter by certified mail, asking the patient to contact the study staff. Record the results of all attempts to contact the patient either by phone or by mail on follow-up form (to be developed).

Attempt to contact the patient's physician - Record the result of the attempt to contact the patient's personal physician, by letter or by phone, for the patient's current address and/or vital status. Other staff in the physician's office, such as the nurse, may also be asked to provide this information.

Other sources of contact to find out about the patient's whereabouts include patient's employer, Social service agencies, the Department of Motor Vehicles, the Police Department, etc. In each instance record the results of the inquiry.

#### **7.4.1.2 Identify reasons for withdrawal**

Patient has died - record date of death and how date of death information is obtained.

Patient is lost to follow-up - All efforts to locate patient have failed. Record whether patient's vital status is known or unknown, and last date of known contact with ENRICHD.

Patient has moved away - The patient has moved away and cannot or will not return for intervention sessions and any scheduled follow-up visits. [optional: If the patient has moved to another ENRICHD center area, it may be possible to keep patient in trial for follow-up visits. The Coordinating Center should be contacted for instructions on how to transfer patient from one center to another.

Physician refuses to continue patient in study - Contact the physician's office and record reasons/circumstances which have influenced the physician's refusal for the patient to continue in the study.

Patient refuses to continue in study - Identify reasons for withdrawal and register whether barriers to participation are solvable. It is important to use good reflective-listening and directive skills to elicit barriers to participation from patient. To the extent possible, to determine willingness of patient to work on solutions to overcome barriers to participation. Record patient reason's for withdrawal and willingness to return (potentially willing vs absolutely unwilling). If patient has dropped out of treatment and is absolutely unwilling to return, negotiate continued participation in follow-up assessment visits.

#### **7.4.1.3 Negotiate solutions to overcome barriers**

Logistical obstacles - When major barriers to participation involve logistical obstacles, first try to identify alternative strategies that the patient may use to overcome these obstacles. If these alternative strategies fall short or are not available, then offer reasonable logistical assistance provided by study resources.

Lack of motivation - Use motivational interviewing techniques to encourage patient reconsidering the decision to withdraw. Suggest an in-home visit to discuss re-entry into study with patient. If family members play in role in decision to drop-out, then try to schedule a phone call or home visit with family members present. Also, contact therapist to discuss motivational problems on the part of the patient.

Recurrent event - If patient is temporarily hospitalized, or otherwise unable to continue intervention sessions because of recurrent event or other health condition, discuss importance of returning to interventions after recovery. Conduct weekly follow-up phone calls to determine status of patient.

## **7.5 References**

Probstfield JL, Russell ML, Insull W, Yusuf S: Dropouts from a clinical trial, their recovery and characterization: A basis for dropout management and prevention. In SA Shumaker, EB Schron, JK Ockene, CT Parker, JL Probstfield, JM Wolle (Eds.): The Handbook of Health Behavior Change. New York: Springer, 1990.

## Appendix: Sample Form for Drop-out Registry

Patient ID:

COMPLETE THIS FORM IF PATIENT HAS DROPPED OUT FROM INTERVENTION OR IS NO LONGER PARTICIPATING IN THE STUDY

- 1) Date of last ENRICHD contact (mo/day/yr)
- 2) Reason for Patient Withdrawal
  - 1: Patient is lost to followup
  - 2: Patient has moved away
  - 3: Patient refuses to continue (go to 4)
  - 4: Physician refuses to continue patient in the study
  - 5: Other (specify)

- 3) List reasons/circumstances of patient's drop-out

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- 4) Vital Status
  - 1: Alive
  - 2: Dead (record date of death plus where information was obtained)
  - 3: Unknown
- 5) Evaluation of patient's willingness to re-enter:
  - 1: perhaps willing
  - 2: absolutely unwilling
- 6) Outcome of drop-out recovery effort:
  - 1: patient re-entered
  - 2: patient refused to re-enter



## **8. CHAPTER 8: Participant Safety and Confidentiality**

### **8.1 Introduction**

The psychosocial intervention will consist of individual and group cognitive-behavioral therapy for all participants, supplemented by antidepressant therapy, as needed. The active treatment phase will last approximately six months, with follow-up for one and one-half to four and one-half years. The experimental treatments for the ENRICHD study are not expected to pose any particular risk. Each participating investigator has primary responsibility for the individual participants under his/her care.

### **8.2 Protocol Review and Study Monitoring**

An independent Data and Safety Monitoring Board (DSMB) will be appointed by NHLBI and charged with monitoring the progress of the study. The DSMB will review and approve the protocol prior to study initiation. During the study the DSMB will meet periodically to review study progress. These reviews will include evaluation of interim data as well as the monitoring of participant safety and the quality of all aspects of study operations.

Prior to study initiation, the study protocol will be reviewed and approved by each center's Institutional Review Board (IRB).

After enrollment, each individual Principal Investigator will monitor safety issues at his/her site continuously and report any problems to the Coordinating Center, which will inform the NHLBI Project Officer.

### **8.3 Exclusions**

Persons with medical or psychological contraindications to the experimental treatment will not be eligible to be enrolled. Exclusions are detailed in Chapter 2.

### **8.4 Informed Consent**

Informed consent will be obtained from each participant before they are enrolled in the study. The consent form will describe the potential risks and benefits of study participation as well as the responsibilities of the participants and the investigators.

### **8.5 Adverse Event Reporting and Discontinuation of Study Treatment**

As treatment progresses and at all follow-up visits, possible adverse effects of the experimental treatment will be assessed. If participant assessment indicates an adverse reaction, the study investigator may, at his/her discretion and according to the psychosocial intervention design described in Chapter 5 of the ENRICHD Protocol, refer the participant for additional medical follow-up, additional individual therapy sessions, and/or assessment for psychopharmacological intervention. Depending on the situation, the change may be temporary or continue throughout the study term. In rare cases the experimental treatment may need to be discontinued, however the participant would continue to be followed.

## 8.6 Preliminary Primary Physician Notification Policy

Circumstances exist that require notification of physicians in the interest of patient welfare. Notification should occur when there is substantial potential for psychological morbidity associated with a patient's psychological status. It is doubtful that notification will have a serious impact on the ENRICHD trial as a consequence of modifications in physicians' behavior.

Preliminary Policy (not yet fully approved by the ENRICHD Steering Committee):

1. At the time of randomization, primary physicians will be notified that their patient is eligible for the study and the reason(s) for eligibility - social isolation, depression, or both.
2. If major depression is present at a subsequent assessment, the primary physician will be notified in writing on each occasion.
3. Primary physicians will be notified in writing and by phone if the patient's condition poses a significant clinical risk at any point in the trial, i.e., serious suicidality as defined in the MOO.
4. The intake Consent Form will specify that primary physicians will be notified of their patients' eligibility for randomization, the reason for being eligible, and that results of psychosocial evaluations might be communicated, if indicated.
5. A standard notification form will be developed and employed.
6. The Coordinating Center will be informed of notification events occurring after randomization.

## 8.7 Protection of Participant Privacy

Privacy in the context of this study includes confidentiality of data and personal information at the Clinical Center and in the handling and reporting of data by the Coordinating Center. It also includes discretion on the part of the clinical center staff and arrangements for physical privacy during interviews and examinations. Each Clinical Center will be responsible for ensuring physical privacy of participants and ensuring that data are stored in a secured area accessible only to ENRICHD staff. These provisions will be monitored during periodic site visits from the Coordinating Center.

## 8.8 Data Security and Confidentiality

The original paper data collection forms will be retained at the clinical centers. They should be stored using the confidentiality procedures provided for other medical records at the institution.

All data transferred to the Coordinating Center will be stored, processed, and analyzed within the Coordinating Center office suite. At the Coordinating Center, all access to office space containing data is controlled through manned reception areas. Visitors are screened by the receptionists and cannot move about without an escort. All office space is locked after working hours. Access to computer data files is controlled by passwords released only to those Coordinating Center personnel who use the files. In addition, critical data files are encrypted.

A backup of the database will be made daily to a second disk drive on the Coordinating Center local area network. Automatic magnetic tape backups of the database also will be made daily. Once a month, the current backup tape will be removed from the cycle and permanently archived at the Coordinating Center's off-site data storage facility.

Output mailed to clinical center staff will identify participants only by ID number.

No individually identifiable information will be distributed to clinical centers. When printed material containing confidential information is to be discarded, it is loaded, transported, and stored under supervision (using a chain of custody control process) until the material can be recycled into paper pulp.

All Coordinating Center staff are required to complete a confidentiality certification procedure upon employment. Policies regarding the confidential nature of the data collected, processed, and stored at the Coordinating Center, are explained to all personnel, who must then sign a "confidentiality certification," before being allowed access to confidential information. In addition to this initial training, the Coordinating Center reinforces the need for careful and confidential handling of data at staff meetings.

## 9. Chapter 9: Data Management Procedures

### 9.1 General Instructions for Completing Forms

All ENRICHD study data should be recorded on official ENRICHD data collection forms provided by the coordinating center. Data will be recorded by study nurse-coordinators, investigators, therapists, or other trained Clinical Center staff. The study case coordinator should check the forms for accuracy, completeness, and legibility, before mailing to the CSCC for data processing and analysis.

Use **black ball point pen** for completing all interview based forms. The first page of all the self-administered forms will contain both general instructions on completing mark-sense forms, and specific instructions to the participant on how to respond to the questionnaire. An administrative area is also on the first page of each booklet or individual form for identification and linkage of the instrument to a particular timepoint (see section 9.5 below). The administrative section should be completed before giving the questionnaire to the patient. Make no erasures and do not use correcting fluid. The optical mark read (OMR) formatted self-administered psychosocial forms should be completed in **#2 pencil**. OMR form corrections can and should be via erasure since the optical scanner and processing software can only correctly score one mark per item. This is an important factor in correctly processing the psychosocial forms, so all self-administered forms should be carefully checked once returned for incomplete erasures, stray marks, skipped items, and items with more than one response indicated.

Print all text responses legibly; do not use cursive writing. Always retain a copy of each form completed either by interview, or self-administered, in the permanent ENRICHD patient file.

Record all times in 24 hour format (also called international time, e.g., 00:00=12 Midnight, 06:00=6AM, 20:00=8PM, etc.).

### 9.2 Missing Data

Do not leave responses blank on a Form. Unanswered responses embedded in question sequence that was validly skipped because the items were not applicable are permitted. Blank responses are not automatically assumed to be “Unknown” or “No”. Be explicit in the recording and entry of data on the study forms. When information is unavailable and will never be known, place a double horizontal line through the space. For example:

Height ===== in.

### 9.3 Permanently Missing Forms

A list of expected forms that have not been received by the CSCC will be generated periodically and sent to the clinical centers. Information necessary for tracing the missing forms will be provided. Included on the expected not received listing will be the patient ID number, the form code, and the visit number for the missing form. When possible, an approximate visit date based on other forms

received for that same patient and visit will be included. Clinic staff are asked to respond promptly regarding the status of the missing form(s).

Locate the copy of the requested form from the patient file, and follow the procedures for re-transmitting a form to the CSCC located in the ENRICHD Data Transfer section of the manual of operations.

