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Stepped Care for Depression in Heart Failure

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Study Protocol
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PRINCIPAL INVESTIGATOR'S NOTE: The final, DSMB- and IRB-approved protocol for this study was completed on 08/26/2018. The current version was submitted to clinicaltrials.gov on 12/29/2022. There are no substantive differences between the 08/26/2018 version and the 12/29/2022 document. The differences are limited to formatting changes that were needed to meet clinicaltrial.gov formatting requirements.

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ORIGINAL PLAN

Study Design

This is a two-arm, parallel groups, single-blind RCT. Both groups will receive usual care from their own nonstudy health care providers throughout the trial, and both will receive a nurse-directed, individually tailored intervention to address deficits in HF self-care (TSC). The difference between the groups is that the intervention arm will receive stepped care for depression (SCD) before TSC, whereas the comparison arm will not. Thus, the trial will compare (UC + SCD + TSC) to (UC + TSC). For simplicity, the following sections will refer to the former as the intervention arm, and the latter as the UC arm.

We selected this design after weighing its pros and cons against those of several alternatives. A key advantage of UC is that it will probably be chosen for a future Phase III multicenter trial. However, since the goal of this study is to achieve better outcomes than we obtained in our recent trial, an alternative would be to compare SCD to CBT instead of to UC. This would permit a direct test of the hypothesis that SCD is superior to CBT, but it is outweighed by two disadvantages. First, if SCD turns out to be superior to CBT, the advantage is likely to be incremental rather than dramatic. There was a 4.5-point difference on the BDI-II and a difference of 27 percentage points in remission rates between the CBT and UC arms of our recent trial, and our goal is to surpass these outcomes. Much larger differences would be desirable, of course, but sample size calculations are based on the *minimum* clinically significant effect size[80], not on the largest effect one might hope to achieve. Whereas a comparison of SCD vs. UC can be powered to detect differences at least as large as the ones found in our previous trial, an SCD vs. CBT comparison would have to be powered to detect a much smaller difference, so a much larger sample would be need. The second disadvantage is that our findings would be less relevant to a future Phase III trial if we were to choose CBT as the comparator instead of UC.

Another alternative would be to use a Sequential Multiple Assignment Randomized Trial (SMART) design[81], which would support rigorous evaluation of the branches within the SCD intervention. A relatively complex SMART design would enable us to compare CBT monotherapy vs. antidepressant monotherapy vs. UC at the initial step. Unfortunately, even a less complex SMART design would require a much larger sample than would be feasible in a single-site study with a standard R01 budget. Thus, a SMART trial would be impractical at this stage of our research. Depending upon the results of the proposed study, however, it might be desirable to test the SCD algorithm in greater detail in a future trial with a SMART design.

A final alternative would be to compare SCD to an attention control (AC) condition instead of to UC. This would determine whether SCD is superior to nonspecific clinical attention. However, the primary purpose of this study is to determine whether SCD yields better outcomes than approaches that have already been tried, not to evaluate the extent to which the effects of stepped care are due to clinical attention. The UC comparator will not determine how much of the effect of SCD is due to clinical attention and how much of it is due to other therapeutic ingredients, but it is a more clinically relevant comparator than an AC control group.

As a single-blind RCT, this study meets the NIH guidance on robust and unbiased design. The outcome assessors will be blinded to group assignment, and we will aim to maintain equipoise, enroll a representative sample, conceal the randomization sequence, maximize adherence and retention, and minimize potential biases, especially ones that can arise post-randomization such as differential attrition and co-intervention bias.

Subjects

Patients with HF and comorbid MD (n=180, *approximately 50% women and 50% minorities*) will be enrolled. The inclusion criteria are 1) stable Class I-III HF, 2) a current major depressive episode, and 3) a baseline BDI-II score >14. Identification of HF will be based on a documented clinical diagnosis, clinical test results consistent with HF (chest x-ray, echocardiography, and/or elevated BNP), and a documented response to medications for HF. Patients with preserved ejection fraction (EF) will be eligible as will those with reduced EF, since neither major depression nor self-care deficits are exclusive to either one of these forms of HF. The presence of MD will be documented by a structured clinical interview at the baseline evaluation. Patients who

have been on *a stable dose of* an antidepressant for at least two months will be eligible as long as they meet the study's depression criteria, as will patients who are not taking an antidepressant at baseline.

