Depression and Self-Care of Heart Failure: A Randomized Controlled Trial
Kenneth E. Freedland, PhD, Principal Investigator

Study Protocol

Protocol Revisions

The DSMB, in its capacity as the Protocol Review Committee, approved revisions on 09/04/2009. Revisions were approved by the WUSM Human Research Protection Office (HRPO).

<table>
<thead>
<tr>
<th>Revised Plan</th>
<th>Notes</th>
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<tr>
<td>Comparator: enhanced usual care (enhanced by HF education)</td>
<td>Committee disagrees with the reviewers about controlling for attention and using SCM as the comparator. EUC is more clinically relevant than supportive clinical management for the outcomes of interest. Change could help to increase the clinical impact of the findings.</td>
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<tr>
<td>HF education – mixture of HFSA and AHA modules</td>
<td>Cardiac research nurse redesigned educational series to better fit study aims &amp; eliminate redundant materials</td>
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<tr>
<td>HF education: provide to both groups.</td>
<td>Design as intended is CBT + EUC vs. EUC alone. (This is just to make it clear that the CBT arm also gets EUC.)</td>
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<td>Eligibility criteria changes: 1) NYHA Class II/III, 2) no LVEF restriction, 3) hospitalized with HF in past year, 4) drop the Framingham HF criteria, 5) hold off on recruitment of patients with DSM-IV minor depression</td>
<td>1) Importance of self-care increases when patients progress to Class II/III. 2) LVEF criteria were not specified in proposal; this simply affirms that patients with either HFrEF or HFpEF will be eligible. 3) Helps to support HF diagnosis. 4) Framingham criteria impractical for use with outpatients. 5) Enrolling patients with minor depression might help recruitment but consensus is that this is outweighed by the possibility that doing so could reduce efficacy and decrease clinical impact of findings. Also would complicate use of ADM as stratification factor.</td>
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<td>Primary outcomes: BDI-II remains primary. HAM-D-17 co-primary depression outcome. SCHFI Maintenance and Confidence co-primaries for self-care. QOL measures relegated to secondary outcomes.</td>
<td>Original plan was to use SCHFI total score, but the authors now state that the total score is obsolete and that only subscale scores should be used. SCHFI Management will not be a co-primary outcome because it is only relevant to patients with a recent exacerbation. Given that we now have two SCHFI subscales as co-primaries, there would be too many “co-primaries” if QOL measures were included, so they will now be counted as secondary outcomes. However, all agree with the original concept that HF-related QOL is an important outcome.</td>
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<td>Secondary outcomes: additional NIH-PROMIS measures</td>
<td>Original plan included only Physical Functioning. Addition of Depression, Anxiety, Fatigue, and two Social functioning scales will provide potentially valuable data. Additional burden is low due to use of computerized adaptive testing.</td>
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<tr>
<td>Collect data on nonstudy antidepressants and guideline-based HF meds throughout follow-up.</td>
<td>Use to examine possibility of co-intervention bias.</td>
</tr>
<tr>
<td>Revised analysis plan for moderators and subgroups</td>
<td>1) Antidepressant use at baseline will be included as originally planned as a main effect since it is a stratification factor. It will also be examined as a moderator (in addition to sex and race as originally planned). 2) Baseline severity of depression &amp; HF were originally proposed as potential moderators. They will still be examined but in secondary analyses rather than in the main analysis, in order to focus on sex, race, &amp; ADM.</td>
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<tr>
<td>Revised analysis plan for covariates</td>
<td>In response to a reviewer’s comment, PI proposed to examine effects of HF chronicity and severity on Tx outcomes. The committee questions whether data will highly reliable since it will be obtained retrospectively. Advice is to examine these and other factors in Aim 3 in exploratory analyses.</td>
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## Biomarker ancillary study (Doug Mann, MD) approved

Dr. Mann’s lab will perform assays for an ancillary study. Due to budget cut, there are insufficient funds for the markers that were originally proposed as part of the trial.

### Protocol revisions approved 05/06/2010:

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<tr>
<td><strong>HF diagnosis must be made or confirmed by attending MD.</strong></td>
<td>We’ve been doing this all along, but this was added just to ensure that we’re not basing eligibility on Dx by a resident.</td>
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<tr>
<td><strong>Increase enrollment by dropping HF hospitalization requirement, adding Class I, using CIDER and echo lists</strong></td>
<td>Hospitalization data usually not needed to support Dx given that we’re recruiting primarily at the Heart &amp; Vascular Center so all enrollees so far are HF patients being followed by WU cardiologists. Okay to enroll Class I as long as Dx is consistent with BNP, echo, and/or cath. HF self-care is less important in Class I than in II/III, but it’s still relevant. CIDER &amp; echo lists will help to identify HF outpatients that are seen at WUMC but not necessarily at the H&amp;V Center.</td>
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<td><strong>Maintain major depression requirement</strong></td>
<td>We haven’t caught up with our recruitment target yet but the consensus is to try to find more patients with major depression instead of including minor depression.</td>
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<td><strong>Treatment fidelity: continue using CBT checklist but put reviews of audio recordings on hold.</strong></td>
<td>We’ve been using the checklist since the start but budget is insufficient to implement audio recording review plan.</td>
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<tr>
<td><strong>Caregiver contacts: continue to offer</strong></td>
<td>So far, none of the caregivers have wanted to participate. Continue to offer, but it’s unlikely that we’re going to wind up with analyzable data on caregivers.</td>
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RESEARCH PLAN

1. Introduction to the Second Revision

We are glad that the reviewers found our revised application to be very responsive to the prior critiques and that they consider the proposed study to be clinically significant. Their enthusiasm was limited by the absence of an attention control group, the potential for differential attrition, and weak pilot data for the six-minute walk test. We agree that these are important issues and have addressed them in this revision.

**Control Group:** We previously proposed to compare the intervention to an enhanced usual care (UC) condition that would not have controlled for attention, but the consensus judgment of the reviewers is that it is necessary to do so. In addition, Reviewer 3 disagreed with our previous position that this would require a three-arm trial. We accept the reviewers’ judgment and have redesigned the trial accordingly. We must note, however, that this poses some challenges. Usual care is nonignorable in this patient population. All of the patients in both arms will be receiving non-study care for their heart failure and for medical comorbidities, and many will be receiving non-study antidepressants. We will enhance usual care in both arms with basic heart failure education to ensure equivalence between groups. For patient safety and ethical reasons, we will also enhance UC in both arms with recommendations to seek medical care if potentially serious medical problems are identified, and with a recommendation that the patient discuss major depression (if present) with his or her own physician. In order to control for attention, we will add supportive clinical management (SCM) sessions to the control condition. Thus, the new design is as follows:

- **Control:** UC + enhancements + attention
- **Intervention:** UC + enhancements + attention + specific treatment components

The choice of a control group often involves difficult tradeoffs\(^1\), and that is certainly the case in this instance. First, this design controls for attention and for variability in health education, but it leaves open the question of how the intervention compares to UC alone. Second, the provision of equal doses of attention to the two groups may decrease some of the between-group effect sizes, compared to the earlier enhanced UC-only control design. Given the profound problems that confront depressed heart failure patients, the specific components of the intervention are likely to account for substantial variance in the outcomes, above and beyond attention and expectancy effects. Nevertheless, this design change makes it necessary for us to reconsider our power and sample size estimates. Third, it also necessitates some changes in how the trial will be staffed, and consideration of how to integrate the provision of attention with the UC enhancements and with the involvement of caregivers. These issues are discussed in further detail in revised research plan.

**Differential Attrition:** We assume that the reviewers were concerned about differential attrition primarily because the proposed control condition provided less patient contact than the experimental intervention. Controlling for attention, as we now propose to do, should minimize the potential for differential attrition. Findings from our pilot study and from ENRICHD also suggest that the risk of differential attrition is reasonably low. There was 12% attrition in the UC arm of the pilot study and 15% in the intervention arm (p=0.99).

Like the proposed trial, ENRICHD used CBT as the primary intervention and compared it to usual care. Reviewers 2 and 3 questioned the relevance of ENRICHD because the participants in that trial were patients who were recovering from an acute MI rather than patients with heart failure. Although ENRICHD did enroll post-MI patients, 330 (14%) of them also had heart failure at entry; 168 were randomized to UC and 162 to the intervention. MI is a common cause of heart failure, and many of the patients who will be recruited for the proposed study will also have a history of MI. Seventeen percent of the HF subgroup in the ENRICHD UC arm, and 14% in the intervention arm, died within 6 months (X\(^2\)=0.58; df=1; p=0.44). Of the survivors, there was 24% attrition at 6 months in the UC arm and 22% in the intervention arm (X\(^2\)=0.08; df=1; p=0.78).

In addition, SADHART-CHF is an ongoing, double-blind, placebo-controlled trial of sertraline for depression in patients with HF. Although the data are still masked, we asked the investigators if they could tell us whether there is any evidence of differential attrition in the latest DSMB report. So far, the attrition rates are nearly identical in Groups “A” and “B” (Wei Jiang, MD, personal communication, July 8, 2008). In summary, our pilot study, ENRICHD, and SADHART-CHF all suggest that the risk of differential attrition is reasonably low.

**Six-Minute Walk Test:** All three reviewers expressed concern about the six-minute walk test because there was although there was a favorable trend, the distance walked at 6 months was not significantly different between groups in the pilot study. This has compelled us to carefully reconsider this outcome. After reviewing numerous studies, we agree with the reviewers’ concerns. The 6MWT is a very useful test. However, a recent systematic review of clinical trials of treatments for heart failure\(^2\) found that only 9 (19%) out of 47 trials of...
pharmacological therapies reported significant increases in 6MWT distance. The proportion was higher (44%) in cardiac resynchronization trials, but this was based on only 6 studies.

Thus, it can be difficult to obtain between-group differences in 6MWT performance, even in relatively large trials of efficacious treatments. Although the 6MWT demonstrates good reproducibility in patients with heart failure, the within-group standard deviations at each measurement point tend to be relatively large, even when the test is carefully standardized.\(^3\) Individual differences in age, gender, obesity, and medical status account for much of this variability.\(^4\) Also, there tends to be within-group variability in the individual trajectories of change over time in 6MWT performance, with some HF patients improving, others remaining stable, and still others deteriorating. We found this in the pilot study, and similar patterns have been found in other studies.\(^5\)

The 6MWT is a useful measure despite these drawbacks, and it plays an important role in HF research. Consequently, we are demoting it from a primary to a secondary outcome rather than dropping it altogether. This raises the question of what the primary HF-related outcome of the trial should be, if not the 6MWT.

In order to address this question, it is necessary to differentiate between surrogate and true end points in heart failure research. In an influential, systematic review of this topic, Anand et al.\(^6\) argued that the true end points in heart failure trials are survival and quality of life. They noted that whereas some treatments for chronic HF have been shown to improve both of these outcomes, others (e.g., flosequinan, pimobendan, and vesnarinone) can create a tradeoff in which survival is improved at the expense of QOL or vice versa. Consequently, it is important to study both. The proposed trial will not be large enough to study survival with adequate power, so it will be included as an exploratory end point, along with cardiac rehospitalizations; we will model time to the combined end point of cardiac rehospitalization or death.

The direct targets of the intervention are depression and heart failure self-care. Improvements in these domains are expected to improve quality of life. Thus, the three primary outcomes of the trial will be depression, heart failure self-care, and HF-related quality of life.

**Depression, Anxiety, and Heart Failure Self-Care:** The Beck Depression Inventory (BDI-II) and the Self-Care of Heart Failure Index (SCHFI), were previously proposed as primary outcomes and are retained in the present revision. Our previous application also listed anxiety, as measured by the Beck Anxiety Inventory, as a primary outcome because many of the depressed patients who were enrolled in the pilot study were also highly anxious, and there was a large difference between groups in anxiety outcomes. However, the patients in the pilot study were not selected on the basis of anxiety, and anxiety was not one of the primary targets of the intervention. Interestingly, a recent study by Gibbons and DeRubeis\(^7\) also suggests that amelioration of anxiety should not be a dominant focus of the proposed intervention. The participants were a subset of the patients who had been assigned to the cognitive therapy arm of a large RCT of treatment for depression.\(^8\) The authors reported that regardless of the severity of anxiety at baseline, more time and effort spent addressing anxiety in the therapy sessions predicted less improvement in both depression and anxiety symptoms over the course of treatment. This reinforces our decision to focus primarily on depression rather than on anxiety in treating patients with both problems. Since anxiety will not be a primary target of the intervention, it has been made a secondary rather than a primary outcome in the revised proposal.

**Quality of Life:** Because quality of life will now be the primary HF-related outcome of the trial, we have reconsidered our approach to QOL measurement. In the previous application, we proposed two widely-used measures, the Minnesota Living With Heart Failure Questionnaire (MLWHFQ) and the Medical Outcomes Study 12-item short form (SF-12). We now plan to replace the MLWHFQ and to augment the SF-12.

The Kansas City Cardiomyopathy Questionnaire (KCCQ)\(^9\) is a 23-item self-report questionnaire designed to assess physical limitations, symptoms, self-efficacy, social interference, and quality of life in patients with heart failure. It is a reliable, well validated instrument that has been used in a number of clinical trials, prognostic studies, and other investigations of heart failure. Recent studies have shown that the KCCQ is more sensitive to change than the MLWHFQ, the SF-12, and the SF-36.\(^9\)\(^,\)\(^10\) Consequently, we are replacing the MLWHFQ with the KCCQ. We also asked John Spertus, MD, MPH, the senior developer of the KCCQ and one of the world’s leading authorities on heart failure outcomes, to serve as a consultant. (See consultant letter).

The SF-12 and the longer SF-36 have been used in hundreds of studies to assess general health-related quality of life. Our pilot study intervention had a significant effect on the Mental but not the Physical component scale of the SF-36. Since we are placing greater emphasis on QOL outcomes in the revised plan, we have searched for a more sensitive measure of the physical component of health-related QOL. Hayes (one of the developers of the SF-36) and colleagues recently published an item response theory (IRT) analysis of the SF-36 physical functioning items. It showed that these items provide adequate coverage of lower but not higher levels of functioning, which helps to explain why the Physical scale is relatively insensitive to improvement.\(^11\)
Hays is also a PROMIS Investigator. The Patient-Reported Outcome Measurement Information System (PROMIS) is an NIH Roadmap Initiative that was created to develop state-of-the-art, IRT-based instruments to measure health outcomes from the patient’s perspective.\(^{12, 13}\) The PROMIS Physical Functioning scale recently became available both as a questionnaire and as an item bank for computerized adaptive testing (CAT), and it is designed to be sensitive to change.\(^{14, 15}\) Since it is a new measure that has not been used before in heart failure research, we will include it as an exploratory outcome to augment rather than replace the SF-12. Dr. Freedland, the Principal Investigator of the proposed trial, has participated in PROMIS conferences and in training workshops on the PROMIS measures and the Assessment Center (AC). The AC is a web-based application that supports CAT, short form, and long form administration of the PROMIS measures.