If no copies of the form in question can be located but the information on the form can be recovered (from lab reports, medical records, etc.), complete a blank form. The clinic should write "Replacement" in the status field of the missing forms report, and also write "Replacement" on the top of the form. Transmit the replacement form to the CSCC.

If an entire form cannot be located and the information cannot be recovered, write "Permanently missing" in the status report. Complete the header section of a blank form and write "Permanently Missing" across the top of the form. Transmit the missing form to the CSCC.

## 9.4 Correcting Errors

Corrections should be made in the following manner:

- Cross out the original response with a single line in such a way that it is still legible.
- Write the correct response above or to the side of the original response.
- Date and initial the correct response.

For example:

What is the patient's Gender? Male X Female \_\_\_

**Do not use white out or erasures at any time.**

## 9.5 Completing the Form Header Fields

Enter the Center ID Number on each participant Form in the administrative use area. A table of the clinical center numbers appears at the end of this chapter for reference. Patient ID Numbers should be transcribed from the ENRICHD Screening ID list provided by the Coordinating Center. The ID numbers will be grouped by hospital within clinical center. The Patient Number consists of the 2 digit hospital identification number followed by the 5 digit patient sequence number, which when combined gives a 7 digit patient ID(see below). The combination of the Center number and the Patient ID together is referred to as the Study ID, and it is this 9 digit form (2 + 7) that the ENRICHD Data Management System (DMS) uses to uniquely identify patients participating in the study. The first patient eligible for the study will be given the first number in sequence from the center specific list supplied by the coordinating center. The second patient eligible will be next

number from that list, etc. For Investigators that have more than one site, each sites should use sequence numbers generated by the CSCC for that site.

**ENRICHD**  
**FOLLOW-UP EXAMINATION FORM (FUX,Version A)**

Center:	<input type="text"/>	<input type="text"/>	Patient ID:	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	Patient Initials:	<input type="text"/>	<input type="text"/>	Visit:	<input type="text"/>
	<input type="text"/>													
Sequence #:		<input type="text"/>	<input type="text"/>	Date:		__ / __ / 19__	Staff ID#:		<input type="text"/>	<input type="text"/>	<input type="text"/>			
				mo.		da.	yr.							

Enter the patient initials. If the middle initial is unknown or does not exist, enter the letter "X" in that box. All 3 boxes for the patient initials must be completed. See the detailed instructions for completing each form to assign the appropriate 2 digit visit number. Some Visit numbers will be preprinted or automatically completed by the data entry software (e.g. eligibility or randomization visits). The date field appearing in the header is "today's date", the date the information was collected or transcribed, not the date keyed. Date formats will always appear in month/day/year order. The final item in the header area is the staff ID#, which will be assigned by the CSCC for each member of the participating clinical center who is authorized to record study information on a paper form or electronic data entry screen. The CSCC must be prospectively informed of any ENRICHD clinical center personnel changes and the need for staff ID# assignment. Valid code numbers for the ENRICHD clinical centers appear below:

## Table of ENRICHD Clinical Center Code Numbers

<u>Clinical Center</u>	<u>Code Number</u>
Duke University Medical Center	01
Rush-Chicago	02
Stanford University	03
University of Alabama, Birmingham	04
University of Miami	05
University of Washington, Seattle	06
Washington University	07
Yale-Harvard center	08

## 9.6 ENRICHD Data Transfer Procedures

Patient information will be transferred to the Coordinating Center in 3 different modes during the course of the study. Diskettes containing electronic versions of the data and any changes (transactions) related to processing that data at the central database will be shipped on a biweekly basis and can be included with the transfer of paper forms (see section 3.2 of DMS Users Guide in Appendix for discussion of those procedures). Self-administered psychosocial questionnaires (such as BDI, ESSI, SEM) recorded on optical mark sense paper forms will be batched and shipped for centralized reading and scoring of those data. Event specific end points documentation materials (enzyme lab sheets, discharge summaries, ECGs, etc.) as described in medical measures (see Chapter 5) will also be forwarded to the Coordinating Center for use by the study end points classification committee. Refer to section 5.8 for procedures related to collection and transfer of end points materials.

## 9.7 Transfer of Forms to the Case Coordinator

### 9.7.1 Collecting and Batching Completed Form Pages

The Case Coordinator will visit each clinical center at least twice monthly. During that visit, the coordinator will review all the data forms that have been completed since the last clinic visit for completeness and correspondence to the patient's clinical record. The coordinator will collect the original and make a photocopy of each completed, reviewed form. The original copy of the form will be sent to the Collaborative Studies Coordinating Center (CSCC) for processing. A copy of each form will remain at the clinic in the patient form binders for at least two years after conclusion of the study. The set of forms collected from a clinic at a monitoring visit will be referred to as a "batch" of forms.

### 9.7.2 The Batch Inventory Sheet

For each batch collected, the case coordinator should complete a Batch Inventory Sheet (BIS). The BIS is a form used to document the number and type of forms in a batch. It provides each center with a record of the forms it sent to the Coordinating Center. Finally, the inventory sheet provides the CSCC with a valuable tool to trace forms in its filing and processing system.

#### Section 1: BATCH IDENTIFICATION

- Item 1) Print the two-digit clinic code (see Appendix A).
- Item 2) Print the name of the case coordinator who is collecting the copies of the forms.
- Item 3) Fill in the month, day and year of the date which the batch was compiled.
- Item 4) Print the name of the person at the clinical center who is giving the copies to the case coordinator.



**ENHANCING RECOVERY IN CORONARY HEART DISEASE  
ENRICHD  
FORMS BATCH INVENTORY SHEET (BIS)**

**Section 1: Batch Identification**

The original and first copy of the following forms are being transferred from clinic/hospital

(2-digit clinical center number) to the case coordinator \_\_\_\_\_ on  
(NAME)  
\_\_\_\_\_/\_\_\_\_\_/19\_\_\_\_ by the clinic/hospital representative \_\_\_\_\_.  
mo. day yr. (NAME)

**Section 2: Inventory of Forms**

7-digit patient number	Data forms	Clinic form count	CSCC form count
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Fill out one line of the BIS for each patient included in the batch being sent to the CSCC for data processing.

- 1) Enter all seven digits of the Patient ID Number in which the first 2 digits are the hospital code number, and the last 5 digits are the sequential patient number (see example below).
- 2) For the given patient number, note which forms are being transferred. Form codes appear in the upper right center of each page heading.

Only completed forms that have been filled out legibly and checked by the investigator and Case coordinator are to be collected and recorded on the BIS.

- 3) Finally, for the given Patient Number, enter the number of forms sent in the boxes provided. For example, below is one line of a completed BIS showing forms collected from hospital 1 for patient 24:

7-digit patient number	Data forms	Clinic form count	CSCC form count
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	_____	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

- 4) After completing as many lines as required, record the total number of forms being shipped with the BIS. This total is obtained by summing the column entitled "Clinic Form Count."

### Section 3 BATCH PROCESSING HISTORY

This area is to be used by CSCC. DO NOT complete this section, leave blank.

#### 9.7.3 Preparing the Batch

The batch should always begin with its corresponding BIS. At the clinic, the case coordinator should place the original BIS on top of the original forms, and place the first copy of the BIS on top of the corresponding photocopies of forms. Do not staple forms together. The forms should be ordered by Patient Number and then by Form type as they appear on the BIS. The direct correspondence between the inventory sheet and the collection of forms facilitates processing and confirmation by the CSCC that the data transfer is complete.

Each batch of forms and the corresponding cover BIS should be joined together by a paper clip, rubber band or placed in a manila envelope. No two batches should be joined together to avoid introducing any potential processing errors with inventory of the batch.

### **9.7.4 Disposition of copies**

The original BIS will be mailed to the CSCC and one photocopy will be retained by the case coordinator with the copies of corresponding data forms. A second copy of the BIS should be filed in the clinical center site for future reference.

## **9.8 Transfer of Forms to the CSCC**

### **9.8.1 Shipping the Batches to the CSCC**

The batches collected during case coordinator visits should be sent to the CSCC as soon as possible and at least twice per month. Batches should be sent by an express package delivery service (e.g. Airborne Express, Federal Express, United Parcel Service, U.S. Postal Service next day delivery). More than one batch may be sent in one envelope. However, each batch should be separate from the other batches within the envelope because each batch is checked and inventoried as a unique collection of data forms for tracking and processing.

Each mailing should contain the following items together in one envelope: (1) the batched group of forms; (2) the corresponding BIS; and (3) any letters or notes about these batches that would explain any discrepancies and relate to the processing of the batch.

Mailing envelopes with data forms should contain only the items mentioned above. Extraneous materials such as letters to investigators or research staff at the CSCC should be sent under separate cover. It is permissible to include data transfer diskettes with paper forms; however, please note the inclusion in the comments area of the BIS.

All batch data mailings should be addressed to:

ENRICHD Central Receiving  
Collaborative Studies Coordinating Center  
University of North Carolina  
137 East Franklin Street, Suite 203  
Chapel Hill, North Carolina 27514-4145

### **9.8.2 Acknowledgment of receipt of batches**

Once a month the CSCC will fax to the Case Coordinator an acknowledgment of batches received by the CSCC. This correspondence will contain identifying information for each batch received since the previous acknowledgment. If this acknowledgment is not received within 3 weeks of the shipment of a batch, the Case Coordinator should contact the CSCC to investigate why confirmation for the batch shipment is overdue.

## **9.9 Questionable Data Queries**

The majority of missing, illegible, and incorrect data values are expected to be discovered and corrected by the clinic staff and the Case Coordinator during their review of the completed ENRICHD data forms prior to their collection. These corrections are made on the original forms

(see General Instructions for Completing Forms section elsewhere in the operations manual for details on how to correct an entry).

After the original forms have been transferred to the CSCC, further problems may be discovered by the Case Coordinator or the clinic staff. In addition, when the data are processed at the CSCC, the editing software will identify missing, extreme, and inconsistent values. In these cases, a Query Log Report (QLR) is used to identify the suspect value, and to document the resolution of the issue.

For problems discovered manually, blank Questionable Data (QDA) forms are provided for use by Case Coordinator and CSCC staff as appropriate.

No matter who discovers the questionable data, only clinical center staff are authorized to determine the appropriate resolution.

The QDAs and QLRs have a separate batch inventory form that should be completed and submitted with each batch of query forms.

### **9.9.1 Completing the Manual Questionable Data Form**

The person identifying the questionable value completes the header section of the QDA form, and section 1 (Identification of Value to be Corrected). The clinic staff member who determines the appropriate resolution (correction, confirmation, etc.) completes Section 2 (Problem Resolution).

#### **9.9.1.1 Form Header Information**

Enter the Patient Number of the patient whose data are in question. Enter the date that this Questionable Data Form is being initiated.

#### **9.9.1.2 Identifying Information (items 1-7)**

This section of the form should be completed by the person detecting a problem with a data value on a form already collected from the investigator or center staff member. The patient's forms binder should be checked to confirm that a Questionable Data Form has not already been generated for this problem. All items should be completed to insure a proper resolution.

Items 1-3: Enter the Form type and date from the original data form containing the item being questioned.

Item 4: Enter the item number and a brief description of the item to be investigated.

Item 5: Enter a brief description of the problem.

Item 6: Enter the name of the person detecting the problem.