The exclusion criteria are: 1) dementia or other cognitive or communication deficits; 2) terminal illness other than HF, 3) insurmountable logistical barriers to participation, 4) age under 25 years, 5) current alcoholism or clinically significant substance abuse, bipolar disorder, schizophrenia, or other psychotic disorder, 6) high risk of suicide, 7) current participation in nonstudy psychotherapy or counseling for depression or other psychiatric conditions, 8) initiation *or modification of* antidepressant therapy within the past two months, and 9) renal or hepatic conditions that would preclude the use of antidepressants. Patients under 25 years old will be excluded due to the FDA black box warning on SSRI antidepressants for patients younger than 25.[82]

Screening and Recruitment

Outpatients with HF will be recruited from the Heart Failure, General Cardiology, and Primary Care Clinics at Washington University Medical Center (WUMC) in St. Louis, as well as from WU faculty cardiology group practices in the St. Louis metropolitan area. We will use clinic schedules to identify potential candidates, work with the staff to facilitate physician referrals, and place study recruitment brochures in the waiting rooms.

Inpatients with HF at Barnes-Jewish Hospital (BJH) at WUMC will be identified via a daily Clinical Investigation & Data Exploration Repository (CIDER) search engine query of the electronic medical record system. With the permission of the patient's physician, the study recruiter will give information about the study to potentially eligible patients and ask for permission to contact them after discharge for further evaluation.

Feasibility: Approximately 3,200 patients with HF received services at WUMC last year. The prevalence of MD in patients with HF is 15% to 20%, so an estimated 480 to 640 HF patients had comorbid MD. There are approximately 600 new cases of HF per annum at WUMC, consistent with 90 to 120 new depressed cases. Thus, we estimate that 795 to 1060 patients with HF and comorbid MD will be treated at WUMC during the study's 3½ year recruitment phase. The target sample of 180 patients represents between 17% and 23% of the estimated pool of potentially eligible patients. This suggests that our enrollment plan is very feasible.

Screening and Consent: Patients who consent to be screened for depression will be asked to complete the Patient Health Questionnaire (PHQ-9).[83;84] Patients who score ≥10 on the PHQ will be asked for written informed consent to participate in the trial and to complete a baseline evaluation. Patients who score >14 on the BDI-II and who meet the DSM-5 criteria for MD will be eligible to participate unless any additional reasons for exclusion (e.g., comorbid alcohol use disorder) are discovered at baseline. It will not be necessary to screen for self-care deficits because virtually all depressed HF patients have self-care deficits. In our recent trial, for example, the mean SCHFI Maintenance score at baseline was almost 40 points below the maximum on this 100-point scale and about 7 points below the mean score of patients seen at HF specialty clinics.[1;85] A brief motivational interview will be included in the enrollment process to promote retention.[86]

Randomization and Allocation Concealment

Eligible patients will be randomized immediately after the baseline evaluation. Randomization will be stratified by nonstudy antidepressant use at enrollment. In our recent study, 33% of the participants were taking a nonstudy antidepressant at enrollment, and all of them continued on their antidepressant throughout the trial, regardless of group assignment. Thus, we anticipate that about 1 out of every 3 enrollees will be on nonstudy antidepressants at baseline. Permuted block randomization with allocation concealment will be used to prevent the study recruiter from guessing the group to which the next patient will be assigned. The study statistician will generate a separate allocation sequence for each stratum, and the allocations will be concealed in sequentially numbered, opaque, sealed security envelopes.[87]

Usual Care

Throughout the study, all participants in both groups will continue to receive medical care from their own nonstudy physicians and other health care providers. Participation in the UC arm will not prevent patients from seeking or obtaining nonstudy care for depression or other psychiatric problems, although few participants in any of our previous trials have sought mental health specialty services during their participation in these studies.

Intervention			Action	Timing	PHQ-9 Criteria (Relative to Baseline)
SCD	TSC	Component			
		CBT-D	Modify	At Week 06	if <10% improvement
				At Week 09	if <25% improvement
				At Week 12	if <50% improvement
				At Week 15	if <75% improvement
		CBT-I	Initiate	Before Week 12	if ≥75% improvement + residual insomnia
				At Week 12	if ≥50% improvement + residual insomnia
				At Week 15	if <50% improvement + residual insomnia
		CBT-M	Initiate	Before Week 18	if PHQ total score <5
				At Week 18	if PHQ total score ≥5
		ADM	Initiate or Modify	At Week 06	if <10% improvement
				At Week 12	if <50% improvement
		Exercise	Initiate	Before Week 12	if ≥75% improvement
				At Week 12	if ≥50% improvement
				At Week 15	if <50% improvement
		Other Self-Care	Initiate	3 weeks after initiating exercise component	

Table 1. Timing and criteria for initiating or modifying intervention components.
Acronyms: SCD = Stepped Care for Depression; TSC = Tailored Self-Care Intervention; CBT-D = CBT for Depression; CBT-I = CBT for Insomnia; CBT-M = CBT Maintenance Phase;ADM = Antidepressant Medication

If there is a significant change in a patient's psychiatric or medical status or nonstudy treatment during the trial that would be incompatible with continued participation, the patient will be withdrawn from the study.