**Surrogate End Points:** Anand et al.\(^6\) evaluated a wide variety of surrogate end points and concluded that all of the ones that have been tested to date have limitations and that so far, there is no single, ideal surrogate marker for mortality in heart failure. Some of the best predictors include exercise capacity as assessed by cardiopulmonary stress testing, plasma natriuretic peptides, left ventricular ejection fraction, and left ventricular remodeling.\(^6, 16\) Of these, natriuretic peptides are the only ones that are feasible to include as pre-post measures in this trial. B-type natriuretic peptide (BNP) is one of the markers that we previously proposed as a secondary outcome, and that is unchanged in the present revision. As discussed above, the 6MWT has some drawbacks as a surrogate end point, but it is still informative and it is much more feasible than serial cardiopulmonary stress testing as a measure of physical functioning. As previously planned, we will obtain echocardiographic data on LVEF and LV remodeling at baseline, but it would be prohibitively expensive to obtain post-treatment echoes. Furthermore, it is unlikely that a 6-month behavioral intervention could produce clinically significant improvements in LV function in patients with heart failure.

**Power and Sample Size:** In the previous application, the target sample size was based primarily on the expected difference in 6MWT distance between the intervention and UC arms. In the revised application, a smaller sample provides sufficient statistical power because the KCCQ is more sensitive to change than the 6MWT. On the other hand, controlling for attention is expected to decrease the between-group effect sizes, particularly with respect to depression and QOL. This offsets some of the reduction in sample size that is made possible by changing the primary HF-related outcome. The net result is a slightly smaller sample size than was proposed in the previous application. This is discussed in further detail in the Power Analysis section.

**Timing of Assessments:** Reviewer 1 noted that the time points for the completion of the self-report questionnaires were not entirely clear. In response to the reviewer’s concern, we are including some additional information about this in the revised application.

**Covariates:** Reviewer 2 noted that since enrollment is tied to the presence of depression rather than to the chronicity of HF, the relationship between the onset of HF and the timing of recruitment is not as much of a concern as it might otherwise have been. The reviewer also pointed out that time since HF diagnosis and severity of HF are important covariates. We agree and have incorporated them into the analysis plan.

**Caregivers:** Reviewer 2 noted that in response to previous comments, we provided more detail about how the caregivers will be involved in CBT. With the addition of an attention control condition, we have added information about the involvement of caregivers in the control group, along with information about how caregiver burden will be assessed in both groups.

**Summary:** We thank the reviewers for their helpful and encouraging comments on the previous application. We have revised the protocol in response to their concerns. Changes and additions to the research plan are in bold type.
2. Specific Aims

Over 5 million Americans have heart failure (HF), and 550,000 new cases are diagnosed annually. HF has profound effects on functioning, quality of life, health care utilization, and survival. Depression is common in patients with HF, and it worsens functional impairment and decreases survival. Treatment of depression might improve these outcomes, yet there have been very few antidepressant trials, and no behavioral intervention trials, for depression in patients with HF. We propose to conduct a randomized, controlled trial (RCT) of a cognitive behavioral intervention for depressed outpatients with HF. The specific aims are:

1. To test the hypothesis that cognitive behavior therapy (CBT) is superior to supportive clinical management (SCM) with respect to the following primary outcomes:
   a. depression
   b. heart failure self-care
   c. heart failure-related quality of life
2. To compare CBT to SCM on the following sets of secondary outcomes:
   a. anxiety
   b. general health-related quality of life
   c. physical activity and six-minute walk test performance
   d. heart failure-related biomarkers
   e. cardiac hospitalization or death (combined endpoint)
3. To identify predictors and moderators of treatment outcomes, including sociodemographic characteristics, severity of depression, severity of heart failure, medical comorbidity, quality of HF care, non-study antidepressants, and participation in cardiac rehabilitation.

3. Background and Significance

3.1 Heart Failure

Heart failure is a clinical syndrome resulting from impairment of heart muscle function, particularly in the left ventricle. It causes dyspnea, fatigue, exercise intolerance, and fluid retention. The New York Heart Association (NYHA) class quantifies the clinical severity of HF according to the extent of functional impairment. Patients in NYHA Class I are not limited by symptoms of HF; those in Class II or III experience dyspnea or other symptoms during ordinary (II) or light (III) exertion, and those in Class IV have symptoms at rest. Left ventricular ejection fraction (LVEF) quantifies the left ventricle’s ability to pump blood. Its capacity to fill during diastole often deteriorates before pump function declines; this is diastolic HF, or HF with preserved systolic function. As the ventricle weakens, LVEF decreases and systolic HF emerges along with neurohormonal activation, myocardial inflammation, and declining aerobic capacity. HF progression is often punctuated by acute exacerbations. Death usually results from HF progression or from sudden cardiac death.

HF predominantly affects elderly individuals. As the U.S. population ages, the incidence of HF is rising along with HF-related hospitalizations and deaths. HF-related deaths increased 28% from 1994 to 2004. In the Framingham Heart Study, median survival after HF onset was 1.7 years in men and 3.2 years in women. Survival rates at 1, 5, and 8 years after HF diagnosis were 57%, 25%, and 20% in men, and 64%, 38%, and 30% in women. The prognosis of HF remains poor, despite advances in medical and surgical management. The total cost of HF in the U.S. for 2007 is estimated to be $33 billion, and the costs are rising every year.

3.2.1 Functional Impairment and Self-Care in Heart Failure

Exertional symptoms and exercise intolerance are cardinal symptoms of HF. The decline in aerobic capacity is due primarily to reduced blood flow to skeletal muscles. As patients become more sedentary due to HF, comorbidities, aging, and/or depression, exertional symptoms recede while symptoms at rest emerge. Inactivity causes a downward spiral of physical deconditioning, skeletal muscle atrophy, worsening exertional symptoms, and further inactivity. This has obvious implications for quality of life (QOL) and for activities of daily living, and it also has prognostic importance. Poor performance on the 6-minute walk test (6MWT) predicts morbidity and mortality in heart failure. Poor aerobic capacity, as measured by peak VO\textsubscript{2} based on cardiopulmonary stress testing, is one of the strongest predictors of survival in HF. In addition, it is the single most important indicator of the need for cardiac transplantation in Stage D heart failure.
Aerobic exercise training is safe and effective in NYHA Class I-III, and it improves exercise tolerance and QOL. The American Heart Association (AHA) recommends a moderate, individualized exercise program for chronic, stable HF. Heart Failure Society of America (HFSA) guidelines recommend individualized exercise and activity as part of comprehensive disease management. HF-ACTION is a large, ongoing, multicenter RCT of exercise training in HF. The findings will yield definitive evidence about therapeutic exercise for patients with HF. It is already known that home-based programs involving walking or other low-intensity exercises can improve functional status and QOL in HF. Thus, interventions that promote ordinary physical activities in daily life can help to maintain or improve functional capacity and QOL in HF.

Physical inactivity is one of several modifiable behavioral factors that affect the course of HF. Others include self-monitoring of HF signs and symptoms, adherence to prescribed medication regimens, avoidance of contraindicated medications, risk factor modification, and dietary management. For example, high sodium intake and failure to monitor fluid retention and weight gain increase the risk of hospitalization for HF. Thus, self-care interventions have an important role in HF management. Self-care behaviors encompass both health maintenance and management activities. HF self-maintenance includes engaging in exercise, following a suitable diet, and adhering to prescribed medications, in order to prevent acute exacerbations and to slow the progression of functional decline. HF self-management requires monitoring of signs and symptoms, utilizing appropriate self-treatment strategies (e.g., self-administration of diuretics), and seeking medical care in a timely manner. RCTs have shown that brief health education and support interventions can improve HF self-care. The interventions may involve the patient, the patient’s spouse, family members, or other caregivers. Some trials show that improving self-care can decrease dietary sodium intake, decrease HF symptoms and improve HF clinic attendance, decrease hospitalizations, and increase survival. The interventions require engaging in ordinary productive activities. Cognitive mediators include 1) increased knowledge of HF and of self care techniques; 2) increased motivation to engage in normal social and productive activities. Maintenance of physical functioning, in turn, facilitates maintenance of social role functioning and permits continued engagement in recreational and productive activities. Cognitive mediators include 1) increased knowledge of HF and of self care techniques; 2) increased motivation to engage in normal social and productive activities.

Multiple mechanisms link improvements in self care to better HF outcomes. The association between self care and physical functioning is behaviorally mediated by adherence to the medication regimen, dietary restrictions, and exercise and physical activity recommendations. Maintenance of physical functioning, in turn, facilitates maintenance of social role functioning and permits continued engagement in recreational and productive activities. Cognitive mediators include 1) increased knowledge of HF and of self care techniques; 2) increased motivation to engage in normal social and productive activities.

3.3 Depression in Patients with Heart Failure

Depression is one of the most common and most disabling of all psychiatric disorders. The Medical Outcomes Study found that depressed outpatients had markedly worse functioning, perceived health, and pain than patients with no chronic conditions. The functional impairment uniquely associated with depression was comparable to or worse than that uniquely associated with major chronic medical conditions such as coronary heart disease. Depression and chronic medical conditions had additive effects on functional impairment. A recent international study found that depression is the 4th leading cause of disease burden, accounting for 4.4% of total disability adjusted life years (DALYs) world-wide in the year 2000. It also found that depression is the leading cause of nonfatal disease burden, accounting for nearly 12% of total disability years worldwide.

Even the most conservative estimates of the prevalence of depression as a heart failure comorbidity suggest that it is very common. Reports of the overall point prevalence of major depression in patients with HF have varied from as low as 11% in a community sample to as high as 36% in patients hospitalized with a primary or secondary diagnosis of HF. In a large study of hospitalized patients with HF, we found that 20% met the DSM-IV criteria for current major depression, 16% met the DSM-IV criteria for minor depression, and 51% scored above the cutoff for depression (≥10) on the Beck Depression Inventory (BDI). The rates were higher in younger patients and in those with more severely disabling heart failure.

Depression and functional impairment are strongly associated in patients with HF. The available evidence suggests that on average, depressed patients do not have worse LV impairment or worse aerobic capacity than nondepressed patients. Thus, the association between depression and functional impairment is not attributable to confounding by the underlying physiological severity of HF. There is probably a reciprocal relationship between depression and impairment in HF, in which the disabling manifestations of HF promote depression, and depression contributes to worsening functional impairment and diminished QOL.

Depression may also indirectly promote functional decline via deleterious effects on HF self-care. Some studies suggest that the majority of patients with HF take most of their cardiac medications as prescribed and attend most of their scheduled follow-up appointments, but even in these studies, approximately 10-20% of patients were not reliably adherent to medications or appointments. One of the largest studies examined...
medication compliance in routine clinical practice using medical and pharmacy claims data over 10 to 17 months in 869 HF patients. Only 50% of the patients had a medication possession ratio (MPR) of 0.80, indicating acceptable compliance. Only 70% of the control group participants in a multidisciplinary HF management intervention trial had a medication compliance rate of >0.80. Thus, nonadherence to prescribed medications is a common problem in HF. Many factors contribute to nonadherence, but depression is one of the most significant. It triples the odds of nonadherence to a wide variety of medical treatment regimens.

Nonadherence to the nonpharmacological aspects of HF self-care is at least as problematic. A study of 82 HF clinic outpatients found that 53% did not follow exercise recommendations and 71% did not follow dietary advice. In 70 patients with HF, half of whom were >65 years old, 23% of the older and 35% of the younger patients were nonadherent to diet, and 33% of the older and 45% of the younger patients were nonadherent to exercise. In a recent European study, 2331 patients were interviewed 12 weeks after hospitalization for HF. Only 63% recalled the standard advice about dietary fat and cholesterol intake. Only 60% remembered dietary salt recommendations, 36% remembered advice to be vaccinated for influenza, and 17% recalled advice to avoid nonsteroidal anti-inflammatory drugs (NSAIDs). Multiple factors contribute to nonadherence to nonpharmacological aspects of HF self-care, but depression is one of the most important. A recent study of 501 HF patients found that it is one of the strongest predictors of nonadherence (OR=0.53; CI 0.35-0.78).

Depression is also a risk factor for hospitalizations and mortality in HF. This has been demonstrated both in heterogeneous cohorts of HF patients and in various patient subsets, including patients with HF of nonischemic etiology, HF patients at high risk for sudden cardiac death, HF patients with chronic kidney disease, and patients with an acute myocardial infarction complicated by heart failure. These effects remain apparent after adjusting for the initial severity of HF. Furthermore, depression has been shown in several studies to increase the risk of developing heart failure, including in older patients with isolated systolic hypertension, patients with a recent acute myocardial infarction, and in elderly community residents. 3.4 Treatment of Depression

The HFSA Guidelines recommend screening patients with HF for depression, and treating depressed patients with selective serotonin reuptake inhibitors (SSRIs). However, this is based on scant evidence about the safety and efficacy of antidepressants in HF. A small (n=10) trial reported less orthostatic hypotension among patients treated with bupropion than with imipramine. Twenty-eight patients with HF and major depression were recently enrolled in a 12 week, open label nefazodone trial. Of 19 completers, 74% showed a 50% decline in depression severity, and there were no serious adverse events. Another recent study of 20 patients with HF and MD reported improved cognitive functioning after antidepressant therapy. A larger, placebo-controlled trial of sertraline for depression in HF is in progress, but the findings are not yet available. Also, physician adherence to this HFSA guideline is limited. There has been little research on antidepressant utilization in HF, but the available evidence suggests that depression is undertreated in patients with HF.

No clinical trials of psychotherapeutic interventions for depression in patients with HF have been published to date. As discussed in the Preliminary Studies section, our pilot study of cognitive behavior therapy (CBT) for depression in HF has been submitted for publication. To our knowledge, no other CBT trials are in progress.