Item 7: Enter the current value of the item to be investigated.

**ENHANCING RECOVERY IN CORONARY HEART DISEASE  
(ENRICHD)**

**QUESTIONABLE DATA FORM (QDA)**

Code#:

Patient ID#:

---

**Section 1: Identification of Value to be Corrected**

1. Form Code:

2. Visit Number:  Sequence Number:

3. Form Date: \_\_\_/\_\_\_/19\_\_\_  
mo. da. yr.

4. Item Number:

Description of Item:

5. Description of problem:

6. Name of Person Detecting Problem:

7. Current Value of Item:

**Section 2: Problem Resolution**

8. CORRECT Value of Item:

(Note: The Correct value must fit into the space allocated in the original question)

9. Comments:

10. Name of Person Providing Correction:

11. Date of Correction: \_\_\_/\_\_\_/19\_\_\_  
mo. da. yr.

### 9.9.1.3 Problem Resolution (items 8-11)

This section should be completed by the person providing the corrected value. This must be a member of the staff at the clinical center where the original data collection form was completed.

Item 8: If the current value is determined to be incorrect, enter the corrected value for the item.

If the current value is missing, enter the value if available from the subject chart. If the value is unavailable, enter the word "missing."

If the current value is confirmed to be correct, enter the word "correct."

Item 9: Enter explanation, justification, etc. if appropriate.

Item 10: Enter the name of the person responsible for resolving the question. This must be a member of the staff at the clinical center where the original data collection form was completed.

Item 11: Enter the date the Problem Resolution section of the form was completed.

### 9.9.1.4 Updating the original Form

After completing the Questionable Data Form, the investigator's copy of the original form page should be updated as appropriate. The investigator or their designate must initial and date all changes made to Forms.

### 9.9.1.5 Handling the Completed Questionable Data form

All three copies of the Questionable Data Form should be stored in the patient's file. The Case Coordinator will collect the first two copies of the form at the next visit. The third copy is retained permanently in the patient's ENRICHD file.

## 9.9.2 Completing the Computer Generated Questionable Log Report

The header section of the QLR form, and section 1 (Identification of Value to be Corrected) are generated from the records processed by the CSCC. The clinic staff member who determines the appropriate resolution (correction, confirmation, etc.) completes only Section 2 (Problem Resolution).

### 9.9.2.1 The Data Query Form Checklist

When the CSCC generates a set of QLRs from a batch of forms that have been processed and edited, a summary of the items flagged in question will be listed. This list contains the patient number, form, and item for each data QLR generated. There is also a check box for the person completing the QLR to use in tracing the completion of query logs. This checklist is for internal use by the Case Coordinator and clinical center and does not have to be returned to the CSCC.

## ENRICHD Questionable Log Report (QLR) Checklist

---

Patient Number	Form & Item#	Check Box
0101401	MHA 3	<input type="checkbox"/>
	BDI 6	<input type="checkbox"/>
0101502	PSS 3	<input type="checkbox"/>
	BDI 4	<input type="checkbox"/>
0101603	MEA 4	<input type="checkbox"/>
0101707	ESS 5	<input type="checkbox"/>
	BDI 6	<input type="checkbox"/>
0101809	BEA 3	<input type="checkbox"/>
	MHA 4	<input type="checkbox"/>

---

### 9.9.2.2 Form Header Information

The patient number of the patient whose data are in question and the date that the QLR was initiated are pre-entered.

### 9.9.2.3 Identifying Information (items 1-7)

This section of the form is generated from records processed by the CSCC in which a problem is detected with a data value on a form already collected from the investigator. The patient's file should be checked to confirm that a previous QDA or QLR has not already been generated for this problem. The original batch identification number is provided to assist the tracing of the data form in question.

Items 1-2: The form type and form date from the original data form containing the item being questioned.

Items 3-4: The item number and its current value to be investigated.

Item 5: A brief description of the problem.

### 9.9.2.4 Problem Resolution (items 6-9)

This section should be completed by the person providing the corrected value. This must be a member of the staff at the clinical center where the original data collection form was completed.

Item 6: If the current value is determined to be incorrect, enter the corrected value for the item.

If the current value is missing, enter the value if available from the patient's chart. If the value is unavailable, enter the word "missing."

If the current value is confirmed to be correct, enter the word "correct."

Item 7: Enter the name of the person responsible for resolving the question. This must be a member of the staff at the clinical center where the original data collection form was completed.

Item 8: Enter explanation, justification, etc. if appropriate.

Item 9: Leave blank, the CSCC will complete this item when the returned QLR is processed.



ENRICHD DMS                      Questionable Log Report                      Page 1

07/14/96                      All Records for Patient

**Section 1: Identification of Value to be Corrected**

1. Patient Number: 0200105      Form: BDI    Version: A    Visit: 01

2. Date of log: 07/16/96              FormSeq#: 00              Line#:000

3. Field: BDIA002

4. Value: 7

5. Description of Problem: Out of edit range

**Section 2: Problem Resolution**

6. Correct Value of Item: \_\_\_\_\_

7. Reviewer Initials: \_\_\_\_\_ Review Date: \_\_\_\_\_

8. Comments: \_\_\_\_\_  
\_\_\_\_\_

9. Data Entry Operator initials: \_\_\_\_\_ Date Corrected in DMS: \_\_\_\_\_

=====

**Section 1: Identification of Value to be Corrected**

1. Patient Number: 0201011      Form: MHA    Version: A    Visit: 01

2. Date of log: 07/16/96              FormSeq#: 00              Line#:000

3. Field: MHAA06D

4. Value: 60

5. Description of Problem: Out of edit range

**Section 2: Problem Resolution**

6. Correct Value of Item: \_\_\_\_\_

7. Reviewer Initials: \_\_\_\_\_ Review Date: \_\_\_\_\_

8. Comments: \_\_\_\_\_  
\_\_\_\_\_

9. Data Entry Operator initials: \_\_\_\_\_ Date Corrected in DMS: \_\_\_\_\_  
=====

**9.9.2.5 Updating the Original Form**

After completing the Questionable Data Form, the clinical center copy of the original data form should be updated as appropriate. The investigator or their designate must initial and date all changes made to data forms.

**9.9.2.6 Handling the Completed Data Query Form**

All three copies of the Questionable Data Form should be stored in the subject's file. The Case Coordinator will collect the first two copies of the form at the next data collection visit. The third copy is retained permanently in the patient's forms file.

**9.9.3 Transfer of Forms to the Case Coordinator**

**9.9.3.1 Collecting and Batching Completed QDA and QLR Forms**

The Case Coordinator will visit the clinical center at least twice monthly. During those visits, the case coordinator will review all the QDA and QLR forms that have been completed since the last clinic visit for completeness and correspondence to the patient's clinical record. The case coordinator will collect the original of each completed, reviewed form. The copy of each form will remain at the clinic in the case binders for at least two years after completion of the study. The set of forms collected from a clinic at a will be referred to as a "batch" of forms.

**9.9.3.2 The Query Inventory Sheet (QIS)**

The Questionable Data Forms (QDA) and the Questionable Log Reports (QLR) should be batched separately from the regular data forms. For each batch collected, the case coordinator should complete a QDA & QLR Query Inventory Sheet (QIS). The QIS is a form used to document the number of QDAs and QLRs in a batch. The QIS provides the clinic with a receipt for the queries already forwarded to the CSCC. It also an indirect record of the forms it sent to CSCC. Finally, it provides the CSCC with a valuable tool to trace queries in its filing and processing system.

**Section 1: BATCH IDENTIFICATION**

Item 1) Print the two-digit clinic code, listed in the Appendix.

Item 2) Print the name of the Case Coordinator who is collecting the copies of the forms.

Item 3) Fill in the month, day and year of the administrative visit at which the batch was collected.

Item 4) Print the name of the person at the clinical center who is giving the copies to the Case Coordinator.

## **Section 2: INVENTORY OF QDA AND QLR FORMS**

Item A) Fill in the number of QDA forms included in this batch.

Item B) Complete the page count of the QLRs included in the batch.

## **Section 3: BATCH PROCESSING HISTORY**

This area is to be used by CSCC. DO NOT complete this section; leave it blank.

### **9.9.3.3 Preparing the Batch**

The batch should always begin with its corresponding Query Inventory Sheet (QIS). At the clinic, the Case coordinator should place the original QIS on top of the original QDA and QLR forms, and place the first copy of the QIS on top of the corresponding first copies of QDA and QLRs. Do not staple forms together. The QDAs should be ordered by patient number. The QLRs should also be ordered by patient numbers as they appear on the batch inventory sheet (QIS).

Each batch of QDAs and QLRs and the corresponding covering QIS should be joined together by a paper clip, rubber band or placed in a manila envelope. No two batches should be joined together.

### **9.9.3.4 Disposition of Copies**

The original QIS will be mailed to the CSCC and the first copy will be retained by the Case Coordinator with the copies of corresponding forms. The second copy of the QIS should be filed in the clinical center for future reference.

**ENHANCING RECOVERY IN CORONARY HEART DISEASE  
(ENRICHD)  
QDA & QLR BATCH QUERY INVENTORY SHEET (QIS)**

**Section 1: Batch Identification**

The original copy of the following QDA and QLR forms are being transferred to the

Case Coordinator \_\_\_\_\_ on \_\_\_\_/\_\_\_\_/19\_\_\_\_  
(NAME) mo. da. yr.

by the Clinic representative \_\_\_\_\_  
(NAME)

**Section 2: Inventory of QDA and QLR Forms**

A. Questionable Data Forms (QDA) 

--	--	--	--	--	--	--	--

 Clinic page count CSCC page count

B. Questionable Logs (QLR) 

--	--	--	--	--	--	--	--

--	--	--	--	--	--	--	--

**Section 3: Batch Processing History (To Be Completed by CSCC):**

\_\_\_\_\_

CSCC Batch Number: \_\_\_\_\_

Date received at CSCC: \_\_\_\_/\_\_\_\_/19\_\_\_\_  
mo. da. yr.

Received by: \_\_\_\_\_

\_\_\_\_\_

## **9.9.4 Transfer of QDAs and QLRs to the CSCC**

### **9.9.4.1 Shipping the Batches**

The batches collected during case coordinator visits should be sent to the CSCC as soon as possible. Batches should be sent by an express package delivery service. More than one batch may be sent in one envelope. However, each batch should be separate from the other batches within the envelope. Shipments may include batches of data queries as well as Forms.

Each mailing should contain the following items together in one envelope: (1) The batches; (2) the corresponding QIS; and (3) any letters or notes about these batches.

All batch data mailings should be addressed to:

ENRICHD Central Receiving  
Collaborative Studies Coordinating Center  
University of North Carolina  
137 East Franklin Street, Suite 203  
Chapel Hill, North Carolina 27514-4145

### **9.9.4.2 Acknowledgment of Receipt of Batches**

Twice a month the CSCC will fax to the Case Coordinator an acknowledgment of batches received by the CSCC. This correspondence will contain identifying information for each batch received since the previous acknowledgment. If this acknowledgment is not received within 3 weeks of the shipment of a batch, the Case Coordinator should contact the CSCC to investigate why the query data transfer batch was not confirmed on time.