All enrollees will be given standard educational brochures about depression *and heart failure* at enrollment. *Assistance will be provided for patients who are unable to read the materials.* With the patient's consent, the patient's personal physician will be informed that the patient has met the criteria for MD and has been enrolled in our trial. Thus, both groups will receive "minimally enhanced" usual care.[88]

Intervention

Overview

Adaptive interventions incorporate decision rules for dynamically modifying the intensity or type of treatment based on the patient's progress or lack thereof.[81] As shown in Table 1, the timing of each intervention component will depend on whether and how rapidly the patient's depression has improved. Inadequate progress will trigger individualized modifications of the CBT for depression (CBT-D) and antidepressant medication (ADM) plans, whereas rapid progress will allow the patient to initiate CBT for residual insomnia (CBT-I) if indicated, enter the CBT maintenance phase (CBT-M), and initiate the home-based physical exercise and other HF self-care intervention components "ahead of schedule."

Stepped care for depression (SCD) will include CBT administered by a trained therapist and antidepressant medication prescribed by the study psychiatrist. The home-based physical exercise component bridges the SCD and Tailored Self-Care (TSC) interventions, because exercise is a component of HF self-care that is also helpful for reducing depressive symptoms.[72] The exercise and other HF self-care components of TSC will be administered in the intervention and UC arms by a trained nurse.

The SCD and TSC sessions will be conducted with individual patients, in person whenever possible and by telephone whenever necessary (e.g., because of transportation barriers or illness exacerbations). The first sessions of CBT and TSC, and evaluations by the study psychiatrist, will be held in person at our clinic.

The PHQ-9 criteria for initiating TSC are the same in both the intervention and UC arms. Thus, TSC will start for patients in both arms as soon as their PHQ-9 total score has improved by ≥75%, at Week 12 if their score has improved 50% to 74%, and Week 15 if their score has improved <50% by then.

Cognitive Behavior Therapy for Depression (CBT-D)

Treatment Manuals: As in our previous trial, the depression intervention will be guided by *Cognitive Therapy of Depression*[40] and *Cognitive Therapy: Basics and Beyond.*[41] *Heart Disease* by Skala, Freedland, and Carney[42] will guide the adaptation of CBT to the cardiac patient population. Modifications of the CBT-D plan for nonresponders will be guided by *Cognitive Therapy for Challenging Problems*.[89]

Clinical Assessments: The clinical evaluation for the first CBT session will include 1) the Dysfunctional Attitudes Scale (DAS)[90;91], the Dysfunctional Attitudes About Health scale[42], 2) a structured problem identification and goal-setting form, and 3) the Techniques for Overcoming Depression (TOD) scale[92]. Patients will also complete an evaluation form after each session. Other clinical tools for CBT will be used as needed.

Treatment Fidelity: Therapists will develop a cognitive conceptualization diagram and a structured treatment plan and revise it as needed, track the delivery of the intervention on a structured treatment process data log and systematically track the use of specific cognitive-behavioral techniques on a session evaluation form. With the patient's permission, sessions will be recorded for supervisory reviews.

Brief Cognitive Behavior Therapy for Insomnia (CBT-I)

Rationale: Insomnia is one of the most common residual symptoms after treatment of major depression, and it increases the risk of relapse.[66;67] Thus, a residual insomnia module may help in many cases to improve depression outcomes and prevent relapse. CBT-I is effective for primary insomnia[93] and for comorbid insomnia in MD.[94] It has also been shown to reduce inflammatory markers in late-life insomnia.[95] Consequently, it may help to reduce systemic inflammation in HF with comorbid insomnia.

Treatment Manual: We will use Germain and Buysse's Brief (3-4 session) Behavioral Treatment of Insomnia protocol[70], a form of CBT-I with proven efficacy.[96;97] It emphasizes stimulus control and sleep restriction procedures. It deemphasizes cognitive restructuring of distorted beliefs about insomnia, although these cognitions will be addressed if clinically indicated as part of CBT for depression.