A.T. Beck originally developed cognitive therapy as a treatment for depression. It has since been applied to many other psychiatric conditions, including anxiety disorders. There is strong evidence that CBT is efficacious for depression in psychiatric patients. It has also been used to treat depressed cardiac patients. CBT was more effective than usual care for post-MI depression in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial. As discussed in the Preliminary Studies section, we have also shown that CBT is efficacious for depression in patients recovering from recent coronary bypass surgery.

Several distinctive elements of CBT make it an especially promising intervention for depression in HF. For example, behavioral activation is a key component of CBT for depression, and it played a prominent role in ENRICHD. The rationale is that depression is associated with inactivity and withdrawal from valued roles and relationships. It helps the patient to resume as many pleasurable and productive activities as possible, and to reengage with potential sources of social support. It is especially useful during the early phase of treatment. It is also readily acceptable to elderly patients, those with limited education, and individuals who might reject treatment if cognitive restructuring and emotion-related elements are introduced too quickly.

Behavioral activation usually includes moderate physical activities; e.g., patients who enjoy shopping often find mall walking to be a pleasant form of exercise. More vigorous exercises may be added, if medically indicated. Moderate exercise is an effective intervention for depression, including in older patients.
Modifiable factors that impede the maintenance of normal activities must be addressed in order for behavioral activation to succeed. Depression and anxiety are associated with physical inactivity and decline in physical functioning in elderly individuals, in patients with coronary disease, and in other chronic illnesses. Some HF symptoms, particularly dyspnea on exertion (DOE), are anxiogenic for many patients, and this can pose an obstacle to physical activities. Fears about safety, uncertainty about the medical risks and benefits of physical activity, diminished self-efficacy, and altered body image must be addressed if they interfere with behavioral activation, and CBT for depression incorporates techniques for doing so.

Depression and other comorbidities interfere with HF self-care. In 122,630 Medicare patients with HF, most had >3 noncardiac comorbidities, and some had 2-3 times as many. The 5 most common were hypertension (55%), diabetes (31%), COPD (26%), eye disorders (24%), and hypercholesterolemia (21%). In addition, 51% had coronary disease, 41% had an arrhythmia, and 22% had valvular disorders. Consequently, the burden of chronic illness self care extends beyond heart failure for most patients. Depressed cardiac patients also tend to be overwhelmed with other problems that compete for time, attention, and energy that could otherwise be devoted to self care. Some of them may be consequences of illness (e.g., unemployment, physical dependency, financial strain, etc.), but others may be unrelated to the patient’s health (e.g., a grandchild who is in legal trouble.) CBT incorporates systematic goal-setting, prioritization, problem-solving, and other techniques to improve the patient’s ability to cope with complex challenges such as these. As a result, patients who initially feel too depressed, overwhelmed, hopeless, or distracted to manage basic HF self care tasks are able to overcome these barriers. As they do so, they regain a sense of having some control over their own health and quality of life. Thus, CBT has considerable potential to reverse the downward spiral of depression, anxiety, poor self care, and diminished functioning that often complicates heart failure.

Another advantage of CBT for patients with heart failure is that it can be delivered by telephone. This eliminates a key barrier to participation for patients who are too ill, functionally impaired, or mobility restricted to participate in face-to-face sessions. Telephone-based CBT was recently shown to be an effective treatment for depression in patients with functional impairment due to multiple sclerosis. Another recent study showed that it improved depression outcomes in primary care patients beginning antidepressant treatment.

Finally, CBT is an acceptable alternative for patients who reject or who cannot tolerate antidepressant medications. It can be combined with antidepressants for patients who can benefit from both modalities. STAR*D findings show that CBT is effective for patients who do not respond to first-line antidepressants.

4. Preliminary Studies

4.1 Pilot Study

The pilot study included 37 outpatients (43% women, 19% racial minorities, age 55±10 years) recruited from the Heart Failure Clinic at Washington University Medical Center. The mean LVEF at enrollment was 43±16. Two (5%) of the patients were in NYHA Class I, 23 (62%) were in Class II, 12 (32%) were in Class III, and patients in Class IV were excluded. Fourteen (38%) met the DSM-IV criteria for minor depression, and 23 (62%) had major depression. Twenty-one (57%) were on a non-study antidepressant at enrollment. After completing the baseline evaluation, the participants were randomly assigned to individual CBT (n=20) or to Usual Care (n=17). The intervention consisted of up to 6 months of weekly, 50-60 minute sessions of CBT. Contacts were tapered if: 1) Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) scores were <10 for >2 weeks, and 2) the patient demonstrated CBT self-therapy and relapse prevention skills. Contacts were initially tapered to biweekly, and then to once per month; the duration was gradually tapered to about 20 minutes. The following measures were obtained at baseline and again at 6 months: 1) the 17-item Hamilton Rating Scale for Depression (HAM-D), 2) the Beck Depression Inventory (BDI), 3) the Beck Anxiety Inventory (BAI), 4) the Medical Outcomes Study Short-Form questionnaire (SF-36), 5) the Cardiac Self-Efficacy Questionnaire (CSEQ), and 6) the 6-minute walk test. In addition, 7 days of actigraphy data was obtained at baseline and again at 6 months from a subgroup of 12 patients (6 from the CBT arm, and 6 from the UC arm.) ANCOVA was use to analyze each outcome, adjusting for nonstudy antidepressants. Group by time interactions were found on the BDI (p<.001), HAM-D (p=.02), BAI (p=.001), SF-36 Mental (p=.01), CSEQ Control Symptoms (p<.01), and Maintain Functioning scores (p=.01), consistent with better psychological and functional outcomes in CBT than UC. 6MWT performance improved 30 yards on average in CBT and 10 yards in UC, but this was not significant. There was no improvement on the SF-36 Physical score. Nonstudy antidepressants had no effect on any outcome, despite trends on the HAM-D (p=.08) and BAI (p=.06). The results are displayed in Figure 1, below, with CBT in red squares and UC in blue diamonds.
The actigraphy substudy was too small to justify statistical analyses, but the graphs revealed an interesting trend. Figure 2 displays 24-hour activity curves at baseline and 6 months. In both groups, activity levels rose between 6:00 and 7:00 a.m. and increased until midday. In the CBT group, a high activity level was sustained until about 8:00 pm, after which it decreased. The same pattern occurred in the UC group at baseline, but not at 6 months. The UC patients still woke up around the same time and were increasingly active during the morning, but they became exhausted around 10:00 or 11:00 a.m. and did not recover until the next morning. Thus, while patients in the CBT subgroup were able to maintain their initial activity pattern over 6 months, daytime activity levels deteriorated in the UC group. The most likely explanation is that intervention includes the “activity-rest cycle.” Many patients overcompensate for fatigue and low aerobic capacity by pushing too hard. Therapists teach them to break demanding tasks into manageable subtasks, to pace activities, and to take preemptive rest breaks. They also assess cognitive distortions that feed the cycle of overactivity and exhaustion. E.g., a patient became exhausted every morning due to futile efforts to do as much housework as she did before developing HF. She was asked to record distressing thoughts before and after housework on a Dysfunctional Thought Record (DTR). It revealed frequent thoughts such as, “I’m letting my family down,” and, “I’m worthless if I can’t do my share of the work around here.” She was encouraged to challenge the validity and utility of these thoughts, and to devise adaptive counterarguments. This enabled her to remain active throughout the entire day, while conserving enough energy to prevent exhaustion.

Budgetary constraints limited the study in several ways. First, the participants had to be recruited from a single clinic. Because every patient received optimal HF care, the results may not be generalizable to patients who are not receiving specialized care. The proposed intervention will incorporate brief, nurse-directed HF education to achieve comparable results in a broader patient population. Second, there were insufficient funds to support therapeutic contacts beyond 6 months; patients who were still in active treatment at 6 months did not have the benefit of the tapered maintenance therapy phase that is a standard part of CBT for depression. Finally, there were also insufficient funds to collect any follow-up data after 6 months, so we do not know whether the gains achieved in CBT were maintained. The proposed trial will overcome these limitations.
4.2 Disease Management of Heart Failure

Drs. Rich, Freedland and Carney conducted the first RCT of multidisciplinary disease management for elderly HF patients. The intervention included patient and family education, a prescribed diet, social service consultation, discharge planning, a medication review, and follow-up. The primary results were reported in the New England Journal of Medicine.\(^\text{116}\) We found that readmission-free 90 day survival occurred in 64\% of treatment arm vs. 54\% of the UC arm (p=0.09). There were 94 readmissions in the UC and 53 in the treatment arm (risk ratio, 0.56; p=0.02). HF readmissions decreased by 56\% in the treatment arm (p=0.04); readmissions for other causes were reduced by 29\% (n.s.) In the UC arm, 16\% had multiple readmissions, compared with 6\% in the treatment group (RR=0.39; p=0.01). QOL improved more from baseline in the treatment group (p=0.001). Due to the reduction in readmissions, the total cost of care was $460 less per patient in the treatment group. This study demonstrates our group’s experience in HF self care training and supportive care.

4.3 Treatment of Depression After Coronary Bypass Surgery

We recently completed the first RCT of treatment of depression after coronary artery bypass graft (CABG) surgery. Depression is a risk factor for cardiac events and mortality in this population.\(^\text{117-119}\) CABG surgery can also cause mild neuropsychological deficits that affect mood, social behavior, and QOL. Many patients have difficulty coping with incisional scars, abrupt shifts in perceived health, unemployment, and feelings of worthlessness. Thus, CBT often focuses on different target problems in depressed CABG patients than in depressed HF patients. Also, a satisfactory response to CBT can often be achieved in fewer sessions in patients recovering from CABG surgery than in those with chronic heart failure.

We enrolled 123 patients (50\% women, 19\% African-American) and randomly assigned them to 12 weeks of CBT (n=41), supportive stress management (SSM; n=42), or usual care (UC; n=40). SSM provided emotional support and targeted coping with depressogenic stressors. It was more supportive and depression-focused than typical cardiac rehabilitation stress management programs. About 50\% of the participants were on non-study antidepressants during the trial. Outcomes were assessed at baseline, after treatment (3 months), and at 6- and 9-month follow-ups. The depression and anxiety outcomes are displayed in Table 1.

The patients were roughly comparable to the participants in our HF pilot study with respect to the severity of depression at baseline, but they were less anxious. CBT was superior to UC on both depression measures at 3 and 9 months, and consistently superior on the anxiety measure. The 6-month depression and anxiety outcomes of CBT were similar to the CHF pilot study, although the CBT-UC depression differences were not significant at 3 months in the CABG study. Most of the CBT-SSM differences were not statistically significant, but all of them trended in the direction of better outcomes with CBT than with SSM. Thus, we have demonstrated the efficacy of CBT for depression and anxiety in two different cardiac patient populations.

<table>
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<tr>
<th>Outcome</th>
<th>CBT (n=41)</th>
<th>SSM (n=42)</th>
<th>UC (n=40)</th>
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<td>Baseline</td>
<td>19.3 (1.0)</td>
<td>20.8 (1.0)</td>
<td>18.5 (1.0)</td>
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<tr>
<td>3 months (^\text{CS})</td>
<td>5.5 (1.0)</td>
<td>7.8 (1.0)</td>
<td>10.7 (1.0)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>6 months</td>
<td>6.6 (1.0)</td>
<td>8.5 (1.0)</td>
<td>8.3 (1.0)</td>
<td>.62</td>
</tr>
<tr>
<td>9 months (^\text{C})</td>
<td>5.5 (1.0)</td>
<td>7.7 (1.0)</td>
<td>10.3 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
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<td>23.7 (1.3)</td>
<td>20.8 (1.4)</td>
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<tr>
<td>3 months (^\text{CS,IS})</td>
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<td>9.3 (1.4)</td>
<td>13.8 (1.4)</td>
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<tr>
<td>6 months</td>
<td>7.8 (1.3)</td>
<td>10.6 (1.4)</td>
<td>10.7 (1.4)</td>
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<td>9 months (^\text{C})</td>
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<td>9.9 (1.4)</td>
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<tr>
<td>Baseline</td>
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<td>18.6 (1.4)</td>
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<tr>
<td>3 months (^\text{C})</td>
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<tr>
<td>6 months (^\text{C})</td>
<td>8.1 (1.4)</td>
<td>11.0 (1.4)</td>
<td>12.7 (1.5)</td>
<td>&lt;.01</td>
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<tr>
<td>9 months (^\text{CS})</td>
<td>9.1 (1.4)</td>
<td>10.1 (1.5)</td>
<td>14.2 (1.5)</td>
<td>.87</td>
</tr>
</tbody>
</table>

Note: Values are covariate-adjusted least-squares mean (SE); p values are for Type 3 fixed effects of group, time, the group by time interaction, and antidepressants (AD). \(^\text{C}\)CBT≠UC. \(^\text{SSM}\)≠UC. \(^\text{ICBT}\)≠SSM.

Table 1. Depression and anxiety outcomes of CBT trial for patients recovering from CABG surgery
4.4 Enhancing Recovery in Coronary Heart Disease (ENRICHD)

Several of the investigators were involved in the ENRICHD trial. Dr. Freedland was a co-investigator, co-chair of the Psychosocial Measurement Committee, a clinical CBT supervisor, and the principal developer of the depression interview designed for ENRICHD, the Depression Interview and Structured Hamilton (DISH).

Dr. Carney was the P.I. at the St. Louis site, chaired the Depression Intervention Subcommittee, and was a member of the Executive and Steering Committees. Dr. Rich was a cardiologist-investigator and on the Medical Endpoints Committee. Dr. Skala was the Research Nurse Coordinator at the St. Louis site, the first chair of the study-wide Research Nurse Coordinators Committee, and co-developer of the DISH.

The aim of ENRICHD was to determine whether survival can be improved in post-MI patients by treating depression and low perceived social support (LPSS). A total of 2,481 patients were randomized to CBT (augmented with sertraline when indicated) or to UC. The psychosocial outcomes favored the intervention; among depressed patients, the mean (SD) change in HAM-D scores was -10.1 (7.8) in the intervention group vs -8.4 (7.7) in the UC group (P<.001). There was no between-group difference in cardiac event-free survival.

It is possible that depression is simply a risk marker rather than a causal risk factor for morbidity and mortality after acute MI. However, an equally plausible explanation is that depression is a causal risk factor, but that the depression difference between the intervention and UC arms was too small to affect medical outcomes.