## **9.10 Problem Clarification Requests**

A Problem Clarification Request is used to document and resolve issues which are not related to specific data fields on the case report forms. For example, if duplicate forms are received, a Problem Clarification Request would be completed at the CSCC asking for verification of the correct form.

### **9.10.1 Completing the Problem Clarification Request**

The Case Coordinator should research the problem with the investigator or his/her designate, and print the response to the question in the section of the form labeled THE SOLUTION. Enter the date the problem was resolved and the name of the person who resolved the problem in the corresponding spaces.

### **9.10.2 Disposition of copies**

The original Request (top page) should be addressed to:

ENRICHD Central Receiving  
Collaborative Studies Coordinating Center  
University of North Carolina  
137 East Franklin Street, Suite 203  
Chapel Hill, North Carolina 27514-4145

The copy of the Problem Clarification Request should be maintained by the Case Coordinator.  
When applicable, a photocopy should be stored in the patient's forms binder.

**ENHANCING RECOVERY IN CORONARY HEART DISEASE  
(ENRICHD)**

**PROBLEM CLARIFICATION REQUEST**

TO:

-----

**THE PROBLEM:**

Date Detected: \_\_\_\_/\_\_\_\_/19 \_\_\_\_ Detected By: \_\_\_\_\_  
Mo Da Yr

Problem Location and Description:

-----

**THE SOLUTION:**

Date Resolved: \_\_\_\_/\_\_\_\_/19 \_\_\_\_ Resolved By: \_\_\_\_\_  
Mo Da Yr

Solution (Please print a response to the problem described above. Use the back of this paper, if necessary):

Please return the completed clarification request to:

ENRICHD Central Receiving  
Collaborative Studies Coordinating Center  
Suite 203, NCNB Plaza  
137 East Franklin Street  
Chapel Hill, NC 27514-414

**APPENDIX A.**

Table of Clinical Center Code Numbers

<u>Clinical Center</u>	<u>Code Number</u>
Duke University Medical Center	01
Rush- St. Luke's Medical Center	02
Stanford University	03
University of Alabama, Birmingham	04
University of Miami	05
University of Washington, Seattle	06
Washington University	07
Yale-Harvard	08



## **10. Chapter 10: Quality Control**

### **10.1 Overall Plan**

The overall functions of quality assurance are: training; supervision and monitoring of the intervention; establishing inter-rater reliability of the DISH measurement and standardization of other measurements; and monitoring of eligibility and enrollment criteria.

#### **10.1.1 The overall training plan involves:**

- Training of the therapists
- Training of the interviewers:
- Training in all data collection/data management protocols
- Training of the case managers

#### **10.1.2 The overall plan for supervision and monitoring of the intervention involves:**

- Adherence to treatment protocol: Treatment Manual; written checklist of clinician adherence to protocol
- Monitoring of performance: weekly site supervision; across-site supervision; audiotapes
- Process Variables to assess if mediating effects of the intervention are working

#### **10.1.3 The overall plan for standardization of the measurements involves:**

- A three month pilot study on all measurements for feasibility and respondent burden purposes
- Computer checklist of interviewers' adherence to data collection protocol
- Computer checklist of interviewers' adherence to data collection of eligibility criteria protocol
- Central Medical Endpoints Committee to review adherence to measurement of primary medical endpoints
- Central ECG Core Lab to review all electrocardiograms for "new onset" q waves
- Case manager monitoring data collection at each site and serving as a liaison to the Coordinating Center for the editing, updating, and transmission of study data.
- Weekly and then monthly conference calls of case managers across sites

#### **10.1.4 The overall plan for monitoring eligibility and enrollment criteria is:**

- Computer checklist of interviewer's adherence to eligibility criteria

- Quality Control data collected by the Coordinating Center to monitor and correct operational data collection
- Case manager monitoring of data collection at each site and serving as a liaison to the Coordinating Center for the editing, updating, and transmission of study data.
- Weekly and then monthly conference calls of case managers across sites

## 10.2 Training: Specific Staff Responsibilities

The following clinic functions/responsibilities have been identified in relation to training in the study protocol: therapists, case managers, and interviewers. Each is described below:

### 10.2.1 Training of the Therapists

The overall goal of training the therapists is to assure equal and adequate implementation of the Psychosocial Intervention across sites. The Psychosocial Intervention relies upon cognitive behavioral and social learning treatment approaches. Highlights of this approach include behavioral activation (including activation of the social network), active problem solving, attention to automatic thoughts, and appropriate skills training (e.g., communication skills) to support these efforts. In addition, the Intervention includes a focus on stress reduction skills, and enhanced coping ability and post MI adjustment/recovery. Initially, individual sessions serve as the basis for treatment. Transition to group-based treatment occurs as sufficient numbers of patients making progress in treatment are gathered at each site. Given this make-up of the Intervention, the training of therapists will be aimed at the use of the requisite cognitive behavioral and social learning strategies, as well as the conduct of individual and group-based sessions with these strategies, according to the description in Chapter 5 of the Protocol (Intervention chapter). In addition, all training will be in the context of maximal psychological and physiological adjustment and adaptation after acute myocardial infarction.

#### a. Qualifications of Therapists

The “gold standard” for delivery of the intervention is assured through the identification, training, and maintenance of qualified therapists. Personal and behavioral qualities of the therapists are discussed in Chapter 5 of the ENRICHD Protocol. Therapists may have either a doctoral or a master’s degree in a suitable discipline, and clinical experience in CBT, counseling, group therapy, and therapeutic strategies to enhance social support.

#### b. Training of the Therapists

Training of the therapists will be done in three different modes: training for cognitive/behavioral and social support therapy; training for group therapy; and intensive supervision for 12 weeks by audiotape.

**1. Training for Cognitive Behavioral and Social Support Therapy.** A group of 8 therapist

supervisors (one from each clinical site) as well as all other therapists convened at the Beck Institute in Philadelphia the week of August 24-28, 1996 for a five-day intensive workshop. The sessions taught by Dr. Aaron Beck, Dr. Judith S. Beck, and other faculty from the Beck Institute in partnership with selected investigators from the ENRICHD Clinical Trial, covered interventions for both depression and perceived low emotional support in acute myocardial infarction patients, with components specific to minority populations, low SES, and post-MI patients.

**2. Training for Group Therapy.** A group consisting of 8 therapist supervisors and one therapist from each site convened at the Beck Institute in Philadelphia the week of October 12-15, 1996 for a four-day intensive workshop on group therapy. The sessions were taught by investigators from the ENRICHD Clinical Trial in partnership with Drs. Aaron and Judith Beck. Refer to the ENRICHD Study Training Schedule, Week of October 12-15. The therapists who did not come for group therapy training in Philadelphia were taught through role-modeling in ongoing group therapy sessions at each site. This training deals with enrolled participants as cardiac patients, issues concerning clinical physiology, stress, and feelings. Training will be devoted to session-by-session explanation of the Manual of Operations for group therapy. Then the workshop participants are divided into three groups and, under the supervision of a Leader and Co-Leader, begin working through an open enrollment session including performing exercises. Refer to Table 2.

**3. Intensive Supervision for 12 Weeks by Audiotape.** As soon as patients enter treatment, each therapist is required to complete 12 weeks of supervised therapy with a suitable patient. Weekly tapes are sent to the Beck Institute by each therapist, followed by an hour of supervision for each therapist with their supervisor via telephone weekly. Thus there is one hour of tape listening and one hour of supervision per week. At the end of 12 weeks, Beck Institute advises which therapists are qualified for official study using a Cognitive Therapy Competency Scale implemented in other multi-site studies.

**4. Remedial Work or Training New Therapists.** For those therapists who, at any point in the three years, do not qualify for inclusion in the study, based on Beck Institute monitoring as outlined above, either a remedial course of intensive training or training a new candidate on an accelerated schedule may be required. Refer to the following process for authorization of additional funds for consultation from the Beck Institute.

**5. Authorization of Additional Funds for Consultation from Beck Institute.** The process for authorization of funds from the Coordinating Center for remedial work, training new therapists, or direct consultation time with Drs. Aaron and Judith Beck is as follows.

The contract between the ENRICHD Program and the Beck Institute provides for direct consultation time with Drs. Aaron and Judith Beck on an "as-needed" basis. Since the Becks will be reimbursed on an hourly basis, it is important to set down some rules about who has the authority to access their time, what is the scope of appropriate subject matter for these consultations, and monitoring and consultation expenses (for the total group and by site). The following guidelines are proposed to share access, use their consultation time to the best advantage, and simultaneously monitor accruing expenses.

1. The usual mechanism of contact between an ENRICHD site (i.e., the Psychotherapy Supervisor or Principal Investigator) will be the regularly scheduled conference call between Beck Institute staff and all the Psychotherapy Supervisors. The routine focus of this conference call includes: fundamental and applied questions about Cognitive Therapy, problems with particularly difficult cases, adjustments tailored to the situation of post-MI patients, and supervisory problems. By discussing patient-specific, therapist-specific, and site-specific problems in this format, we expect that all Psychotherapy Supervisors will share knowledge and concerns, thereby minimizing site-effect drift in therapy technique over time.
2. When a Psychotherapy Supervisor, Principal Investigator, or any other person designated by a Principal Investigator feels a need to discuss a problem with Drs. Aaron or Judith Beck--at greater length or in private, or when remedial supervision is required for a specific therapist--the Supervisor or PI should contact a member of the "Beck Institute Consultation Committee" and make a formal request for consultation time, specifying the following:
  - the reason for the consultation, including an explanation of why the matter cannot be pursued within the confines of the monthly conference call for Psychotherapy Supervisors;
  - the minimum and maximum number of hours of consultation time requested;
  - when the consultation is likely to take place; and
  - the person(s) participating in the consultation, who will be responsible for limiting the consultation to the approved period of time.
3. The ENRICHD Program's "Beck Institute Consultation Committee" will consist of three Psychotherapy Supervisors, Carl Thoresen (to facilitate integration between individual cognitive therapy and group therapy), and James Hosking (representing the Coordinating Center). This Committee of five will schedule conference calls on an as-needed basis to process all formal requests for consultation time with Drs. Aaron and Judith Beck in a timely manner.
4. The goals of the "Beck Institute Consultation Committee" are:
  - (a) To oversee and prudently manage the budget funds allocated for consultation time with Drs. Aaron and Judith Beck;
  - (b) To enable all sites to access a modest amount of direct consultation time with Drs. Aaron and Judith Beck on an equitable basis;
  - (c) To enable sites to arrange for remedial work for staff psychotherapists who begin to fail quality assurance monitoring;
  - (d) To enable sites to arrange for accelerated training for replacement psychotherapists recruited after the beginning of the study;

- (e) To assist Psychotherapy Supervisors with unique or particularly difficult supervision problems;
  - (f) Generally, to assign a priority level to all formal requests for consultation time with Drs. Aaron and Judith Beck--fulfilling important requests so long as funds are available, postponing or denying less urgent requests when funds are low.
5. The Committee will communicate its decisions directly to the applicant and the Beck Institute, so that Drs. Aaron and Judith Beck will have knowledge of the persons authorized to access ENRICHD Program consultation time and funds.
  6. Any person affiliated with the ENRICHD Program who accesses Drs. Aaron or Judith Beck for consultation without the prior approval of the Beck Institute Consultation Committee shall be personally responsible for that consultation expense.
  7. Any Principal Investigator who chooses to arrange for consultations with Drs. Aaron or Judith Beck with funds from outside the ENRICHD Program budget may do so--but that Principal Investigator should notify the Beck Institute Consultation Committee of his/her intentions and arrangements, so that the Committee can take these "outside" arrangements into account when allocating resources.