Clinical Assessments: A score ≥1 on PHQ-9 "sleep" item will be used to define the presence of residual insomnia.The Pittsburgh Sleep Quality Index (PSQI)[98] will be administered at the initiation of CBT-I (see Table 1). The PSQI will provide information about the patient's sleep patterns that will guide the intervention.

CBT Maintenance Phase (CBT-M)

The maintenance phase of CBT will begin when the patient scores below 5 on the PHQ-9, if there is no residual insomnia. If the patient scores below 5 on the PHQ-9 but has residual insomnia, the maintenance phase will start when the CBT-I module has been completed. If the PHQ-9 score is still ≥5 at Week 18, the maintenance phase will start at that point. This phase will consist of brief (10-20 minute) telephone contacts to assist the patient in maintaining the gains that were achieved during CBT-D and CBT-I, and longer (20-40 minute) telephone contacts if needed to address a relapse of depression. The frequency of contacts will taper to biweekly for the first month of CBT-M, and then monthly for three additional months.

CBT Supervision

A weekly CBT group supervision meeting will be held to discuss clinical issues and implementation of the treatment protocol. Cases will be systematically reviewed at each "inadequate progress" decision point listed in Table 1. These reviews will examine all relevant clinical assessments and the therapist's cognitive case conceptualization, treatment goals and plan, treatment fidelity measures, and treatment barriers. A modified treatment plan will be developed based on the review, and its implementation will be discussed at the next meeting. Brief reviews will also be conducted at decision points that are based on adequate or rapid progress, to assist in planning the next steps. For example, one will be conducted at Week 12 if the patient's PHQ score has improved ≥50% and residual insomnia is present, and the patient's CBT-I plan will be discussed.

Pharmacotherapy

Nonstudy Antidepressants: A third of the patients in our recent trial were taking nonstudy antidepressants at enrollment. The most common were fluoxetine (16%), citalopram (15%), escitalopram (11%), paroxetine (11%), and sertraline (10%). SSRIs are likely to comprise the majority of nonstudy antidepressants in this trial.

Study Antidepressants: The study psychiatrist will choose from four antidepressants, including sertraline, escitalopram, bupropion XL, and mirtazapine. Sertraline and escitalopram are SSRIs, mirtazapine is a tetracyclic, and bupropion is an atypical antidepressant. All four are considered safe for most cardiac patients[13;14;99-102] but we will monitor side effects and adjust medications and dosages as needed. The choice will depend whether the patient has prior experience with any of them, and if so, how well she or he tolerated and responded to the medication. A favorable prior experience determine the drug of choice for the patient's initial step, and an unfavorable experience will eliminate it as an option. If there are no relevant prior experiences or potential drug-drug interactions or other contraindications to consider, the selection order will be 1) sertraline, 2) escitalopram, 3) bupropion, and 4) mirtazapine, based on established safety and efficacy.

The study psychiatrist will meet at Week 6 with patients in the intervention arm who have improved <10% on the PHQ-9, and at Week 12 for those who have improved <50% by then. No patient will receive any study medications between baseline and Week 6, *although a dosage adjustment will be recommended if a patient enters the study on subtherapeutic dose of a nonstudy antidepressant.* Study medications may be initiated at Week 6 or 12 depending upon the patient's progress by these assessment points, and when necessary, the study medication regimen will be modified at Week 12 for patients who initiated a study medication at Week 6.

Study medications will be initiated at the lowest therapeutic dosage for depression (sertraline 50 mg/day, escitalopram 10 mg/day, bupropion XL 150 mg/day, mirtazapine 15 mg/day) and then increased if necessary up to the maximum dosage (sertraline 200 mg/day, escitalopram 20 mg/day, bupropion 450 mg/day, mirtazapine 45 mg/day). Inability to tolerate a particular medication will trigger a switch to a different one.

Medication Adherence: Patients will be asked to bring their bottles for pill counts at the 12- and 18-week assessment visits. Counts will be conducted via follow-up telephone calls when patients forget to bring their pill bottles to a visit. The adherence level will be defined as the percentage of doses taken as prescribed.