This led us to investigate whether depressed patients who responded to the ENRICHD intervention had better medical outcomes compared to depressed nonresponders. This analysis was limited to patients with recurrent major depression. Patients whose depression did not respond to CBT were at higher risk for late mortality (i.e., starting at 6 months) than were patients who did respond. As a result, we incorporated procedures in our CHF pilot and post-CABG trials for early identification and remediation of nonresponse to CBT. Many of the techniques we utilized are described in J.S. Beck’s manual, Cognitive Therapy for Challenging Problems: What To Do When The Basics Don’t Work. This may help to explain how we were able to achieve better depression outcomes in our CHF pilot study and our post-CABG trial than in ENRICHD.

We also sought to identify mediators of response to CBT within the treatment arm. This was of interest because the intervention was individualized in order to address each patient’s unique needs and problems. Consequently, no two ENRICHD patients received precisely the same intervention. The independent predictors of better depression outcomes as measured by the BDI were 1) receiving a high proportion of the depression-related components of CBT such as behavioral activation, problem-solving, cognitive restructuring, etc. (p<.01), and 2) completing a high proportion of CBT homework assignments (p<.02). These findings are consistent with a “dose-response” relationship between CBT and depression outcomes in post-MI patients.

4.5 CBT for Depression in Patients with Diabetes

Dr. Freedland was a co-investigator and Patrick J. Lustman, PhD was the Principal Investigator of the first randomized, controlled trial of CBT for major depression in patients with Type 2 diabetes. Fifty-one patients were randomly assigned to 10 weeks of CBT or to UC; all patients in both groups received diabetes education. Eight-five percent of the patients in the CBT group compared with 27% of those in the UC group achieved remission of depression (p<.001). Post-treatment glycosylated hemoglobin levels did not differ between groups, but at a 6-month follow-up, glycosylated hemoglobin levels were significantly better in the CBT group than in the UC group (p=0.03). Interestingly, as shown in Figure 3, compliance with blood glucose self-monitoring was worse in the CBT than in the UC group during the treatment phase. Furthermore, poor compliance with blood glucose self-monitoring was an independent predictor of nonremission of depression within the CBT group. These results alerted us to the risk that CBT for depression in chronically medically ill patients could potentially interfere with rather than promote medical self-care, by competing for the patient's time, effort, and attention. Consequently, we now see self-care as an integral component of our cognitive-behavioral interventions for medical patients.

Figure 3. Compliance with blood glucose self-monitoring in CBT (white bars) vs usual care (striped bars).
4.6 Telephone-Based Coping Skills Training for Patients Awaiting Lung Transplantation

Most of our previous CBT trials have relied primarily on face-to-face therapy sessions, interspersed with telephone sessions as needed. A recent study of patients with end stage pulmonary disease who were awaiting lung transplantation was the first in which we delivered a cognitive behavioral intervention almost entirely via telephone. This study was a two-site, field-initiated, collaborative clinical trial (James A. Blumenthal, Ph.D., Principal Investigator at Duke University; Robert M. Carney, PhD, Co-Principal Investigator at Washington University.) We randomly assigned 328 patients with to 12 weeks of telephone-based coping skills training (CST) or to usual care (UC). Compared with UC, CST produced lower scores on perceived stress, anxiety, depressive symptoms, and negative affect and improved scores on mental health functioning, optimism, vitality, and perceived social support. Survival rates did not differ between the groups.126

Telephone-based therapy was the only option for this trial, because patients from at least 20 states are on the lung transplant waiting lists at Duke and Washington University. Although it was usually possible to arrange a brief, face-to-face contact with the therapist during one of the patient’s initial meetings with the lung transplant team, further face-to-face contacts were simply not possible. One of the therapists for the proposed study (Iris Csik, LCSW) was a therapist for the lung transplant trial, and Dr. Freedland was the clinical supervisor at our site. This experience, along with recent telephone-based trials from other research groups69,113, led us to conclude that telephone-based CBT is a feasible alternative for patients with heart failure who are unable to attend weekly therapy sessions because of their medical condition, transportation barriers, or other constraints. However, this does not negate the clinical value of face-to-face therapeutic contacts whenever they are possible. The therapeutic approach we are proposing can be described as providing as many face-to-face contacts as possible, and as many telephone-based contacts as necessary.

4.7 Observational Studies of Depression in Heart Failure

Our 1991 study of major depression in 60 HF patients was the first ever reported. Seventeen percent met the DSM-III-R criteria for MD during their index admission. There were trends toward more inpatient days at 3 months, and higher mortality in the depressed (50%) than the nondepressed patients (29%) over one year. This provided the first evidence that MD is prevalent in HF, and that it may be a risk factor for mortality.127

We interviewed 682 hospitalized HF patients; 20% met the DSM-IV criteria for a current major depressive episode, 16% for a minor depressive episode, and 51% scored above the BDI >10 cutoff for depression. As shown in Figure 4, however, the prevalence of MD differed between groups defined by age and NYHA Class. In both age groups, the prevalence increased along with HF-related functional impairment. Depression is especially problematic in younger, functionally impaired patients; 1/3 of younger patients in Class III, and 2/3 of those in Class IV, met the criteria for major depression.61

Dr. Freedland was also a co-author of a recent secondary analysis of HF among participants in the ENRICHD trial; Major depression was observed in 43% in the HF group compared with 36% in the non-HF group (p<.001). There was a 38% increase in the odds of HF in patients with major depression, after adjustment for sociodemographic factors and medical comorbidities (adjusted OR 1.38, 95% CI 1.09-1.76).128
5. Research Design and Methods

5.1 Introduction

**Conceptual Model:** The primary hypothesis is that CBT is superior to supportive clinical management (SCM) for depression, HF self care, and quality of life. Depression interferes with self care and contributes to functional impairment. It decreases self-efficacy for HF self care and for other adaptive activities. Inadequate self care affects functional outcomes directly (e.g., by decreasing physical activity) and indirectly (e.g., by delaying medical care), and fosters illness beliefs that contribute to hopelessness and helplessness. Physical inactivity accelerates aerobic deconditioning, increases dyspnea and fatigue, and decreases self-efficacy for self care. Depression and functional decline are associated with poor QOL and shortened survival.

Conceivably, intervention at any point in this complex of maladaptive cognitions and behaviors might suffice to improve all of the primary outcomes. However, the intervention targets multiple points, so that gains in each domain will reinforce gains in others.125 Beck’s cognitive model51-56, 130-132 is the principal basis for CBT, including cognitive modification strategies such as identifying and challenging dysfunctional health beliefs. CBT includes other elements such as problem-solving and behavioral activation. Behavioral activation plays a central role in promoting physical and social functioning and is a key ingredients of CBT for depression.99 Physical activity and exercise have also been shown to improve mood in depressed patients.104

Self-efficacy is a key mediator of self care interventions.52, 53 Bandura’s social learning theory is the foundation of approaches to enhancing self-efficacy.133-136 This theory incorporates social influences on self-efficacy expectations and other cognitions137 and is the basis for intervening indirectly in self-efficacy, e.g., working with caregivers to help them provide support to enhance the patient’s self-efficacy for self care.

Cognitive-behavioral techniques can also be used to promote self care. The problem-solving component of CBT is important in this regard, as it helps patients and caregivers cope with the demands of multimorbidity; e.g., many HF patients also have hypertension, renal insufficiency, diabetes, and other conditions that pose competing demands on time, effort, and coping resources. CBT incorporates problem-solving techniques that help patients and caregivers develop more efficient and less stressful strategies for managing the demands of chronic multimorbidity. This is especially important for depressed HF patients, since depression itself is yet another comorbidity, and it is one that makes it more difficult to cope with all of the others.

The main disadvantage of testing a multifaceted intervention is that some of its putatively therapeutic ingredients may be redundant or inert. Our pilot study experience suggests that all of the ingredients are likely to be helpful. Nevertheless, if the proposed trial is successful, dismantling studies will be needed to address this question.138 We will conduct process analyses to determine which components of the intervention have the strongest relationships to the primary outcomes, in order to inform subsequent dismantling trial proposals.

**Design Overview:** The proposed study is a two arm, single-blind, randomized, controlled clinical trial. Patients who have been hospitalized for HF, and cardiology outpatients who are being treated for HF, will be screened for eligibility. Eligible patients will be in NYHA Class I-III HF that has been present for >3 months, and will screen positive either for DSM-IV major depression or for minor depression with a past history of major depression. Patients who meet these criteria and who agree to participate will complete a baseline evaluation and then be randomly assigned to CBT or to SCM. All participants will receive HF education, and those who meet the DSM-IV criteria for major depression will be advised to discuss this disorder with their own physician. The aims of the cognitive-behavioral intervention are to decrease depression and improve HF self-care, functioning, and QOL. Participants in the intervention arm will receive up to 6 months of weekly CBT, and maintenance therapy between 6 months and 1 year after randomization. A follow-up evaluation will be conducted at 6 months, and a more limited evaluation will be conducted at 1 year. Follow-up assessors will be blinded to participants’ group membership. Participants will also be asked to complete several self-report questionnaires on a regular basis throughout the study. Rehospitalization data will be collected for 12 months, and mortality data on all participants will be collected until the end of the follow-up phase of the study.

5.2 Subjects

The sample will consist of 240 patients who meet all of the following inclusion criteria: 1) Heart failure clinically diagnosed at least 3 months prior to screening; 2) HF diagnosis confirmed by the Framingham Criteria139, via review of the patient’s medical records; 3) currently in NYHA Class I, II, or III; 4) meets the DSM-IV criteria for a current major depressive episode, or for current minor depression with a past history of at least one major depressive episode; and 5) scores ≥14 on the Beck Depression Inventory (BDI-II)140.
The Framingham Criteria for Heart Failure require the simultaneous presence of ≥2 major criteria, or 1 major criterion plus ≥2 minor criteria. The minor criteria must not be attributable to another medical condition. The major criteria are: 1) paroxysmal nocturnal dyspnea, 2) neck vein distension, 3) rales, 4) radiographic cardiomegaly, 5) acute pulmonary edema, 6) S3 gallop, 7) increased central venous pressure (>16 cm H\textsubscript{2}O at right atrium), 8) hepatojugular reflex, and 9) weight loss >4.5 kg in 5 days in response to treatment. The minor criteria are: 1) bilateral ankle edema, 2) nocturnal cough, 3) dyspnea on ordinary exertion, 4) hepatomegaly, 5) pleural effusion, 6) decrease in vital capacity by ≥ 1/3 of peak, and 7) tachycardia.

The New York Heart Association (NYHA) functional classification categorizes the functional severity of HF as: Class I (very mild); no limitation of physical activity. Class II (mild); slight limitation of physical activity, ordinary physical activity results in fatigue, palpitations, or dyspnea. Class III (moderate); marked limitation of physical activity, light activity causes fatigue, palpitation, or dyspnea. Class IV (severe); unable to carry out any physical activity without discomfort, symptoms of cardiac insufficiency at rest; discomfort increases if any physical activity is undertaken. Most enrollees will be in Class II or III. Although patients in Class I have minimal functional impairment attributable to HF, they will have significant functional impairment attributable to depression in order to meet the study criteria for depression. Patients in Class IV will be ineligible; they are too ill for behavioral activation and lack the endurance needed to cooperate with the study.

Patients meeting any of the following exclusion criteria will be ineligible: 1) Exclusion by the patient’s own physician; 2) dementia or other significant cognitive or communication deficits; 3) major mobility-limiting physical disability, 4) poor one-year prognosis due to a condition other than HF, 5) insurmountable logistical barriers to participation in laboratory assessment visits, 6) <30 years old, 7) alcoholism or substance abuse, bipolar disorder, schizophrenia, or other psychotic disorder, 8) high risk of suicide, 9) current participation in non-study psychotherapy or counseling for depression or other psychiatric problems, 10) initiated antidepressant therapy in the past 8 weeks, and 11) hospitalized for HF or ACS in the past month.

5.3 Recruitment, Screening, and Measurement

5.3.1 Recruitment Procedures

**Inpatients** who have been admitted with HF to a cardiology unit at Barnes-Jewish Hospital (BJH) or Christian Hospital (CH) will be identified via systematic surveillance of admission lists. Partial waivers of HIPAA authorization for screening and recruitment purposes will be sought for this purpose from the WUMC Human Research Protection Office and from the CH Institutional Review Board. The study recruiters will seek the attending physician’s written permission to approach patients identified as potential study candidates. With permission, the recruiter will briefly explain the study to the patient and provide a study brochure. Patients who express interest in the study will be asked to call our center after hospital discharge to initiate telephone screening. Permission will be obtained to contact patients who do not call us within 1 week of discharge.

**Outpatients** with HF will be identified, with the written permission of the patients’ physicians, from the heart failure clinics, general cardiology clinics, and cardiology faculty group practices that are part of the Barnes-Jewish-Christian (BJC) health care network, the largest in the St. Louis metropolitan area. We will place study recruitment posters and brochures at these sites, and work with the staff to facilitate physician referrals. The brochures will describe the study and ask interested patients to call our center to initiate a telephone screening session. We will also seek permission to place study brochures at other major cardiac care facilities in St. Louis. Potentially eligible patients may also hear about the study via publicity, e.g., when it is posted on WUMC web sites that publicize RCTs. Our recruiters will respond to inquiries and provide brochures.

**Local Heart Failure Population:** Over 600 new cases of HF are treated each year at WUMC, and at least 2,000 additional, existing cases are followed annually. There are >200 incident cases at CH each year. The overall community prevalence of HF is approximately 2%; it increases with age, ranging from about 2-3% from ages 60-69, about 5% from 70-79 and about 9% among individuals >80 years old. Minor or major depression is present in over 30% of patients with HF. Thus, this is a large population.

5.3.2 Screening Procedures

Screening procedures will ensure a high probability that patients who screen positive for eligibility will be confirmed as eligible at baseline. During the initial telephone screening, the study will be explained again, and any questions that the patient has about it will be addressed. With the patient’s permission, the study may also be discussed with the patient’s spouse, other family members, or other caregivers.
The recruiter will then administer 1) a screening form to determine whether the patient meets any exclusion criteria; 2) the Patient Health Questionnaire (PHQ-9)\textsuperscript{143} depression screening instrument; and 3) a brief psychiatric history interview to probe for past episodes of MD and for past or current treatment of depression. If the patient screens positive on the PHQ-9 for major depression or for minor depression with a past history of major depression, and does not meet any exclusion criteria, a baseline evaluation appointment will be scheduled, along with a pre-visit telephone call. An echocardiography appointment will also be scheduled in conjunction with the baseline evaluation, if the patient has not had a usable clinical echocardiogram within the past 12 months. An IRB-approved consent form, a self-report version of the PHQ-9, and a copy of the BDI-II will be mailed to the patient. The patient will be asked to complete the questionnaires 1-2 days prior to the scheduled visit. The baseline evaluation will be postponed or cancelled unless the patient continues to screen positive for minor or major depression, and scores $\geq 14$ on the BDI-II. With the patient’s permission, the patient’s primary caregiver will be invited to participate and asked to sign a separate, IRB-approved consent form. Although we will encourage caregivers to participate in the study, consenting patients will be allowed to participate regardless of whether their primary caregiver also agrees to participate.