### **10.2.2 Training of the Interviewers/Data Collectors**

Initial training was conducted in June, 1996 for the pilot study and for those interviewers/case managers who will be responsible for training the rest of the interviewers at each site. The model was "train-the-trainer." The training was planned at this time in order to accommodate training for both the 3-month pilot study and the first year of the ENRICHD clinical trial. However, since most of the interviewers/case managers were hired close to study enrollment, the same training will be repeated in September for the Overall Trial.

Training for the pilot study took 2 days and included the following activities: overview of the study and study protocol; review of the eligibility criteria; specific instructions on interviewing for the DISH and the BLESSED; review of the Screening/Recruitment Visits; specific instructions on ascertaining the medical eligibility criteria from the charts; and data management procedures. In addition, data collection on all the psychological measurements were done: introduction to the laptop computer-based system with screen data entry and editing, edits, and data transmission. Role playing was used for training on the DISH. Videotapes were taken of the training and were sent to each site for training of interviewers/data collectors, which might have to be done if attrition of data collectors occurs during the study. The following agenda describes the contents of the ENRICHD Pilot Study Training Manual:

Introduction to ENRICHD Design and Goals

Overview of ENRICHD Pilot Study

Medical Eligibility Criteria

Screening Logs and Informed Consent

Medical Record Abstraction Training

DSM-IV Diagnosis of Depression & Hamilton Rating

General Principles of Interviewing

Interviewer Training for DISH and SBT

Social Isolation and Psychosocial Forms

Minority Recruitment

Data Management Procedures

a. Quality Assurance of Data Collectors/Interviewers

Upon successful completion of training, the data collectors/interviewers will be routinely evaluated for quality assurance. The quality of their data forms, timeliness, and completeness of work will be routinely assessed. Quality control forms will be gathered from the sites for regular quality control checks.

### **10.2.3 Training the Case Managers**

The case-manager (or case coordinator) will be responsible for initial contacts and education regarding risk factors of cardiovascular disease and recovery after myocardial infarction before randomization and for insuring attendance at follow-up exams for both the usual care and intervention participants. For the intervention participants only, the case manager will be responsible for assistance in their care and treatment during the course of treatment. The case-manager will facilitate attendance at sessions, give limited instrumental social support, facilitate medical treatment, and coordinate psychopharmacology (refer to Chapter 3 of the ENRICHD Protocol). In addition, depending upon the clinical site's specification, the case-manager might coordinate other interviewers/data collectors' activities regarding screening and enrollment and data collection of measurements. Duties and responsibilities of the case manager are discussed in Chapter 3, pages 15-17, of the ENRICHD Protocol.

a. Training of Case Managers

Case managers will be centrally trained in September in the overall Training for the Clinical Trial. The topics for training will include: screening, recruitment, and eligibility procedures and forms; medical record abstraction; a panel discussion by Case Coordinators on enrollment and adherence principles, minority recruitment, training for health education; psychosocial measurement procedures and forms; data management system features; follow-up and endpoints procedures and

forms; data management system utilities and practice session; randomization procedures and telephone randomization system; and data transfer procedures for paper forms. Refer to Training Manual for Clinical Trial. Training will be given over 3 days. Refer to Table 3 for the content of the Training for the Clinical Trial.

### **10.3 Supervision and Monitoring of the Intervention**

#### **10.3.1 Adherence to Treatment Protocol**

Adherence to treatment protocol will be accomplished by the development of a Treatment Operational Manual describing the goals of each session and a written checklist of clinician adherence to treatment protocol.

- a) Treatment Operational Manual: Refer to Intervention Chapter 5.
- b) Written Checklist of Clinician Adherence to Treatment Protocol, Required Forms, and Measures

Clinicians can monitor the integrity of their own performance daily within general prescribed techniques on an appropriate tracking form. This form will also ensure adherence to the protocol and standardization across sites. Protocol adherence will be developed for each session using the Treatment Operational Manual as the reference. The protocol will be monitored frequently by supervisory staff on an individual basis and the supervisory staff will provide feedback to the clinicians.

#### **10.3.2 Monitoring of Performance of Intervention**

Supervision of therapists is an important way to enhance treatment fidelity. Ongoing supervision and feedback is critical in ensuring that interventions are implemented in the manner intended. Supervision should include two components: (1) continuous monitoring of treatment implementation, and (2) provisions for corrective action (Sechrest et al., 1979). The literature suggests that careful supervision is key to the success of cognitive behavior therapy intervention trials. For example, the failure of the NIMH Treatment of Depression Collaborative Research Program to demonstrate that cognitive behavior therapy was superior to a control condition has been attributed to lax supervision. While therapists in that trial received intensive training and supervision during the pilot phase of the study, the supervision and monitoring of therapists during the trial was minimal. During that trial, therapists participated in monthly consultation calls, occasional group calls, and additional calls if videotape monitoring revealed significant departures from the protocol. In contrast, other controlled trials which have incorporated at least weekly supervision have demonstrated the efficacy of cognitive behavioral therapy (Hollon, 1992; Rush, 1977). This underscores the importance of continuous supervision of therapists in addition to training (Shaw & Pilkonis, personal communications, 1996).

Since the ENRICHD trial is an efficacy trial, supervision of therapists has a high priority. In an efficacy trial one is interested in testing the intervention(s) under ideal circumstances, which includes well trained therapists who deliver the treatment as planned and in a competent manner. To ensure this optimal implementation, ongoing supervision and feedback is important.

a. **Local Clinical Supervision of Therapists.** There are four goals for local clinical supervision of at therapists at the eight ENRICHD centers. They are as follows:

1. To ensure that the intervention protocols as specified by the manual of operations are implemented and to provide corrective feedback to therapists.
2. To supervise the clinical work of the therapists to ensure quality care of patients.
3. To monitor the needs of patients.
4. To make decisions regarding treatment planning with respect to: a) implementation of modules; b) aspects of the intervention to emphasize; c) transition to group; and d) referral to pharmacotherapy.

In order to conduct a responsible trial, it is recommended that the supervision protocol outlined below is implemented.

#### Individual and Group/Case Conference Supervision

Individual and group/case conference supervision are strongly recommended. Individual supervision offers an opportunity to focus on particular therapists' cases. The group/case conference supervision could provide a forum for therapists to benefit from each others' work, to capitalize on opportunities for consultation and collaboration, to receive additional didactic training, and to benefit from the support of the other therapists and supervisor. The supervisor has the discretion to determine the balance between individual and group.

#### Frequency of Contacts

Weekly supervision is essential throughout the trial. Two hours of direct supervision per week per therapist is the minimum. The two-hour weekly supervision can be done individually or with a group of therapists. The supervisor will have the discretion to increase the amount of supervision as needed for particular therapists. This is particularly likely in the case of inexperienced therapists or for therapists with difficult patients. In addition, therapists should be encouraged to seek supervision on an as-needed basis.

#### Supervision Format

In order to ensure that the procedures are appropriate for the patients and to avoid therapist drift, it is essential that supervisors make direct observations of therapist work. This can be accomplished by a variety of procedures including reviewing audiotapes of the sessions. It is recommended that one tape per therapist per week be reviewed by the supervisor, with that review serving as the basis for supervision sessions. In addition, as the trial progresses and therapists demonstrate competency with the Intervention, the therapists at the site may meet together without the site supervisor and review their tapes, collecting comments and feedback. These comments and feedback could then be utilized in group supervision with



the site supervisor, thereby providing a more time cost-effective method of supervision.

Prior to supervision, it is important for therapists to review their own tapes and to be prepared to bring up points/issues about their sessions with the supervisor.

### Supervisory Log

Documentation of supervision will be accomplished with the use of a supervisory log. The log involves having the therapist indicate the date of the contact, the duration of supervision, the therapist(s), and a general comment about type of supervision (e.g., individual supervision for 6 individual cases).

### Progress Note

A brief progress note is recommended for each session contact. The following information is to be obtained: a) date, b) assessment of compliance, c) general impression of patient, and d) issues to be followed up next session.

### Therapist and Supervisor Networks

Separate trial-wide email networks are recommended for therapists and for supervisors. This will provide an opportunity to share information and to benefit from consultation across the trial. In addition, supervisors will participate in conference calls once a week for the first 6 months; twice a week for the second 6 months; and then monthly for years 3 and 4. These conference calls will be done in conjunction with the Beck Institute. In addition, during years 3 and 4, there will be additional monthly phone calls among the ENRICHD investigators without the Beck Institute. The conference calls are intended to provide a context to discuss issues related to supervision and implementation of the intervention.

**b. Across-Site Monitoring of Therapists' Individual and Group Sessions.** Audiotapes will be done on all patients. Audiotapes will help to ensure integrity and specificity of the treatment (i.e., clinician is treating the problem specified by the patient) and to also discriminate between strong and weak treatments. **About 20% of the tapes will be randomly selected at each site for review by the Beck Institute.** The tapes will be used both for within-site and across-site review of the therapy. Beck Institute will monitor integrity of the therapy by all therapists by randomly selecting 20% of the patients at each site, then randomly selecting two individual session tapes for each patient (a beginning session and a mid-to-late session of individual therapy) and two tapes per group during group therapy for Years 1, 2, and 3. Therapist difficulties will be brought up in supervisors' phone supervision sessions, or sooner, if needed. If difficulties persist, Beck Institute will undertake remedial work with errant therapists, if required, and will establish a time limit for remedying cognitive therapy practice. Therapists who are unable to improve by the deadline will be discussed as possibly needing replacement.

**c. Supervising Individual and Group Supervisors.** Beginning October 1996, supervisors will convene weekly for the first six months through 90-minute telephone conferences to discuss

supervision issues. A Beck Institute supervisor will be moderator for the group. At the seventh month, conferences will occur bi-weekly. Conference calls will continue for the duration of the study (i.e., Years 2, 3, and 4) on a monthly basis following the first year (or less if deemed appropriate).

### 10.3.3 Process Variables

#### a. Definition of Process Variable

Process measures refer to those psychosocial measures that will help explain the mechanisms of action of the various treatments or help us understand why some subjects show a better response to treatment than others. They will be analyzed to determine, for example, factors that clarify the mechanisms by which the treatment has an effect on the outcome variables, that reveal the time course of improvement, and/or indicate that the treatment had some integrity. They may be used for both clinical and research purposes. Some will be used for only quality assurance, to indicate that the intervention was delivered in the manner planned.