\subsection*{5.3.3 Baseline Evaluation}

**Depression Interview:** The Depression Interview and Structured Hamilton (DISH)\textsuperscript{120} will be administered at baseline to determine whether 1) the patient meets the DSM-IV criteria for a current major depressive episode or a current minor depressive episode with a past history of major depression; 2) the depressive symptoms are causing significant impairment in one or more important areas of functioning; and 3) the patient does not meet any psychiatric exclusion criteria. The current version of the DISH also incorporates 1) assessments of generalized anxiety disorder and panic disorder; 2) the 17-item Hamilton Rating Scale for Depression (HAM-D)\textsuperscript{144}, the Hamilton Anxiety Rating Scale\textsuperscript{145}, and the clinician-rated version of the Inventory of Depressive Symptomatology (IDS-C)\textsuperscript{146}. The DISH Functional Impairment Supplement (FIS), developed for our previous HF studies, will also be administered to obtain data on functional limitations, daily activities, exercise, and other health behaviors. The DISH usually requires about 60 minutes for depressed patients. If the results indicate that the patient is ineligible to participate, the baseline evaluation will terminate at this point. If the results confirm eligibility, the remaining portions of the baseline evaluation will be completed.

**Echocardiogram:** If the patient has not had a clinical echocardiogram in the past 12 months, one will be obtained. Transthoracic two-dimensional, Doppler, and color flow echocardiography will be performed in 4 standard views (parasternal long- and short-axis, and apical 4- and 2-chamber views.) Images will be digitized for off-line analysis. Studies will be performed by experienced cardiac sonographers to ensure optimal visualization of the LV endocardial borders and cardiac chambers. LV volume and EF will be calculated by the method of summation of disks (modified Simpson’s rule) from the apical four-chamber view at end-expiratory end-diastole and end-systole at end-expiration. Other data will include LV mass, cardiomyopathy classification, RV function, pericardial effusion, E/A wave measures, and valvular stenosis and regurgitation. The primary echocardiographic measure is left ventricular ejection fraction (LVEF). Diastolic function (e.g., E/A ratio) measures are also of interest, as diastolic dysfunction contributes to exercise intolerance in HF.\textsuperscript{147-149}

**Blood Tests:** Blood samples will be drawn in the morning to minimize circadian variation. Patients will recline and rest for 10 min. prior to the blood draw. The assays will be performed by Quest Diagnostics, Inc.

B-Type Natriuretic Peptide (BNP): B-type natriuretic peptide is secreted by the ventricles in response to end-diastolic pressure and volume.\textsuperscript{150} BNP is widely used for HF diagnosis and risk stratification.\textsuperscript{151} Its diagnostic odds ratio for systolic HF is 11.6 (95% C.I., 8.4-16.1) against a criterion of LVEF $\leq 40\%$. When tested against clinical HF criteria, OR=$30.9$ (95% C.I., 27.0-35.4). Each $100$ pg/ml increase in BNP is associated with a $35\%$ increase in the relative risk of death among patients with HF.\textsuperscript{152} BNP levels also correlate inversely with 6-minute walk test performance in patients with heart failure.\textsuperscript{153}

Despite high sensitivity and prognostic value, BNP has modest specificity\textsuperscript{139} and relatively high intra-individual biologic variation over time. Although numerous studies have demonstrated statistically significant declines in BNP associated with clinical improvement, studies with longer-term monitoring patients with HF have yielded changes in BNP that do not exceed the level of intra-individual biological variance.\textsuperscript{151} Thus, it may be difficult to detect clinically significant differences in BNP, so it will be evaluated as a secondary outcome. BNP is also needed to characterize the sample, and it is the only marker of HF severity that is feasible to obtain both at baseline and at 6 months; it will be used as a time-dependent covariate for other analyses. A $\geq 1$ mL blood sample will be collected in a 5ml EDTA lavender-top plastic tube and centrifuged within 30 min at 1,500g for 20 min. Plasma will be separated, pipetted into a plastic container, and frozen for transport.
High-Sensitivity C-Reactive Protein (hs-CRP): CRP is produced by hepatocytes in response to IL-6 and other pro-inflammatory cytokines. It increases during inflammatory responses to injury or infection.\textsuperscript{154} It has been studied in relation to coronary heart disease\textsuperscript{155, 156} and heart failure.\textsuperscript{157} Despite some negative studies\textsuperscript{6-9, 158}, many studies have also shown that CRP is associated with depression and is markedly elevated in major depression.\textsuperscript{159-165} CRP has attracted considerable interest as a candidate mediator of the relationship between depression and adverse outcomes in heart disease.\textsuperscript{163, 166-170} Although CRP increases acutely during exercise, regular exercise is associated longitudinally with lower CRP.\textsuperscript{171} Furthermore, there is evidence of a moderately strong inverse correlation between CRP and aerobic capacity in HF.\textsuperscript{172} We therefore propose to test the effect of the intervention on CRP as a secondary hypothesis. A 500 ml blood specimen will be collected for the hsCRP assay in a plain red top tube. The sample will be centrifuged within 30 min at 1,500 x g for 20 min. The serum will be separated, pipetted into a plastic container, and kept at room temperature for transport.

Basic Metabolic Panel (BMP): The BMP includes glucose, calcium, sodium, potassium, CO2, chloride, blood urea nitrogen (BUN), and creatinine. Several of these tests are particularly relevant in heart failure. Creatinine and BUN levels predict mortality in ambulatory patients with chronic HF\textsuperscript{173-175}, and sodium levels predict short-term mortality in patients hospitalized with worsening HF.\textsuperscript{176} A 4.5 ml sample will be drawn in a lithium heparin tube. The sample will be centrifuged within 30 min at 1,500 x g for 20 min. The plasma will be separated and pipetted into a plastic screw cap container and kept at room temperature for transport.

Complete Blood Count (CBC): A CBC will also be obtained. Anemia has been shown in several large studies to predict mortality and other medical outcomes in HF.\textsuperscript{177-183} It also correlates with functional impairment in HF, and even mild anemia is associated with worse symptoms, impairment, and mortality.\textsuperscript{184} A 5 ml blood sample will be collected in an EDTA lavender-top tube and kept at ambient temperature for transport.

6-Minute Walk Test (6MWT): The 6MWT, a well-validated submaximal exercise test, is used extensively in HF research.\textsuperscript{185, 186} It has excellent test-retest reliability when carefully standardized. In RESOLVD, 768 patients were tested twice at baseline and at 18 and 43 weeks. The intraclass correlations for the repeated tests were 0.90, 0.88, and 0.91, respectively.\textsuperscript{187} Its reliability has been confirmed in other studies.\textsuperscript{3, 188, 189}

As a submaximal test, the 6MWT corresponds more closely than maximal exercise stress testing to the demands of daily activities.\textsuperscript{187, 190, 191} It also has prognostic value in HF. In the Studies of Left Ventricular Dysfunction (SOLVD) Registry Substudy, the 6MWT and LVEF were equally strong predictors of mortality and HF rehospitalization in 898 patients over an average of 242 follow-up days.\textsuperscript{26} This has also been demonstrated in smaller studies. For example, a measure of LV dysfunction and 6MWT distance were two strongest predictors of survival in 214 patients with mild to moderate HF over an average of 34 months of follow-up.\textsuperscript{186} Evidence concerning the 6MWT’s sensitivity to change and its utility as an outcome measure is not as consistent. In pharmacological trials, significant effects on the 6MWT are more common for patients relatively severe HF and for interventions that also produce significant improvement in symptoms.\textsuperscript{2}

In contrast, the 6MWT has proven to be more consistently sensitive to change in studies involving exercise. Several RCTs have used it as an outcome measure and have detected group differences. A recent RCT compared a 12-week, home-based, walking exercise program to UC in 79 patients with HF, most of whom were in Class II. The exercise group improved significantly more than the UC group on the 6MWT (1337+272 vs 1264+255 feet, p=.001).\textsuperscript{5} In an RCT of a low intensity, home-based exercise intervention vs a health education control condition in 32 women in Class II/III HF with preserved systolic function, there was more improvement on the 6MWT in the intervention than the control group (840 +/- 366 ft to 1043 +/- 317 ft in the exercise group, vs. 824+367 ft to 732+408 ft in the control group; p=.002).\textsuperscript{40} In an uncontrolled, 12 week trial of exercise training in 30 elderly men with Class III HF, the 6MWT distance increased by 8.1% (p<.001).\textsuperscript{191}

The Exercise Rehabilitation Trial (EXERT) is a notable exception. This trial randomly assigned 181 patients in Class I-III systolic HF to 3 months of supervised exercise plus 9 months of home exercise, or to usual care. There were significant increases in 6MWT distance in the exercise (22+5 meters) and control (15+5 m) groups at 3 months (p<.01), and again at 12 months (17+8 m vs 20+9 m; p<.05). Although trends were evident, no significant between-group differences were found at either time.\textsuperscript{33} Similarly, our own pilot study (n=37) showed favorable trends toward between-group differences at 6 months, but they were not statistically significant.

Participants will complete a carefully standardized 6MWT on a measured course. The walk test will follow the echocardiogram, if one is obtained. The baseline and 6-month walk tests will be performed at approximately the same time of day to minimize extraneous variance due to circadian variability in oxygen uptake and heart rate,\textsuperscript{188} will follow a standardized (Guyatt) symptom-limited protocol in which no encouragement is given.\textsuperscript{185} This provides a more representative sample of typical performance than alternate protocols that provide encouragement. Staff who conduct the 6MWT will be blinded to group assignment.
**Actigraphy**: An actigraph is a wristwatch-like accelerometer that measures the frequency, intensity, and duration of physical activity. Unlike the 6MWT, actigraphy measures activity patterns rather than submaximal physical performance. It has been used to study activity and sleep patterns in many different populations, including in HF. A recent study of 39 patients with mild-to-moderate HF, 22 of whom also had sleep apnea and 17 of whom did not, used actigraphy to study 24 hour activity patterns. In addition to nighttime and sleep-related actigraphic differences, the sleep apnea group had lower daytime activity duration (15.2±1.2 h vs 16.3±1.0 h; p<.01) and total daytime activity counts X 10^4 (2.3±8.1 vs 2.9±9.7; p=.06). Actigraphy was also used in a recent study of 58 patients with stable systolic HF. The mean daytime activity count/min. was 54.4±23.0. Daytime activity correlated with age (r=-.28), NYHA class (r=-.37), time in bed (r=-.31) and wake time (r=-.32). Actigraphy has also been used in research on depression. For example, it was recently used to compare activity levels in 16 patients with fibromyalgia, 6 fibromyalgia patients with comorbid depression, 9 with recurrent major depression, and 28 healthy controls. The mean ± s.e. daytime activity levels in these groups were 191.4±8.5 vs. 148.4±9.7 vs. 182.4±7.8 vs. 192.4±4.3. The activity level in the fibromyalgia with comorbid depression group was significantly lower than the levels in all 3 of the other groups.

Other studies have examined the effects of depression treatment on activity levels. For example, in a recent study of 17 outpatients with seasonal affective disorder (SAD) and 17 matched controls, the SAD group had 43% lower daytime activity at baseline than the controls (p=.006). The activity level increased significantly in the SAD group over 4 weeks of treatment but did not change in the control group (p=.001). As another example, activity levels were studied in 25 patients with major depression treated with imipramine, and 27 treated with fluvoxamine. The metric used in this study was a percentage calculated as the number of activity counts per epoch divided by the maximum possible count. At baseline, the percentages were 6.7±3.2 in the imipramine group and 7.3±3.5 in the fluvoxamine group. After 4 weeks of treatment, there was significantly increased activity in the imipramine (8.6±3.5) but not the fluvoxamine (7.4±3.7) group (p<.001).

These examples illustrate the effects that depression can have on activity levels, both in otherwise healthy individuals and in medically ill patient groups. They also illustrate the effects that treatment of depression can have on activity levels. As discussed in section 4.1, our pilot study results also suggest that baseline activity levels can be maintained for at least 6 months in depressed patients with HF, by treatment with CBT.

The participants will be given an actigraph (Respironics Actiwatch AW-16) to wear on their nondominant wrist for 7 days, starting at the baseline visit. They will be asked to wear the device 24 hours a day. The unit is waterproof, so it can be worn while bathing. If patients elect to remove the device during bathing or at other times, they will be instructed to press the event button. The participants will also be asked to maintain a simple, structured, activity log during the actigraphy week. The log has been used in previous studies.

The device will be programmed to record motion at 1 minute intervals. The recording threshold will be configured per manufacturer instructions for collection of activity counts. Participants will be asked to return the device and the log in a prepaid mailer. The data will be downloaded and edited at our lab. The data files will be sent to the Biostatistics Consulting Center for analysis by Dr. Shannon’s group.

**Self-Report Questionnaires – Primary Outcomes**

*Beck Depression Inventory (BDI-II):* The BDI-II is a 21-item measure of depression symptoms. The items assess individual symptoms on a 0-3 scale, for a total score range of 0-63. The BDI-II is one of the most widely used depression measures and is used extensively in research on depression in patients with heart disease.