#### b. Process Measures

Key clinical forms and measures to be employed in the Cognitive Therapy for Depression (CT) individual intervention were reviewed and were classified into three groups:

- “Process measure” -- routinely administered for all patients, and coded on a summary sheet to be submitted to the Coordinating Center
- “Routine clinical tools” -- routinely administered for all patients. Any difficulties completing these forms as recommended should be at the discretion of the site supervisor
- “Optional clinical tools” -- therapists are encouraged to use these forms and measures, but the therapist’s own judgment is sufficient for deciding whether to use or skip these forms

#### Process Measures for Cognitive Behavioral Therapy

Hamilton Depression Scale (17-item SIGH-D)	Therapist	Therapist repeats HAM-D at session 0 if intake HAM-D was done two or more weeks ago
Beck Depression Inventory (21-item version)	Patient	Weekly before sessions

#### **Process Measures for Cognitive Behavioral Therapy, cont.**

Individual Therapy Homework Form  (Matt & Pat are developing)	Therapist	Weekly
Automatic Thoughts Questionnaire  (Kendall & Hollon, p.1980)	Patient	Session 0 and Session #6, at end of sessions
Case summary Worksheet  (J. Beck, p.315-318)	Therapist	One at initial evaluation and one at conclusion of individual therapy
Required Forms and Measures  (David Clark)	Therapist	

**Routine Clinical Measures**

Therapy Notes  (J. Beck, p. 61)	Therapist	Weekly
Therapy Report Form  (J. Beck, p. 42)	Patient	Weekly
Dysfunctional Thoughts Record  (J. Beck, p. 126)		Weekly Initially by therapist, gradually by patient

**Optional Clinical Measures**

Activity Chart  (J. Beck, p. 202)	Patient	Weekly
Activity Ratings  (J. Beck, p. 203)	Patient	Weekly
AT Adaptive Response Card	Patient	Ad lib

(J. Beck, p. 113)		
Coping Cards	Patient	Ad lib
(J. Beck, p. 215-216)		
Session Bridging Worksheet	Patient	Weekly
(J. Beck, p. 49)		
Dysfunctional Attitudes Scale	Patient	Session 0 and Session #6, at end of session
(Burns, p. 241-249)		
Emotion Chart	Patient	Ad lib
(J. Beck, p. 99)		
Emotional Intensity Scale	Patient	Ad lib
(J. Beck, p. 101-102)		
Automatic Thoughts Worksheet	Patient	Ad lib
(J. Beck, p. 119)		
Beliefs Worksheet	Patient	Ad lib
(J. Beck, p. 151-152)		

**Optional Clinical Measures, cont.**

Problem-Solving Worksheet	Patient	Ad lib
(J. Beck, p. 195)		
Homework Schedule Cards	Patient	Ad lib
(J. Beck, p. 263)		
Reason for Not Doing Self-Help Assignments	Patient	Ad lib
(A. Beck, et al., p. 408)		

**Process Measures for Low Perceived Social Support**

Activity Chart  (J. Beck, p. 202)	Patient	Weekly
Activity Ratings  (J. Beck, p. 203 - modified to rate “degree of support” and “degree of satisfaction”)	Patient	Weekly
Duke Social Support Questionnaire  (to be provided)	Patient	Session 0 and six-month evaluation point
McLeod Interpersonal Conflict Scale  (to be provided)	Patient	Session 0 and six-month evaluation point
Individual Therapy Homework Form  (Matt & Pat are developing Oct 1st)	Therapist	Weekly

**Routine Clinical Measures**

Social Network in Adult Life assessment and diagram	Therapist	Session 0 and end of individual therapy
People in my life	Patient	Session 0 and end of individual therapy

**Optional Clinical Measures**

Network improvement form  
  
Help from people in your social network

Belief barriers to social support

Non verbal communication

Problem solving

Key clinical forms and measures to be employed in the Pharmacotherapy individual intervention were reviewed and two groups were defined:

- “Process measure” -- routinely administered for all patients, and coded on a summary sheet to be submitted to the Coordinating Center immediately at the conclusion of the individual therapy
- “Routine clinical tools” -- routinely administered for all patients. Any difficulties completing these forms should be discussed with the Site Supervisor.

### **Process Measures for Pharmacotherapy**

- Medication dose and frequency over time
- Frequency and duration of all contacts with pharmacotherapist or clinical manager
- Measures of functional impairment -- self-report and clinician-rated

### **Routine Clinical Measures**

- Concurrent medications

### **Process Measures for Group Therapy**

- Degree of active participation in group therapy sessions
- Group size, recorded weekly
- Group therapy homework form, recorded weekly
- Post-therapy evaluation questionnaire
- Self-efficacy in group form (4 items), recorded weekly
- Activity logs, recorded weekly

### **Process Measures for All Three Therapies (i.e. Non-Specific Measures)**

- Treatment Expectations Form (by patient at Session 0 and six-month evaluation point) (form already developed by Process Measures Subcommittee; see CT for Depression)

MOO Appendix)

- Patient Satisfaction Form (session 0 and 6 months)
- Self-efficacy scale (by patient at session 0, end of individual, and end of group therapy)
- Quality of patient-therapist relationship (by patient; one-time rating)
- Compliance with homework in all therapy conditions
- Attendance at all individual and group sessions

### **Process Measures for Follow-up Phone Calls**

- Beck Depression Inventory (monthly)
- Activity Chart and Ratings (monthly)

## **10.4 Standardization of Measurements**

### **10.4.1 Monitoring of the Interviewers/Data Collectors**

The work of the interviewers/data collectors will be monitored through the completeness and timeliness of data transmissions to the Coordinating Center. Depending on the volume of activity of a clinical site, forms of adherence to data collection protocol and adherence to data collection of eligibility protocol will be checked by the interviewers/data collectors, computerized, verified, and transmitted weekly or every two weeks on a regular schedule. The responsibilities of the interviewers/data collectors include:

- 1) Collecting data on all the primary endpoint measurements
- 2) Monitoring data quality control by submitting computer checklist of adherence to data collection protocol and eligibility protocol
- 3) Serving as a liaison to the Data Coordinating Center for the editing, updating, and transmission of study data
- 4) Running computerized patient and study status reports

Refer to Chapter in Manual of Operations on Responsibilities of Coordinating Center.

### **10.4.2 Central Medical Endpoints Committee**

The responsibility of this committee is to validate the evidence of the primary endpoints of mortality and recurrent myocardial infarction and other medical endpoints according to criteria. The committee will be composed of cardiologists, one member from each site. Refer to the Chapter in Manual of Operations on Medical Endpoints Data Collection and Review Procedures.

### 10.4.3 Electrocardiology

Electrocardiograms will be collected for two purposes: validation of the medical eligibility criteria and to identify new-onset q waves as a criterion for detection of recurrent myocardial infarction, one of the primary endpoints.

#### a. Quality Assurance of the Index ECG

Quality assurance of the ECG component in large hospitals that recruit significant numbers of patients will be very little problem. It will likely be easy to obtain all the eligibility ECGs in those individuals. There is significant pressure to reduce the enzyme criterion to levels where false-positives are common, and if this is the case and there is no scrutiny of ECGs, the ENRICHD trial could have major difficulties. **Therefore, the recommendation is for the cardiologist at the local ENRICHD sites read 100% of the index ECGs for the first six months of Year 2. They will track inter-rater reliability between their diagnosis and that of the hospital reader. The QA Committee will evaluate the inter-rater reliability across all 8 sites and at that time recommend that a certain percentage will be randomly selected from each site for overreading. The QA Committee recommends that the Eligibility Committee define the ECG criterion for myocardial infarction to be used across sites.**

#### b. Core ECG Laboratory

The responsibility of this laboratory is to read all the electrocardiograms from all sites of the ENRICHD clinical trial, specifically for the purposes of identifying new-onset q waves. Electrocardiograms will be taken at baseline, 6-month follow-up, and 18-month follow-up for the length of study. The Core Lab will be directed by a cardiologist and cardiology fellows trained to performance criteria and reproducibility in q-wave criteria and detection. Refer to the Manual of Operations for description of the Core ECG Laboratory.

### 10.4.4 Inter-Rater Reliability of the DISH

#### a. Initial Reliability Assessments

Reliability of diagnosis of major and minor depression is an important issue for eligibility. Once interviewers have been trained, an initial assessment period will be needed to ensure proper diagnostic use of the DISH interview. During the first three months of enrollment, 10 percent of all interviews conducted will be double rated by the interviewer and a designated individual at the clinical site. This individual may be the case manager (if properly trained) or the therapist supervisor. Rating by this individual may occur in person or by use of videotape; audiotapes are not sensitive to nonverbal cues and hence are not acceptable for reliability purposes. Based on an anticipated 30 interviews by each interviewer during these months, 3 interviews will be available for rating at the end of 6 months. Interviews of individuals enrolled and not enrolled into the trial will be equally important. Ratings will be judged by overall ratings (no depression, minor depression, major depression) rather than item by item. Rating sheets will be sent to the Coordinating Center for calculation of kappa statistics. An inter-rater reliability of 0.7 (kappa statistic) is the minimum



acceptable reliability for each interviewer; lower reliability will necessitate additional training and/or a change in personnel. Similar procedures will be used for new interviewers throughout the ENRICHD trial.

b. Ongoing Reliability Assessments

After the initial three-month period, 5 percent of all interviews will be double rated as described above, to ensure continuing quality control and to prevent drift in diagnostic criteria. Based on anticipated numbers of interviews, one interview per month per rater would be needed to reach this goal.



# 11. Psychopharmacological Intervention

## 11.1 Goals of Psychopharmacology

The goal of psychopharmacology is to ensure that patients with more severe forms of depression and those who fail to benefit adequately from the ENRICHD CBT/Group intervention are provided the full range of therapeutic options for depression. Although it is important to optimize patients' opportunity to achieve full resolution of depression, it is essential to safeguard the intent of ENRICHD to examine the effectiveness of psychosocial interventions in post-MI depression and social isolation. Thus, there is an incentive to impose a relatively high threshold for instituting psychopharmacology at the time of intake and randomization. Simultaneously, the need to ensure rapid remission of depression, to mitigate the presumed post-MI risks, argues for a low threshold for considering psychopharmacology if the response to CBT/Group is inadequate.

For these reasons, the criterion adopted for considering psychopharmacology at intake represents severe depression (Hamilton Depression Scale score  $\geq 24$ ), which the clinical literature suggests may require either pharmacotherapy or a combination of psychotherapy and drug therapy for an optimal treatment response (AHCPR Clinical Practice Guidelines: Treatment for Major Depression, 1993). Employing this rather strict criterion, however, will ensure that the majority of ENRICHD patients will be provided an opportunity to benefit from the CBT/Group intervention alone.

Some depressed patients may not achieve an adequate response to CBT. As noted in the Individual Cognitive Behavior Therapy section of the Manual of Operations, patients with major depression who have not achieved at least a 50% reduction in BDI scores by the 6th week of CBT treatment will be referred to the study psychiatrist for consideration of antidepressant therapy. Treating psychotherapists should also consider referring patients for a psychopharmacology assessment at any time during treatment if, in their clinical judgment, the patient is not responding adequately to CBT.

Finally, socially isolated patients or depressed patients who are undergoing or have completed the CBT/Group intervention may develop major depression during the course of the intervention period and should be referred for psychopharmacology evaluation if moderately severe depression (HDS  $\geq 20$ ) is present or if the response to "refresher" CBT is deemed inadequate.