*Self-Care of Heart Failure Index (SCHFI):* The SCHFI is a 15-item self-report measure that assesses the frequency of HF self-care maintenance practices such as weight monitoring and physical activity; HF self-care management behaviors such as symptom recognition and treatment initiation; and self-confidence about the ability to perform HF self-care. Each item is rated on a 1-4 scale. Scores are transformed so that the maximum subscale score is 100 and the maximum total for the entire SCHFI is 300. The SCHFI was tested on 760 HF patients (age 70.4±12 years, 51% male; 16% Class I, 19% Class II, 50% Class III, 15% Class IV) from 7 sites across the U.S. Total SCHFI Index scores were 192±42 (range, 80-268); subscale scores were 67±17 for self-maintenance, 61±21 for self-management, and 65±17 for self-confidence. Confirmatory factor analysis confirmed the predicted subscale structure. The reliabilities of the total SCHFI score (alpha=.76), Self-Care Management subscale (.70) and Self-Care Self-Confidence (.82) scales were adequate. The reliability of the Self-Care Maintenance subscale (.56) was lower because of high endorsement on one item (“Getting a flu shot every year.”) Reliability increased to .60 when this item was omitted. Because the subscale reliabilities are not as high as the total score reliability, it will use only the SCHFI total score as an outcome measure. The SCHFI is similar in some ways to the Sullivan et al. Cardiac Self-Efficacy Scale (CSEQ) that we used in our pilot study. Like the SCHFI, the CSEQ assesses the patient’s confidence in his or her ability to control symptoms and maintain functioning. However, the CSEQ was intended primarily for patients with CHD.
Kansas City Cardiomyopathy Questionnaire (KCCQ): The KCCQ\textsuperscript{8} is now the leading measure of heart failure-related quality of life. It is a 23-item self-report questionnaire designed to assess physical limitations, symptoms, self-efficacy, social interference, and quality of life in patients with HF. Scores range from 0-100, with higher scores representing better perceived health and QOL. It is a reliable, well validated instrument that has been used in a number of clinical trials, prognostic studies, and other investigations of HF. Recent studies show that it is more sensitive to change than the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), the SF-12, and the SF-36.\textsuperscript{9,10}

Self-Report Questionnaires – Secondary Outcomes

SF-12: The 12-item Medical Outcomes Study Short-Form Health Survey\textsuperscript{196} is a widely-used measure of health-related quality of life. The items were derived from the SF-36. The SF-12 Physical and Mental component scores correlated 0.91 and 0.94 with their SF-36 counterparts. The 2-week test-retest correlations were 0.89 and 0.76 for these scores. The median validity estimates for the SF-12 Physical and Mental scores were 0.67 and 0.97, respectively. We used the longer SF-36 in our pilot study, but we will use the SF-12 in this trial to reduce subject burden. Based on the pilot study, we predict that the Physical score will not differ significantly, but the Mental component score will be \geq 20\% higher in the CBT than the SCM arm at 6 months.

PROMIS Physical Functioning Questionnaire (PFQ): The PROMIS Physical Functioning Questionnaire (PFQ) measures the physical component of general health-related QOL.\textsuperscript{12-14} To minimize respondent burden, we will utilize the computerized adaptive testing (CAT) version. It will either be self-administered or interviewer-administered, depending upon whether the patient is able to use a computer. In most cases, the patient’s score will be based on approximately 3 to 4 items.

Health Behavior Diary: A structured health behavior diary (HBD) will be used to assess adherence to prescribed medications, diet, exercise, and other self care behaviors. The HBD is currently being used at our lab in a study of recovery from acute coronary syndrome. Minor modifications will be needed to make it suitable for patients with HF. For example, an item pertaining to self-monitoring of edema will have to be added. The HBD is a web-based form that can be completed at home by patients who are comfortable with using computers and the internet. Other patients will be given a notebook with blank HBD forms that will be reviewed during brief, monthly follow-up calls. Based on our current studies, we expect at least 50\% of the participants to opt for the web-based version.

Beck Anxiety Inventory (BAI): The BAI\textsuperscript{199,200} is a widely-used, 21-item anxiety questionnaire, that assesses self-reported anxiety symptoms over the past week. Each item is rated on a 0-3 scale, so that the total scores can range from 0-63. The score ranges are interpreted as: 0-9, normal level of anxiety; 10-18, mild-moderate anxiety; 19-29, moderate-severe anxiety; 30-63, severe anxiety. According to these ranges, the average patient in the CBT arm of our pilot study improved from moderate-severe to normal anxiety over 6 months.

Caregiver Burden: Two measures will be administered to consenting primary caregivers to determine whether there is equivalent caregiver burden between groups at baseline, and to determine the effects of the intervention on caregiver burden. The 12-item short form Zarit Burden Interview\textsuperscript{201,202} was originally developed for caregivers of individuals with Alzheimers disease; it is also used in research on other chronically ill elderly populations including HF patients. Each item is self-rated on a 0-4 scale; higher scores represent heavier burden. The SF-12 has also been used in recent studies to assess QOL in caregivers of HF patients.\textsuperscript{203,204} It will be administered along with the Zarit scale.

5.3.4 Six-Month (Post-Treatment) Evaluation

All of the patient and caregiver measures except the echocardiogram will be repeated at 6 months. The 6-month evaluation will be conducted in the morning to minimize circadian variability in biomarkers and 6MWT results. The assessment staff will be blinded to the patient’s group assignment. The actigraphy and questionnaire procedures at 6 months will be identical to those described above for the baseline assessment.

5.3.4 Interim and 12-Month Self-Report Assessments

As discussed above, the participants will be asked to complete the self-report questionnaires at baseline and 6 months, including the BDI, SCHFI, KCCQ, BAI, SF-12, and PROMIS PFQ. They will also be asked to complete the same questionnaire battery at 3 and 9 months. Caregivers will repeat the Zarit and SF-12 scales at 12 months. The complete assessment schedule is displayed in Table 2.
5.3.5 Medical Outcomes

Participants will be contacted by telephone at 3, 6, 9, and 12 months to obtain self-report measures and to identify changes in medical care and hospitalizations. Medical records will be obtained to document hospitalizations. Date of death will be documented for deaths that occur with the 4.5 year follow-up phase.

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<th>Measure</th>
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<th>6 Mo.</th>
<th>9 Mo.</th>
<th>12 Mo.</th>
<th>&lt;4.5 year Follow-up</th>
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Table 2. Assessment schedule. *The screening BDI-II will also be used as the baseline measure of self-reported depression, since it will be obtained 1-2 days before the baseline visit. The baseline and 6-month laboratory visits will include the DISH, blood tests, 6MWT, and initiation of one week of actigraphy. **The baseline visit will also include a research echocardiogram, if the patient has not had a suitable clinical study in the past 12 months. Participants will be given instructions at the baseline visit in how to complete the self-report questionnaires. They will be asked to complete the questionnaires within 2-3 days of each scheduled visit or telephone follow-up contact. ***Participants will be asked to complete the HBD on a weekly basis throughout the first 6 months after randomization, and for one week at the 9mo. and 12mo. follow-ups.

5.4 Heart Failure Education and Medical Care Recommendations

Introduction: Participants in both groups will receive heart failure education and standard medical care recommendations. These will be brief, nurse-administered interventions to enhance the patient’s usual medical care, address any potential medical safety issues, and introduce the HF self-care educational materials.

Medical Care Recommendations: At baseline, a study nurse will review the patient’s medical records and interview the patient for further information on medical history, current health status, and medications. If problems are identified that have been clinically evaluated or that are not being treated (e.g., the patient has hypertension but is not currently taking any medications for it, or the patient has recently developed orthostatic hypotension but has not reported it to his or her physician), the nurse will advise the patient to discuss this with his or her own physician. The advice will be provided verbally and reinforced with a written reminder. The nurse will consult with the cardiologist co-investigator if there are any questions about these recommendations.

The DISH interview includes a thorough review of current and prior treatments for depression. If the DSM-IV criteria for major depression are met, the nurse will advise the patient to discuss this with his or her physician. Patients who screen positive for major psychiatric disorders (e.g., bipolar disorder or schizophrenia) will be excluded from participation in the trial and will be advised to discuss this with their physician. The nurse will consult with the psychiatrist co-investigator and/or the principal investigator if any questions arise.
Heart Failure Education: At baseline, the patient will be given HF education materials from the Heart Failure Society of America. There are 11 modules: 1) Taking Control of Your Heart Failure; 2) How to Follow a Low-Sodium Diet; 3) Heart Failure Medicines; 4) Self-Care: Following Your Treatment Plan and Dealing with Your Symptoms; 5) Exercise and Activity; 6) Managing Feelings About Heart Failure; 7) Tips for Family and Friends; 8) Lifestyle Changes: Managing Other Chronic conditions; 9) Advance Care Planning; 10) Heart Rhythm Problems; and 11) How to Evaluate Claims of New Heart Failure Treatments and Cures.

The modules range from 8 to 22 pages, including illustrations. It takes most patients no more than about 30 minutes to read even the longest modules. Both the patient and the primary caregiver will be advised to read the materials at their own pace, but they will be urged to complete them within 1 month. A cardiac nurse will contact the patient 1 week after the baseline visit, and again at 1 month. Each contact will last about 30 minutes. The nurse will discuss the educational materials and respond to the patient's and caregiver's questions about heart failure.

5.5 Randomization

Random assignment to CBT or to SCM will be performed after the completion of the baseline assessments. Thus, randomization will take place approximately 1 week after the baseline laboratory visit, after the patient has completed the self-report questionnaires and 7 days of actigraphy. SAS Version 9.1.3 software will be used to generate the random assignments. Permuted block randomization will be used to minimize transient imbalances between the CBT and SCM arms. The patient's study ID number will be entered into the FORMS system's menu-driven randomization utility program at the end of the baseline assessment week, and the program will return the group assignment. The nurse will then notify the patient by telephone. FORMS will also place the patient in the CBT or SCM treatment scheduling cue. The patient's group assignment will be concealed from the study personnel who will conduct the 6-month outcome evaluations.

5.6 Intervention Delivery Parameters

Contacts: Participants in both the CBT and the SCM arms will receive up to 6 months of individual contacts with an experienced therapist, plus 4 maintenance therapy contacts between the end of intensive treatment (EIT) and 12 months after randomization. Whenever possible, the treatment sessions will be held at our research clinic, but to facilitate participation, as many sessions as necessary will be conducted by telephone. The sessions will initially be scheduled on a weekly basis and last approximately 50 minutes. The minimum duration for a full therapeutic session is 20 minutes; any therapist contacts with the patient lasting <20 minutes will be classified as brief therapeutic contacts, brief administrative contacts (e.g., to reschedule an appointment), or other contacts. Interim contacts will be scheduled as needed for crisis management and for severe or worsening depression.

Treatment Process Data (TPD) Log: The P.I. developed a standardized treatment process data log for the ENRICHD trial and has utilized similar logs in several other studies. The therapists use the log to document therapy sessions, brief contacts, significant other contacts, missed or cancelled sessions, homework assignments, homework adherence, and data pertaining to the patient's clinical progress and the EIT criteria.

End of Active Treatment: EIT will occur at 6 months, or sooner if: 1) At least 12 weeks have elapsed since randomization; 2) at least 12 full CBT sessions have been completed; 3) the BDI-II score has been <14 for at least two weeks; 4) the BAI score has been <10 for at least two weeks. In the CBT arm, additional EIT criteria include: 5) the patient has met his or her behavioral activation and self care goals for at least 4 weeks; and 6) the patient has demonstrated adequate knowledge of CBT self-therapy and relapse prevention techniques. When the EIT criteria have been met, the frequency of therapeutic contacts will be decreased to: twice during the first month and once a month during the remaining months. The duration of post-EIT therapeutic contacts will be reduced to 20-30 minutes. One or two additional sessions, of up to 50 minutes, may be scheduled if the patient is having a relapse of depression, as indicated by a BDI-II score ≥14.

5.7 Cognitive Behavior Therapy

Rationale: CBT was originally developed for depressive and anxiety disorders, and its efficacy for these conditions has been demonstrated in numerous studies. As we discussed in a recent book, CBT has been adapted for use in a variety of medical patient populations, and it is used as an intervention in trials involving medical patient populations primarily because cognitive-behavioral principles and techniques can be applied to
a variety of problematic health-related behaviors and cognitions. It was adapted for the treatment of depression and low perceived social support in the ENRICHD trial. It was also tested as a treatment for citalopram-resistant depression in the STAR*D trial. It was as effective as other antidepressants, and better tolerated. Interpersonal therapy (IPT) is another form of psychotherapy that has empirical support as a treatment for depression. However, there is less evidence for IPT than for CBT, particularly in medically ill populations, and IPT was recently found to be ineffective for depression in patients with coronary heart disease.

**Protocol:** The intervention will follow widely accepted CBT principles and techniques. It will be manualized but flexible, and collaborative goal-setting and individual tailoring will be encouraged. It will be based on the following manuals: 1) *Cognitive Therapy: Basics and Beyond*, by J.S. Beck, PhD. This is one of the most widely used CBT manuals. It was the core treatment manual in the ENRICHD clinical trial, and we have used it in several subsequent clinical trials at our center. 2) *Cognitive Therapy For Challenging Problems: What To Do When The Basics Don't Work*, by Judith S. Beck, PhD. This manual complements Dr. Beck’s earlier book. This manual was very helpful in our pilot study, because of the complex and difficult problems with which most heart failure patients are confronted. 3) *Heart Disease*, by Judith A. Skala, PhD, Kenneth E. Freedland, PhD, and Robert M. Carney, PhD. This manual is part of the Hoegrefe series, Advances in Psychotherapy – Evidence-Based Practice. Its development was supported in part by Exploratory/Development Research Grant No. R21MH052629 from the National Institute of Mental Health. It focuses on how to apply CBT to patients with heart disease, with particular reference to treatment of depression, anxiety, and related problems.

The *Heart Disease* manual is particularly relevant to the proposed trial; e.g., it discusses cognitive-behavioral approaches to distressing cognitions about cardiac symptoms that are often associated with excess functional impairment. As another example, it discusses how to adapt behavioral activation techniques to cardiac patients to address safety concerns, to overcome barriers to resumption of normal activities, and to encourage participation in an exercise regimen that has been approved by the patient’s physician. It also provides several clinical assessment tools (discussed below) that are tailored for use with cardiac patients.

CBT is goal-oriented and problem-focused, emphasizes collaboration between the patient and the therapist, and encourages the active participation of the patient. These principles can be applied in the context of a clinical trial, but they have to employed in a manner that is consistent with the aims of the trial. It is relatively common for patients to enter CBT with tentative goals that would not help to further these aims. For example, some patients initially view therapy as an opportunity to complain about the health care system, rather than to work on clinically relevant problems or to work toward attainable goals. In the proposed study, it will therefore be necessary for the therapist to guide the collaborative goal-setting process toward specific trial objectives, including reduction of emotional distress, improvement of heart failure self-care, resumption of pleasurable and productive activities, and measurable increases in physical functioning.