## 11.2 Eligibility for Psychopharmacology

Candidates for antidepressant treatment will:

1. Fulfill DSM-IV criteria for Major Depression

**and**

2. Score  $\geq$  24 on the **baseline** 17-item Hamilton Depression Scale rating

**or**

Have an inadequate response to individual CBT, i.e.,  $<$  50% reduction in BDI ratings after 5 weeks of therapy; be judged to have an inadequate response to CBT during "refresher" sessions following depression relapse

**or**

Score  $\geq$  20 on the 17-item Hamilton Depression Scale during the 12 month period after enrollment completing the CBT/Group therapy intervention

Candidates for antidepressant therapy will be referred to community providers for depression management rather than receive treatment by the ENRICHD psychiatrist if they fulfill any of the following criteria:

1. DSM-IV Major Depression with Psychosis
2. Judged to be a serious suicide risk (see MOO Depression Intervention)
3. Severe major depression requiring electroconvulsive therapy
4. Active alcohol or substance abuse
5. History of sensitivity to sertraline or other newer generation antidepressants.
6. Medical condition judged to be a contraindication to SSRI treatment (e.g., liver failure, drug-drug interactions)
7. Patient or primary physician/cardiologist unwillingness to accept pharmacological treatment

### 11.3 Evaluation of Patients who are taking Psychopharmacological Medications at the time of Enrollment.

The ENRICHD psychiatrist at each site needs to review the safety and apparent efficacy of any antidepressants used in patients on antidepressants at the time of enrollment. The review will occur through discussion of the case with the case-coordinator (or other individuals involved in the patient's assessment) and should occur within three weeks of enrollment.

1. Safety. The safety of the medication will be considered from a statement of potential harmful effects of the medication as used in patients with cardiovascular disease and interactions with other medications the patient may be taking. A decision to intervene with the treating physician will be based on the discretion of the local ENRICHD psychiatrist.
2. Efficacy. The efficacy of antidepressants the patient may be taking at the time of enrollment will be considered in terms of medication type, dose, length, and the patient's response. The decision to intervene (e.g., to call the local psychiatrist or other physician treating the patient) will be left with the local ENRICHD psychiatrist.

The ENRICHD psychiatrist should review the status of patients on medications at entry 3 and 6 months and more often as indicated.

### 11.4 Psychopharmacology Evaluation and Treatment Protocol

Patients will be referred to ENRICHD psychiatrists for evaluation and possible antidepressant treatment (with the exceptions noted above). Study psychiatrists will employ a standard history and diagnostic assessment to confirm the presence of the psychopharmacology eligibility criteria and will determine by appropriate physical examination or laboratory findings that depression symptoms are not attributable to underlying medical or metabolic conditions (e.g., hypothyroidism, electrolyte disturbances).

Informed consent for antidepressant treatment will be obtained.

Concurrence for initiating antidepressant treatment will be obtained from the patient's primary physician/cardiologist.

## 11.5 Sertraline Administration

Sertraline will be prescribed as the initial antidepressant for qualified patients. This agent was selected because it offers a preferred profile for safety and effectiveness in the treatment of major depression in the context of cardiovascular disease (Glassman et al, 1993; Preskorn et al, 1992; Preskorn et al, 1994; Preskorn et al, 1995; Ketter et al, 1995; Nemeroff et al, 1996). Patients with a history of sensitivity to or a prior lack of response to sertraline will be prescribed an alternative agent, according to the guiding principles described below.

Sertraline will be provided without charge, packaged in bottles of 30 scored tablets.

Patients will be evaluated weekly as needed and feasible for the first 3-5 weeks of treatment; thereafter, patients will be assessed at 2-4 week intervals as needed and as feasible.

The starting dose of sertraline will be 50 mg per day, given in the morning with meals. This dose will be maintained for at least 2 weeks. In the absence of dose-limiting adverse effects, the dose may be increased to 100 mg per day for 2 weeks and further increases, if necessary, to a maximum daily dose of 200 mg per day are permitted. In frail patients, sertraline treatment can be initiated at 25 mg per day for the first week, increasing the dose to 50 mg after one week as described above. Doses may be decreased at any time if necessary due to adverse effects. In the absence of an adequate therapeutic response, patients unable to tolerate 25 mg per day or unable to tolerate an increase to a higher dose after 4 weeks of therapy will be considered for alternative antidepressant treatment (see below).

Sertraline treatment will be maintained throughout the 12 month intervention period for patients who achieve a therapeutic response.

ENRICHD psychiatrists will monitor concomitant drug administration to identify possible drug incompatibilities, e.g., coumadin, terfenadine, and will alert the primary physician/cardiologist to the need to monitor anticoagulation status for patients receiving coumadin. The potential for drug-drug interactions is high in ENRICHD patients, who will likely be prescribed an array of cardiovascular agents. It is important that ENRICHD psychiatrists keep abreast of the rapidly evolving literature indicating that antidepressants possess potent, but variable, influences on the hepatic P450 isoenzyme systems determining the metabolic fate of many cardiac drugs (Preskorn et al, 1994; Preskorn et al, 1995; Ketter et al, 1995; Nemeroff et al, 1996).

Short-acting benzodiazepine hypnotics or anxiolytics (oxazepam, lorazepam, temazepam) or chloral hydrate will be permitted for short term use (3 - 14 days) when sleep or anxiety are causing significant distress or interfering with function. The amount and dose will be carefully recorded.

## 11.6 Alternative Antidepressant Treatment

Patients with a history of sensitivity to or a prior inadequate response to sertraline, those unable to tolerate sertraline due to emergent adverse effects, and those who fail to achieve an adequate response during the ENRICHD trial will be considered for alternative antidepressant treatment.

The selection of an alternative agent will be made at the discretion of the treating psychiatrist based upon the specific needs of each patient. Selection will be limited to the agents listed in Table 1 after

considering the potential advantages and disadvantages for each agent. Starting and maximum doses for each agent are provided in Table 2.

Starting doses will be maintained for at least 2 weeks. Smaller starting doses than those recommended in Table 2 may be employed for selected patients, if needed. In the absence of dose-limiting adverse effects, doses may be gradually increased over 2-4 weeks to the maximum recommended dose levels. Doses may be decreased at any time if necessary due to adverse effects. In the absence of an adequate therapeutic response, patients unable to tolerate the recommended starting dose or unable to tolerate an increase to a higher dose after 4 weeks of therapy will be referred to community providers for further management of their depression.

Alternative antidepressant medications will be prescribed at the patients' expense. Medication will be dispensed in the minimum quantity necessary to provide coverage for the interval between follow-up visits.

## **11.7 Psychopharmacology Maintenance and Termination**

The frequency of periodic follow-up assessments during the course of psychopharmacology will be determined at the discretion of the treating psychiatrist, with a minimum of at least monthly visits during the maintenance phase of psychopharmacology is maintained.

Patients who achieve a therapeutic response to antidepressant treatment will be maintained on medication for 12 months, at which time antidepressant therapy can be withdrawn. Patients who require extended psychopharmacology will be referred for further treatment in the community.

Rarely during the 12 month intervention period, patients might develop psychosis, be judged at risk for suicide, require hospitalization or otherwise require more intensive intervention than can be effectively provided by ENRICHD psychiatrists. Such patients will be referred for appropriate ongoing care in the community.

## **11.8 REFERENCES**

- Depression Guideline Panel: Depression In Primary Care. Vols. 1 and 2. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service; 1993. Agency for Health Care Policy and Research Publication Nos. 93-0050 and 93-0051.
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- Nemeroff, C.B., et al: Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 1996; 153:311-320.

Preskorn, S.H., et al.: Somatic therapy for major depressive disorder: selection of an antidepressant. *J Clin Psychiatry* 53:9 (suppl): 5, 1992.

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Preskorn, S.H., et al: Advances in the psychopharmacology of depressive disorders. In, Principles and Practice of Pharmacotherapy, Janicak, P.G., et al. (Ed.), Williams & Wilkins, 1995; Vol. 1 (2), pp. 1-24.



TABLE 1

Agent*	Reported Advantages	Potential Disadvantages
Sertraline (Zoloft)	Intermediate half-life - once/daily dosing Linear kinetics Minimal age effects on clearance Non-anticholinergic No sign. effect on cardiac conduction, BP	Moderate effects on P-450 2D6 hepatic isoenzyme -- drug interaction risk
Paroxetine (Paxil)	Intermediate half-life - once/daily dosing Fewer GI adverse effects reported No sign. effect on cardiac conduction, BP	Anticholinergic Non-linear kinetics Age effects on clearance Potent effects on P-450 2D6 -- drug interaction risk
Venlafaxine (Effexor)	Minimal effects on hepatic P-450 system	Short-half life (twice/day dosing required) Hypertensive in older patients in higher doses Prominent nausea Modestly increases serum cholesterol
Nefazodone (Serzone)	Sedating Non-anticholinergic No sign. effect on cardiac conduction Infrequent sexual dysfunction	Short-half life (twice/day dosing required) Non-linear kinetics Potent effects on P-450 3A3/4 -- drug interaction risk Mildly hypotensive
Bupropion (Wellbutrin)	Non-anticholinergic No sign. effects on cardiac conduction, EF, BP Infrequent sexual dysfunction	Short-half life (twice/day dosing required) Risk of seizures, especially at higher doses Restlessness can occur
Nortriptyline (Pamelor)	Established efficacy in severe depression Defined optimal plasma concentrations (50-150 ng/ml)	Anticholinergic Orthostatic hypotension <b>Contraindicated in presence of cardiac conduction delay</b>

\* Fluoxetine (Prozac) excluded due to its prolonged elimination half-life

**TABLE 2**

<b>Agent</b>	<b>Starting Dose mg/day</b>	<b>Maximum Dose mg/day</b>
Nortriptyline (Pamelor)	25	100
Sertraline (Zoloft)	50	200
Paroxetine (Paxil)	10	50
Venlafaxine (Effexor)	75	225
Nefazodone (Serzone)	50	600
Bupropion (Wellbutrin)	75	450

### **ENRICHD Final Follow-up Visits**

The ENRICHD protocol currently specifies that all patients are to be followed for hospitalizations and mortality until a common termination date, 18 months after the last patient was randomized. Randomization ended October 31, 1999, which makes the 18 month period end April 30, 2001. The protocol specifies that “Clinical centers will be given a short window (e.g., two weeks) just before the follow-up termination date, within which to contact each of their participants to screen for any potential endpoints since the last contact.” For the following reasons, the original procedures for a final visit were modified. First, given the large fraction of participants who are difficult to contact by phone, some of the clinical centers anticipate serious difficulty in increasing staffing to handle this short-term increase in activity. Second, this approach will generate a bolus of hospitalizations to be documented right at the end of the study. Finally, this plan will mean that the last follow-up ECG for some participants will be as much as 12 months before the end of follow-up.

During the last 6 months of follow-up (November, 2000 – April 2001) the following modification to the closeout procedures will go into effect:

- 1) During the period November 1, 2000 – April 30, 2001, phone contacts are replaced by clinic visits.
- 2) Follow-up for each participant is terminated at their last visit during that interval.
- 3) Documentation of all hospitalizations will be completed by July 31, 2001.