The study’s Manual of Operations will delineate trial-specific elements of the treatment protocol. It will include modules focusing on heart failure self-care and physical functioning, designed to build on the nurse-directed health education intervention discussed in Section 5.4 above. To this end, the therapy team will read the HF patient education materials and several review papers and chapters on clinical aspects of heart failure, and will be given related inservice presentations by the cardiac nurse educator and cardiologist co-investigator.

Manualized protocols range from highly structured to very flexible. Highly structured protocols facilitate standardization and reproducibility but are not suitable for complex, individualized interventions that depend on collaborative goal-setting and on skilful treatment planning and decision-making. Flexible, semistructured protocols are more appropriate for interventions with these characteristics, such as our CBT protocol.

Although details will vary according to individual patient needs, the intervention will follow this general plan:

1. Initial clinical evaluation, induction into therapy, and collaborative goal-setting.
2. Contact with patient’s cardiologist and/or primary care physician for input on treatment planning, especially for behavioral activation and HF self care plans.
3. Initiation of the behavioral activation plan and introduction to activity-rest cycle management.
4. Integration of HF self care education and activity-rest into behavioral activation plan.
5. Modification of distressing automatic thoughts.
6. Applications of problem-solving techniques, especially for coping with multimorbidity and related stressors, challenges to self care adherence, and barriers to physical and social activation.
7. Focus on significant other / family relationship issues (e.g., caregiving, independence, role expectations, role fulfillment).
8. Modification of distressing or otherwise maladaptive attitudes and beliefs.
10. Maintenance phase consolidation of gains, application of skills to new problems.
Clinical Tools: A variety of instruments, such as the Dysfunctional Thought Record and its variants, are part of the standard “toolkit” of CBT. We have developed several instruments designed specifically for use in cognitive therapy for cardiac patients, and have utilized them in previous studies. The most commonly used instruments are discussed and reproduced in the *Heart Disease* manual. They include: 1) The CBT Problem List (PLIST). This form provides a structured format for collaboratively setting and prioritizing target problems. It also provides a set of patient ratings of each problem, e.g., “How willing are you to work on this problem with your therapist?” These items are rated on 4-point scales ranging from 0 (not at all) to 3 (very much). This form is especially useful in the setting of clinical trials, as it helps therapists harmonize the patient’s goals with the trial’s objectives. 2) The Cognitive Therapy for Cardiac Patients Treatment Planning Table. This form crosstabulates 12 different cognitive-behavioral mediators of change (e.g., behavioral activation) with 9 target-of-change categories, divided into two subcategories (Distress and Stressors.) Therapists use it as part of the individualized treatment planning process for each session, and also to track the delivery of the intervention. For example, a particular therapy session might focus on anxiogenic cognitive distortions about exertional dyspnea. In documenting the session, the therapist would check two cells in the mediator-of-change row pertaining to “identifying, challenging, and changing automatic thoughts and cognitive distortions; these cells would be in the Anxiety and Heart Disease columns. 3) The Dysfunctional Attitudes About Health scale. This 20-item questionnaire is a supplement to the widely-used Dysfunctional Attitudes Scale. Each item represents a common but distressing or otherwise maladaptive attitude about health, derived from a review of hundreds of cases. Examples include, “I can’t accomplish anything if I’m sick,” “I have to put other people’s needs first, even if doing so might hurt my own health,” and “It’s useless to try to stay healthy, because people get sick no matter what they do.” This questionnaire is usually administered around the 3rd session to clarify health-related attitudes that may be contributing the patient’s distress and that could potentially interfere with beneficial health behavior change. It is usually re-administered near the end of intensive treatment.

Clinical Supervision of CBT: The therapists will be professionals with extensive prior training and experience with CBT. However, even highly experienced therapists require clinical supervision when delivering manualized interventions in the setting of a clinical trial, to ensure protocol adherence. The P.I. is an experienced cognitive behavior therapist and therapy supervisor, and a Founding Fellow of the Academy of Cognitive Therapy. He will hold weekly, two-hour, CBT supervision meetings during the first 6 months of the trial, after which the frequency will be reduced to biweekly. The first hour of each meeting will include case presentations, clinical problem-solving, and protocol adherence reviews. In the second hour, the supervisor and therapists will listen to an audio recording of a recent treatment session and independently code it on the NIMH Collaborative Study Psychotherapy Rating Scale (CSPRS). They will also discuss protocol adherence questions about the session, if there are any.

5.8 Supportive Clinical Management

Rationale: The primary purpose of the supportive clinical management (SCM) condition is to control for the clinical attention that will be given to the participants in the CBT arm of the trial, along with other standard threats to internal validity. Both groups will continue to receive usual care during the trial for heart failure, depression, and other comorbidities. Usual care will be enhanced in both arms with nurse-directed HF education and recommendations to consult with a physician if major depression is diagnosed or if medical problems are identified. SCM controls for attention by providing supportive discussions of the patient’s depression, HF and other medical problems, and other salient stressors. Most of the support will be nondirective, but directive support will be provided when indicated. For example, when patients are unsure about whether to contact their physician about worsening HF signs or symptoms, the therapist will advise them to do so.

Attention control conditions (also known as common factor or nonspecific treatment controls) must encourage an expectancy of positive gains, on the part of the patient as well as the therapist. This is generally achieved by providing the patient with a description of the rationale for supportive clinical management, actively listening to the patient’s problems and concerns, and providing emotional and informational support. This helps to equate the demand characteristics of the groups.

The SCM attention control condition proposed for this trial is a modified version of the clinical management condition that was developed for the NIMH Treatment of Depression Collaborative Research Program (TDCRP). A similar control condition, also based on the TDCRP approach, was recently employed in the Canadian Cardiac Randomized Evaluation of Antidepressant and
Psychotherapy Efficacy (CREATE) trial, which evaluated citalopram and interpersonal psychotherapy for depression in patients with stable coronary artery disease.208, 220

The core treatment manual for the SCM condition will be the TD CRP Clinical Management Manual.221 Unlike CREATE and the TDCRP, there are no antidepressant or pill placebo arms in this trial. Consequently, the protocol will be modified to address non-study rather than study medications. This includes both the patient’s nonstudy antidepressant (if he or she is taking one), and his or her nonstudy medications for HF and for medical comorbidities. In the manualized protocol, the first session focuses primarily on establishing a positive relationship with the patient, reviewing symptoms of depression, and providing a rationale for the intervention. Relationship-building, symptom and medication reviews, and encouragement continue to play a role in subsequent sessions. To differentiate clinical management from CBT or IPT, the manual prescribes certain interpersonal processes and interventions, and prohibits others. Prescribed approaches include: 1) attention to interpersonal context factors, e.g., providing reassurance if the patient feels criticized by family, friends, or peers for being depressed or debilitated; 2) psychological support and conveyance of a sense of hope and optimism; 3) instruction, education, and information giving about depression (and, in this case, coping with medical illness); 4) advice, e.g., about how to resolve stressful situations; and 5) providing the patient with opportunities to “ventilate” about feelings, fears, doubts, etc. Prohibited approaches include: 1) extended focus on specific psychological themes, especially interpersonal relationships and cognitive distortions; 2) psychological interpretation of interpersonal events, feelings, losses, or cognitions; 3) clarification of the patient’s feelings towards others or toward the therapist; 4) specific behavioral instructions; 5) psychodynamic explanations of depression; and 6) extended interpersonal interactions outside of the therapeutic context.

Clinical Supervision of SCM: The therapists will be professionals with extensive prior training and experience with supportive psychotherapy. In clinical trials, however, even highly experienced therapists require clinical supervision to ensure protocol adherence. Dr. Carney (co-investigator) is an experienced psychotherapist and therapy supervisor. Mirroring the CBT supervision procedures discussed above, Dr. Carney will hold weekly, two-hour, SCM supervision meetings during the first 6 months of the trial, after which the frequency will be reduced to biweekly. The first hour of each meeting will include case presentations, clinical problem-solving, and protocol adherence reviews. In the second hour, the supervisor and therapists will listen to an audio recording of a recent treatment session and independently code it on the NIMH Collaborative Study Psychotherapy Rating Scale (CSPRS).215 They will also discuss protocol adherence questions about the session, if there are any.

5.9 Assessment of Therapists’ Protocol Adherence

The CSPRS215 was designed to assess therapy protocol adherence in the NIMH Treatment of Depression Collaborative Study. One of its subscales assesses adherence to the CBT protocol, and another assesses adherence to the Clinical Management (CM) protocol. As discussed above, CSPRS ratings will be obtained as part of the clinical supervision process. In addition, the CBT supervisor (KEF) will rate 5 of the session recordings for each of the SCM therapists, and the SCM supervisor (RMC) will rate 5 recordings for each of the CBT therapist, for a total of 20 recordings to be independently rated by both clinical supervisors. The ratings will then be averaged between the supervisors. If the therapists adhere to their respective treatment protocols, the CBT therapists will have higher scores than the SCM therapists on the CBT scale. The SCM therapists may have somewhat higher scores than the CBT therapists on the CM scale. However, the CBT therapists should not score too low on the CM scale because it includes some of the key “common” or “nonspecific” factors that are part of most forms of psychotherapy, including CBT. Thus, we would expect high CM scores for the SCM therapists and average to moderately high CM scores for the CBT therapists.

5.10 Caregiver Contacts (CBT and SCM Arms)

Rationale: The burden of caregiving affects both the caregiver and the patient.204, 222-226 The emotional well-being of the caregiver affects the emotional and functional status of the HF patient.203 Caregiver support can influence chronic illness self care, mood, and functioning in both positive and negative ways.227 The caregiver component of the intervention will be based on Fisher’s model of social support in chronic illness.228-230 Fisher differentiates between directive and nondirective support.
Examples of the former include performing tasks for the patient, giving instructions, or telling the patient how to respond to a medical development. Examples of the latter include assisting the patient’s efforts to perform tasks, facilitating patient decision-making, and expressing empathy.

Both kinds of support can be helpful or counterproductive, depending on the circumstances; e.g., a patient may need more directive support during the first week after hospital discharge, but may begin to resent it unless there is a timely transition to more nondirective support as the patient’s functional capacity improves. Mismatched support can create friction between patients and caregivers and contribute to patient beliefs about helplessness or worthlessness. It also increases caregiver stress, which can redound on the patient’s sense of isolation and role failure.

Intervention: Caregivers can benefit from supportive interventions. Thus, with both the patient’s permission and the caregiver’s consent, the therapists in both the CBT and the SCM arms will include the primary caregiver in joint treatment sessions and/or have individual contacts with the primary caregiver on a monthly basis during the 6-month intervention phase. The therapists will encourage the involvement of consenting caregivers. As discussed elsewhere, the study recruiters will also work to enlist caregiver involvement during the recruitment and informed consent processes. Thus, caregiver participation is expected to be the rule rather than the exception.

Just as patients need the right mixture of nondirective and directive support, so do caregivers. The therapists will provide the balance of nondirective and directive support that best suits the individual caregiver. In the CBT arm (but not in the SCM arm), the therapist will also follow a protocol-based agenda that will include discussion of the patient’s depression, functional impairment, and HF self-care deficits, and the caregiver’s role in supporting the patient’s efforts to overcome these problems. They will collaboratively develop a plan for the caregiver to follow in helping the patient, with particular attention to the provision and timing of directive vs. nondirective support.

5.10 Statistical Analysis

5.10.1 Introduction

A trial of patients with HF and depression poses a high likelihood of attrition due to death, loss to follow-up, or noncompliance. Estimates of the expected attrition rates are presented in the power analysis section. We intend to follow the intent-to-treat (ITT) principle through the use of multiple imputation procedures that permit valid inferences when there are missing data that can be considered plausibly missing at random (MAR), i.e. the missingness is related to the observed outcome. Obsolete alternatives such as single imputation methods such as last observation carried forward (LOCF) or listwise deletion can bias treatment effect estimates. Data will be checked to ensure that model assumptions are met, and transformations will be applied as needed. Hypothesis tests will be two-tailed. There are 3 primary outcome measures (BDI, SCHFI, and KCCQ). To ensure family-wise control of the Type I error rate for the primary outcomes, we will set $\alpha$ at 0.05/3 = 0.016 per comparison. We will set $\alpha$ at 0.05 per comparison for the secondary outcomes. The data will be analyzed with the SAS© statistical software package, Version 9.1.3.

5.10.2 Primary Outcomes

Statistical Model: The trial’s randomized, repeated measures data will be fitted to a linear mixed model to test for CBT vs. SCM differences over time on each outcome. This model permits specification of both fixed and random effects. The autoregressive AR(1) covariance structure will be modeled to account for the correlation between repeated within-subject measurements. An equally-spaced, balanced design will be utilized. Thus, all design cells will have an equal number of experimental units, and all time intervals will be equally spaced. Due to the medical frailty of the study population, however, missing data are expected due to attrition. The mixed model has the flexibility to model both unbalanced data and unequally-spaced measurements. Mixed models can handle the former situation if the data are missing at random, and the latter condition through a spatial covariance structure that treats time as a spatial process in one dimension.

Randomization usually eliminates systematic, between-group differences at baseline but does not guarantee that important prognostic factors (i.e., baseline variables that predict outcomes) will remain balanced after attrition, and differential attrition can bias the results. If differential attrition occurs, its effects will be assessed by: 1) comparing the attrited groups on prognostic variables and 2) documenting the reasons for
discontinuation (e.g., dropout, withdrawal, death) to determine whether the attrition was systematic or random. Adjustment for imbalances, e.g., in chronicity or severity of HF, will be performed in secondary analyses.

The primary analyses will follow the intention-to-treat (ITT) principle; i.e., all randomized patients will be included in the analysis. An alternate approach, the per protocol (PP) or as-treated principle, limits analyses to the participants who were actually exposed to the condition to which they were assigned. Porta et al recommend using both methods if there has been substantial attrition. Jo advocates a third strategy, complier average causal effect (CACE) estimation, which will be useful if there is substantial noncompliance (e.g., patients who participate in the follow-ups but who miss numerous treatment sessions). CACE analysis can estimate the intervention effect for compliers, regardless of treatment assignment for noncompliers. Compliance data for this analysis will come primarily from the Treatment Process Data log (TPD). Relevant baseline covariate information will be used to increase precision in CACE estimates. Secondary PP and CACE estimation analyses will be performed to complement the primary ITT analyses.