The closeout visit is identical to the annual ENRICHD visit. Data collection consists of the BDI and ESSI forms, a 12-lead ECG, the Follow-up exam form (FUX) and Spirituality Experiences Scale (SES). The participant tracking form completed at baseline (TRK) should be updated to capture current locator information. Consent for future follow-up and access to the patient medical records should be obtained. Following the visit, hospitalizations identified during the interview will be documented in the usual way (submission of NOE, HOS and/or DCT forms with end points case materials).

There are three significant advantages to this approach: it spreads the closeout workload (both patient contacts and documentation of hospitalizations) over a six month interval; it allows an ECG at the end of follow-up for each participant, and it provides an opportunity to obtain consent for future contact.

The closeout visit procedures require all participants to have a clinic visit during the last 6 months of the ENRICHD trial rather than phone contacts. At this visit, all patients other than “hard refusals” should be contacted and encouraged to allow a final examination. Stress the value to the study of complete follow-up on all participants. Specifically, those who have been on telephone follow-up only should be asked for a final exam. The Coordinating Center will be requesting information on patients currently lost to follow-up to initiate “skip-tracing” procedures.

## ENRICHD PSYCHOSOCIAL DATA COLLECTION SCHEDULE

Psychosocial Measures Form	Form Mnemonic	Baseline	3 mo	6 mo	9 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo
ENRICHD Social Support Instrument	ESSI	All		All		All	All		All		All		All
Beck Depression Inventory	BDI	All		All		All	All		All		All		All
Depression Interview and Structured Hamilton	DISH	All		All									
Longitudinal Course Chart	LCC					All							
Perceived Social Support Scale	PSSS	All		All									
Health Quality of Life	HQL			800									
Ladder of Life	LOL			800									
Life Satisfaction Scale	LSS			800									
Social Network Questionnaire	SNQ	800		800									
Perceived Stress Scale	PSS	400		400									
Self-efficacy Scale	SEM	400		400									
Interpersonal Support Evaluation List	ISEL	400		400									
Telephone contact: identification of potential events, contact information update	TCF		All		All			All		All		All	

**Legend:** All = All randomized patients

400/800 = First 400/800 patients randomized



## ENRICHD Medical Measures Data Collection

Name of Form	Form Mnemonic	Time Point	Visit Number
Tracking	TRK	Screening	01
CAGE	CAG	Screening	01
Medical Eligibility	MEA	Screening	01
Medical History	MHA	Baseline	02
Baseline Examination (with ECG)	BEA	Baseline	02
Randomization Worksheet	RAN	Baseline	02
Telephone Contact	TCF	Follow-up	3,5
Follow up Examination (with ECG) 6,18, 30, 42 & 54 mo	FUX	Follow-up	4, 7, 9, 10,13
ECG 6,18, 30, 42 & 54 mo	ECG	Follow-up	4, 7, 9, 10,13
Notification of Event	NOE	Follow-up	per event
Hospitalization and Secondary Events	HOS	Follow-up	per event
Death Certificate	DCT	Follow-up	per event

### Follow-up Visit Collection Schedule

Month: 3    6    9    12    18    24    30    36    42    48    54  
 Visit #: 03    04    05    06    07    08    09    10    11    12    13

### Clinic Visit Post Randomization

Month: 6    19    30    42    54  
 Visit #: 04    07    09    10    13

### Phone Contacts Post-Randomization

Month: 3    9    12    24    36    48  
 Visit #: 03    05    06    08    10    12

## ENRICHD Intervention Quality Control Sampling Plan

### A. Individual Therapy

Each calendar year (July 1 - June 30) for each therapist, the Beck Institute will review tapes of two individual therapy sessions with each of four randomly selected patients. For each patient, one tape will be randomly selected from session 1-3, and one from the last 4 sessions. Therapists will not be told that a patient has been selected while therapy is ongoing for that patient. This will be implemented through the following procedure:

1. Each June, the clinical centers will send a list of ENRICHD therapists to the Coordinating Center.
2. The Coordinating Center will retrospectively randomly select two sessions within individual therapy for each therapist. For each selected participant, the Coordinating Center will randomly select one of sessions 1-3 and one of the last 4 sessions.
3. The Coordinating Center will notify a designated staff member at the clinical center (by email) that the qualifying patient for that therapist should have tapes sent to the Beck Institute for monitoring. The sessions for which tapes are to be sent will also be specified. The PI of each center will identify the individual to be responsible for identifying the patients and shipping the selected tapes. The person should not be therapist, and should not be a blinded outcome assessor.
4. The designated staff member will mail the selected tapes to the Beck Institute as soon as it is available. None of the Intervention staff should be aware that a tape has been selected. The Case-Coordinator will notify the Coordinating Center (by email) of the ID of the selected patient and the date the tape was mailed to the Beck Institute and the session numbers.
5. The Beck Institute will evaluate the internal consistency of the delivery therapy and rate the therapist by the Cognitive Therapy Competency Scale (Table 3).

To improve communications among the clinical site, coordinating center and the Beck Institute, monitoring of the quality assurance individual and group session intervention tapes at the Beck Institute will continue with the following administrative procedures:

- a) To increase the quality of the feedback received on the monitored tapes, the Beck Institute will email suggestions to the therapist supervisor.
- b) The Beck Institute will fax the cognitive rating scale to both the intervention therapist and the supervisor.
- c) When the Coordinating Center prompts the sites to send in their randomly selected tapes for quality assurance, the Beck Institute will receive a copy of that email. Similarly when the site dispatches the selected tapes to the Beck Institute, they will email the Beck Institute and copy the coordinating center providing, the date, tape session number and name of therapist.

### B. Group Therapy

Each calendar year (July 1 - June 30) for each clinical center, the Beck Institute will review tapes of two group therapy sessions for each of two randomly selected groups. For each group, one tape will be randomly selected from the first 3 sessions, and one from the last 3 sessions. Therapists will not be told that a group has been selected. This will be implemented through the following procedure:

1. The Coordinating Center will retrospectively randomly select two sessions for the same group. For each selected group, the Coordinating Center will randomly select one of the first three sessions and one of the last 3 sessions.
2. The Coordinating Center will notify the clinical center designated site center (by email - with a copy to the Beck Institute of the email) that the group should have tapes sent to the Beck Institute for monitoring.
4. The designated center member will mail the selected early tapes to the Beck Institute as soon as it is available. None of the Intervention staff should be aware that a tape has been selected. The designated center member will notify the Coordinating Center (by email) of the first session date for the selected group and the date the tape were mailed to the Beck Institute.
5. The Beck Institute will evaluate the tapes using Group Therapy Rating Scale (Refer to Table 7). The provision of communications will be the same as described above for monitoring of tapes of individual therapy.



## **Randomization Worksheet - RAN, Version C**

The revised ENRICHD Randomization Worksheet (version C dated 03/31/98) is used to record MI criteria, assure patients meet current protocol eligibility criteria defining low social support, and to accommodate the coding scheme for DSM-IV diagnosis of depression from the DISH version 2D (revised 03/31/98). In order to randomize patients into the ENRICHD trial from **April 6, 1998** onwards, version C of the RAN and the diagnostic summary codes from the DSF associated with DISH version 2D dated 03/31/98 **must be used together**.

### **A. Patient Demographics--**

1--3. No change was made to questions 1-3. Responses are self-explanatory.

### **B. Inclusion Criteria--**

4. Informed consent criteria remains the same, all patients must provide informed consent in order to be randomized.

5a. Cardiac enzymes should be taken directly from MEA question 2 where the lab values for the index MI were verified, and meet expanded criteria for elevated enzymes. The expanded criteria include the following cases: 1) enzymes  $\geq 2$  times upper limit of normal (ULN); 2) if MBCK is not  $\geq 2$  times ULN, there is a distinct rising and falling pattern; 3) If an interventional procedure is done acutely, and either elevated enzymes are associated with ST segment elevation, or enzymes are  $\geq 3$  times ULN and ST segment depression is present.

5b. ECG evidence of MI or presence of MI symptoms should come from MEA questions 3 and 4. If either ECG evidence or MI symptoms were present then answer "Yes" to 5b. Both RAN questions 5a **and** 5b must be answered "Yes" in order for the patient to meet inclusion criteria.

6. Completion of Baseline assessment remains unchanged and is self-explanatory.

### **C. Screening Instrument Scores--**

With the expansion of the qualifying criteria for low perceived social support this section has been changed the most from RAN version B by both adding additional ESSi item value questions and replacing a qualifying BDI score with a modified ESSi summary score. The existing protocol criteria for defining low social support based on the ESSi has been retained (occurrence of responses to two or more items, excluding ESSi question 4 on chores, where the patient indicated an item value of 2 or lower.). The "help with daily chores" question still does not contribute towards eligibility. Thus, only patients with low item scores on at least two questions with a value of 2 or lower can qualify based on low social support. A second criteria is now approved for defining low perceived social support, which consists of scoring at a value of 3 or lower on 2 questions (not question 4 on chores or #7 on marital status) and having a modified summary ESSi score of less than or equal to 18. (The modified ESSi score is the sum of the 5 qualifying questions: 1, 2, 3, 5, 6.) Patients are eligible for entry into the trial for low perceived social support using either ESSi criteria 1 or 2.

### **ESSI Criteria 1**

7a. ESSI question number with first score  $\leq 2$ . Provide the number of the question (not score values) where the patient had a response of 2 or lower to that item. ESSI question 4 on daily chores cannot be used. If no question has a score of 2 or lower, enter "0".

7b. ESSI question number with second score  $\leq 2$ . Provide the number of the second question (not score values) where the patient had a response of 2 or lower to that item. ESSI question 4 on chores cannot be used. If no second question has a score of 2 or lower, enter "0".

### **ESSI Criteria 2**

8a. ESSI question number with first score  $\leq 3$ . Provide the number of the question (not score values) where the patient had a response of 3 or lower to that item. ESSI question 4 on daily chores and question 7 on marital status cannot be used. If no question has a score of 3 or lower, enter "0".

8b. ESSI question number with second score  $\leq 3$ . Provide the number of the second question (not score values) where the patient had a response of 3 or lower to that item. Both ESSI question 4 on chores and question 7 on marital status cannot be used to qualify with this 2nd criteria. If no second question has a score of 3 or lower, enter "0".

8c. ESSI score for the patient. Enter the summary total score from the qualifying ESSI by summing the five items 1, 2, 3, 5, and 6 together. Patients must score 18 or lower to be eligible on the basis of criteria 2 for low perceived social support.

9. DIS score from DISH. Enter the score from the 03/31/98 version 2D of the DISH. To be eligible on the basis of depression patients can have diagnostic summary codes of 4, 5, 7, 9, or 10. Patients with a history of depression, and a current diagnosis of minor depression with duration of 7 days or longer are eligible. Patients with a history of depression, and a current diagnosis of major depression with duration of 7 days or longer are also eligible. Patients with no history of depression, but with a diagnosis of major depression of duration 14 days or longer also qualify for entry into the trial.

10. Dysthymia score from DISH. No change in the coding scheme on DISH version 2D. A value of "1" indicates dysthymia, and qualifies a patient on that basis for entry.

### **D. Randomization Assignment--**

11. Treatment assignment. Check the box indicating assignment to either Intervention or Usual care after the Voice Randomization System provides the allocation for eligible patients.

12. ENRICHHD Treatment ID number. Record the treatment number provided by the Voice Randomization System at the time of randomization.