Model Specification: To analyze both trends over measurement occasions and between-group differences within measurement occasions, the model will include the following fixed effects: one between-subject factor for treatment group (CBT vs. SCM), a within-subject factor for time, and the treatment x time interaction. We will specify a single random effect for subject, which will allow inference from the fixed effects to be generalized to the larger target population. Each model will adjust for antidepressant use as a time-dependent covariate.

Each primary outcome will be measured at 5 occasions, spaced 3 months apart, and adjacent measurements are likely to correlate within subjects. A variance components structure for the random effect of subject will be selected to account for two sources of variation, i.e., between-subject (σ^2_0) and within-subject (σ^2_1) error. In addition to the main effects, the main a priori contrast is H_0: μ_{CBT(6-mo)} = μ_{SCM(6-mo)} vs the alternative hypothesis, denoted “Contrast” in the Power Analysis section; this contrast tests the primary post-treatment difference between groups at 6 months. A secondary contrast will test the between-group difference at 3 months, at the mid-point of the intervention phase, to test whether there are significant differences between the groups relatively early, before the end of active intervention. Additional secondary contrasts will compare within-group changes from 6 months to 9 and 12 months, to determine whether the gains achieved during the 6-month active intervention phase are maintained over time.

5.10.3 Secondary Outcomes

Statistical Models: The linear mixed model is appropriate for the secondary combined endpoint of time to hospitalization or death. Cox proportional hazards model is often used to assess the effects of predictors on the log-hazard associated with a distribution of survival or event times. The hazard ratio (HR) is the parameter of interest; it measures the effects of the predictor variables on the hazard function. The model is able to account for censored data. Two important model assumptions are required for valid inference: linearity of the continuous covariates, and proportional odds. Graphical methods are typically used to assess these conditions. For the former assumption, this can suggest an appropriate functional form for a continuous covariate. If a violation of the proportional odds assumption is found, then an interaction term can be used in the model, constructed by forming the product of log(time) and the nonproportional variable. A stratified analysis of the non-proportional variable can be implemented as well.

Model Specification: Cardiac-related hospitalizations (e.g., acute exacerbations of HF) that require a stay of ≥24 hours will be treated as events. Observations will be censored at the end of the follow-up, or when the patient is lost to follow-up. The origin of time will coincide with randomization, to yield the strongest possible effect on the hazard. Tied event times will be handled by the method of Efron. The relationship between the log-hazard and the treatment effect will be assessed. Given the randomized design, there is no rationale a priori inclusion of covariates other than antidepressant use. However, if imbalances on key characteristics are discovered, post hoc analyses will be conducted to adjust for these differences.

Functional Data Analysis (FDA): Dr. Shannon’s core laboratory will perform secondary analyses on the actigraphy data, using advanced, nonparametric functional data analytic methods. FDA methods are used in many different areas of research and engineering to analyze curves and functions, and they are able to detect patterns that are not discernible from standard statistical methods such as factor analysis. The FDA analyses will yield profile scores that can be used to classify subgroups of patients (e.g., patients who become exhausted in the late morning or early afternoon, versus patients who are able to sustain normal activity levels until evening.) It will also yield indices that cannot be extracted from standard analyses of actigraphic data. For example, it utilizes derivatives to characterize periods during which activity levels are accelerating or...
decelerating. One of the potential applications of this technique is to identify, in individual patients, periods that herald impending exhaustion. This information could be used in CBT to complement the "activity-rest cycle" technique and to pinpoint the times of day when it would be especially important for the patient to employ.

5.10.4 Subgroup, Moderator, and Mediator Analyses

Planned subgroup analyses will be performed to determine whether the effects of treatment differ by gender and minority status. Planned moderator analyses will also be performed to determine whether age, baseline severity of depression, or baseline severity or chronicity of heart failure moderate the effects of treatment. An additional secondary analysis will examine potential mediators of the effects of treatment within the intervention arm. Different candidate mediators will be relevant to different outcomes. For example, exercise data from the Health Behavior Diary will be examined as a potential mediator of changes in activity level (as measured by actigraphy) and in 6-minute walk test performance, and changes in dysfunctional attitudes about health (as assessed by the DAS-H) will be examined as a candidate mediator of changes in self care behavior. OLS multiple regression will be used for these analyses.

5.10.5 Power Analysis

**Background:** The expectation of incomplete data affects the power and sample size estimates. A conversion factor was applied to a range of sample size estimates to accommodate up to 25% attrition by 6 months, based on our prior HF studies and our other clinical trial experience. Although an ITT analysis will be performed, the power estimates are based on per protocol (completer) analysis. With a planned sample of $N_0 = 240$ enrolled patients, we expect to have $N_6 = (240 \times 0.25) = 180$ completers for the 6-month outcomes. Table 3 displays estimated population parameters from the pilot study and relevant published studies for the primary outcomes. This provides the basis for the computation of outcome-specific power curve plots presented in Figure 5. These plots (power vs $N$) define the minimum clinically meaningful treatment difference (i.e., the effect size) for each primary outcome at the 6-month measurement occasions. **The power estimates take the follow-up measurements into account and assume comparable maintenance of gains between groups. They also reflect reductions in expected between-group differences, due to the attention component in the control group (SCM), which was absent in the previously-proposed UC control design.**

The linear mixed model will be used to estimate power for the three primary outcomes: 1) Beck Depression Inventory (BDI-II); 2) Self-Care of Heart Failure Index (SCHFI); and 3) Kansas City Cardiomyopathy questionnaire (KCCQ). The proposed sample size provides power $>0.80$ for all three primary outcomes with a multiple comparison-adjusted $\alpha$ of 0.016 per comparison. Once the necessary sample size for the primary analyses was determined, this sample size was then used to determine the minimum detectable effect sizes for selected secondary outcomes, with power=0.80 and $\alpha=0.05$ per comparison. These include 1) 6-minute walk test distance; 2) actigraphy indices; 3) Beck Anxiety Inventory (BAI); and 4) SF-12. The power to model the secondary combined endpoint of time to hospitalization or death was estimated with a method specific to the Cox regression model.

**Power Estimation Procedures:** Power estimates from the linear mixed model were derived from a simulation study and based on a 4-step procedure (see below). Model parameters were estimated from our pilot study, reports of other behavioral and pharmacological trials for HF patients, and studies of depression and related factors in patients with other disabling conditions. These sources also provided estimates of the prevalence of antidepressant use. The 4-step procedure was as follows: 1) simulate the data pattern using estimates from previous studies; 2) use SAS Proc Mixed to fit the mixed model to the simulated datasets; 3) derive the F values from model effects; 4) compute power via functions based on F distribution critical values. PASS power analysis software was used to compute minimum detectable effect size estimates for the Cox proportional hazards model.
Table 3. **Effect sizes.** The cell values for the primary outcomes represent group means, based on hypothesized clinically significant differences between groups. The cell values for the secondary outcomes represent group means for the minimum detectable effect size, given the sample size requirements for the primary outcome analyses and the estimates of within-group standard deviations aggregated over measurement occasions. The standard deviations are presented on the next page.

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**Figure 5.** Power curves for the three primary outcome measures, based on the hypothesized effects sizes presented above in Table 3. The dashed lines represent treatment by time interactions. A significant interaction would indicate that the groups differ with respect to the course of change from baseline to 6 months. The solid blue lines represent planned post-treatment contrasts at 6 months. A significant contrast would indicate a between-group difference in the outcome.
Parameter Estimates for Power Analysis: Primary Outcomes

Beck Depression Inventory (BDI-II): Population means and variances were estimated from the pilot study, ENRICHD secondary analyses, and our other studies with cardiac patients. The estimated pooled standard deviation is 6.0. The estimated correlation (rho) between adjacent measurement occasions within subjects is $\rho=0.55$. The cutoff for clinical depression is 14, and the minimum clinically significant difference on the BDI-II is 3 points. Differences of approximately this size have been found in the pilot study, our post-CABG depression trial, ENRICHD, and other depression treatment studies with cardiac patients. Given these values, a per protocol (completer) sample n=180 is needed to detect a treatment by time interaction with a power of 0.81; the power for the planned between-group contrast at 6 months is 0.82.

Self-Care of Heart Failure Index (SCHFI): This measure was originally evaluated in 760 HF patients. The mean±sd total scores at baseline were 192±42. Comparison of patients with more vs. less experience with HF self-care yielded a 20-point difference. The estimated pooled standard deviation for this study is 42.0, and the estimated $\rho=0.50$. With a per protocol n=180, the power to detect the predicted treatment by time interaction is 0.80; the power for the planned between-group contrast at 6 months is 0.85.

Kansas City Cardiomyopathy Questionnaire (KCCQ): Based on aggregated values from several previous studies, the estimated pooled standard deviation is 22.0 and the estimated $\rho=0.50$. Moderate improvement in HF symptoms and functioning is associated with approximately a 10-point gain on the KCCQ. A recent study found that a 10-point decline in KCCQ scores was associated with a 16% greater risk of cardiovascular death or hospitalization in patients with HF. Another recent study compared of depressed and nondepressed HF patients reported a between-group difference of approximately 20 points. With a per protocol n=180, the power to detect the predicted treatment by time interaction is 0.80; the power for the planned between-group contrast at 6 months is 0.85.

Parameter Estimates for Power Analysis: Secondary Outcomes

Introduction: The power analyses for the primary outcomes indicated that a per protocol (completer) sample size of 180 is needed to test the primary hypotheses with power >0.80. An enrolled sample of 240, with up to 25% attrition, yields a completer sample of 180. The power analyses for the secondary outcomes fixed the sample size at 180 and solved for power, with an adjusted alpha of 0.05 per comparison. Power is less than 0.80 for some of the secondary outcomes. These outcomes will nevertheless be of interest in planning future studies.

Beck Anxiety Inventory (BAI): Based on the pilot study and our post-CABG depression trial, the estimated pooled s.d. is 9.3, and the estimated correlation between adjacent measurement occasions is $\rho=0.55$. With a completer sample of 180, there is >0.80 power to test the treatment by time interaction and the planned 6-month contrast. The smallest detectable difference is 4 points.

6-Minute Walk Test (6MWT): Based on the pilot study and on several other studies, the estimated pooled standard deviation is 111 yards, and the estimated $\rho=0.70$. With n=180, there is 0.80 power to detect a between-group difference of 47 yards at 6 months. A difference of this magnitude would be obtained, for example, if there were an improvement of 25 yards in the SMC group and 72 yards in the CBT group. To put this into perspective, a recent study showed that a 20% increase in 6MWT distance was associated with a significant improvement in KCCQ scores.

Actigraphy: Actigraphy data were obtained in a study of patients with vs without a disabling disorder and with or without depression. Mean daytime activity was reported for each group. We focused on the medically ill groups with or without comorbid depression, and viewed the higher activity in the former patients (+43; 20% increase) as an indicator of expected post-treatment activity. Comparison of the depressed patients to a healthy control group showed a difference of 10 points. For the proposed study, assuming n=180, pooled sd=29.0, $\rho=0.50$ and counts of 148/min in both groups at baseline, there is power $\geq0.80$ to detect a 13-point post-treatment difference (e.g., SCM=160, CBT=173).

C-reactive Protein (CRP): Parameters were estimated from 2 studies. Xue et al. examined hsCRP levels in chronic HF. We expect >80% of the sample to be in Class II/III, so hsCRP means of 3.8 mg/L are likely. A second article addressed the prognostic value of a cut-off value (>3 mg/L) and its effect on hazard for mortality. With an estimated pooled sd of 3.8 (since this marker is highly variable within groups) and estimate $\rho=0.50$, the minimum detectable difference between groups is 1.8 mg/L.
B-Type Natriuretic Peptide (BNP): Based on previous studies of HF patients\textsuperscript{246, 251}, the estimated pooled standard deviation is 375 and the estimated $\rho=0.50$. There is 0.80 power to detect a between-group difference as small as 170.

SF-12 Medical Outcomes Study Short Form (SF-12): The SF-12 has a physical and a mental component score. Power is assessed for each. Based on the pilot study and another recent HF study\textsuperscript{246}, the estimated pooled standard deviation is 10.6 for the Mental component and 8.7 for the Physical component. The estimated correlations are $\rho=0.10$ and $\rho=0.67$. The minimum detectable differences are 6.0 and 3.7 for Mental and Physical. With moderate symptomatic improvement, HF improve 1.9 and 3.2 points on these scales, respectively.\textsuperscript{246}

Combined Endpoint - Cardiac Hospitalization or Death: Power estimates for this secondary outcome were produced using the PASS\textsuperscript{\textregistered} power analysis software. The module computes either sample size or power for a selected range of hazard ratio ($HR$) effect sizes. These estimates are based on the null hypothesis that there is no linear relationship between the primary predictor of interest, $X$ and the log-hazard (e.g., $H_0$: $\beta = 0$) versus a two-sided alternative (e.g., $H_a$: $\beta \neq 0$). For our study, $X$ is a binary variable that represents the treatment effect (1=CBT, 0=SCM) on the log-hazard for hospitalization or death. If the intervention is effective, we would expect to see a decrease in the log-hazard, which corresponds to $HR < e^0 = 1$. For a meaningful effect estimate, we used a range of 3 $HR$s (0.9, 0.8 and 0.7) representing a 10%, 20% and 30% reduction in the hazard for hospitalization or death. Since our treatment variable is binary (0/1), the standard deviation is equal to 0.5. For the fourth parameter, $R^2 = 0$ (univariate model). Based on previous literature\textsuperscript{74, 252}, we estimate that approximately 40% of the participants will experience cardiac hospitalization or death during the follow-up.

5.11 Study Timeline

![Study Timeline](https://jamanetwork.com/)

The 3-month start-up phase will include development of the Manual of Operations, staff training, acquisition materials, creation of study forms, and other start-up activities. Patient screening and recruitment will begin immediately after start-up and continue for 3.5 years, to allow for at least 12 months of follow-up on the last enrolled patient. The start of the 4.5-year treatment phase will coincide with the recruitment of the first patient randomly assigned to the intervention arm. The treatment and follow-up phases are of equal length, because the treatment phase includes CBT maintenance therapy contacts between the end of active treatment (3-6 months post-randomization) and 12 months post-randomization. The data cleaning and preparation portions of the statistical analysis phase will begin while treatment and follow-up data are still being collected. Final analyses will begin after the completion of data collection, around Month 57. Preparation of the primary manuscript will begin while the outcome analyses are being planned.
References

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