Tailored Self-Care (TSC) Intervention

Home-Based Exercise Component

Rationale: The ACCF/AHA heart failure guidelines state that "Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status (Level of Evidence: A)".[103] The AHA self-care guideline also recommends individually tailored exercise, even for patients with severe, symptomatic left ventricular dysfunction.[10] Both guidelines cite the HF-ACTION trial[104] as providing the most definitive evidence. HF-ACTION showed that moderate exercise predicts a >30% reduction in risk of all-cause mortality or hospitalization[105] and significant improvements in perceived health status.[106] It also showed that physical exercise reduces depressive symptoms in patients with HF.[71] Other studies suggest that aerobic exercise reduces depressive symptoms in older adults with MD[72] and that it is also effective when used to augment antidepressant medications in clinically depressed adults.[107]

In short, aerobic exercise is a facet of HF self-care that also helps to decrease depression. Unfortunately, depression predicts low physical activity and nonadherence to exercise in patients with heart failure.[108;109] Thus, it is difficult for depressed patients to engage in the very activities that could help to relieve their depression. The sequential intervention strategy addresses this Catch-22 by treating the patient's depression with CBT and with antidepressant medications before starting the home-based exercise component.

Protocol: The home-based exercise component of the intervention is a slightly modified version of the HF-ACTION protocol for home-based exercise. The HF-ACTION protocol called for five 40-minute sessions per week of walking or cycling, at 60-70% of the patient's heart rate reserve (HRR). However, a cardiopulmonary exercise test was required to determine the patient's HRR. An alternative that does not require an exercise test is to base the intensity target on the Borg Perceived Exertion Scale.[110] The standard initial intensity level will be a Borg rating of 11-12 (light exertion), e.g., "walking around a grocery store or similar activities that require some effort but not enough to speed up your breathing." However, patients who are severely deconditioned or symptomatic will be instructed to start with activities rated as 9-10 (very light), e.g., "chores like folding clothes that seem to take little effort." The target intensity will be activities that are rated 13-14 (moderate), e.g., "brisk

walking or other activities that require moderate effort and speed your heart rate and breathing but don't make you out of breath." Patients will start at the initial intensity for at least 10-15 minutes per day, at least 3 days per week, and gradually progress over 2-3 weeks to 30 minutes of moderate exercise per day 5 days per week.[111]

Monitoring and Adherence: Patients will keep a physical activity log and record their daily pedometer totals. The TSC nurse will schedule weekly 20 minute telephone contacts with the patient to formulate the initial intensity, duration, and type of exercise, gradually increase the exercise program toward the target level, address questions and concerns, use motivational interviewing to help the patient develop and maintain self-motivating cognitions, and use standard problem-solving techniques to address barriers to exercise.

Other Self-Care Component

HF Self-Care: There are three dimensions of HF self-care: 1) maintenance behaviors that can prevent acute exacerbations and help to slow the progression of HF, 2) management of acute exacerbations, and 3) confidence in self-care knowledge and skills. According to the AHA Scientific Statement on HF self-care[10], maintenance includes, *in addition to physical activity and exercise,* dietary and medication adherence, symptom monitoring, fluid restriction, alcohol restriction, weight management, and smoking cessation. Deficits in HF maintenance can precipitate acute exacerbations and hospitalizations. Effective HF self-management includes appropriate responses to worsening signs and symptoms, particularly edema and dyspnea.

HF self-care requires patient education, but education alone is insufficient.[112] It is necessary for patients to develop knowledge, beliefs, and attitudes that support appropriate self-care behaviors, along with the requisite skills. Deficits in any of these domains can interfere with self-care and affect HF outcomes.[10]

Assessment and Intervention: The Self-Care of Heart Failure Index (SCHFI)[113;114] is the most widely used questionnaire for assessing HF self-care behaviors and confidence. The TSC nurse will use the SCHFI to identify self-care deficits, and then interview the patient to evaluate and prioritize the patient's self-care deficits and barriers to effective self-care. Based on this evaluation, the nurse will assemble an individually tailored packet of educational materials and self-monitoring tools from the HF patient education libraries of the Heart Failure Society of America[115] and the American Heart Association[116], as well as from several HF patient education handouts that have been published in major medical journals.[117-120] In addition, self-care materials for patients with a left ventricular assist device (LVAD)[121] will be provided when appropriate.

After an initial face-to-face session, weekly 20-minute TSC telephone sessions will start with the Exercise component and continue through the Other Self-Care component. There will be up to 9 TSC contacts (3 for the exercise phase and 6 for the other self-care phase). Contacts may be shortened (10-15 minutes) and the frequency decreased to biweekly if all of the self-care goals have been met. TSC contacts will end by Week 24.

The Other Self-Care contacts will include 1) a brief review of physical exercise over the past week, along with activity scheduling and problem-solving to promote maintenance of exercise; 2) collaborative prioritization of other self-care goals; 3) development of specific plans to modify self-care maintenance behavior deficits (in the order determined by the prioritization process); 4) cognitive restructuring to address low self-care confidence; and 5) implementation of maintenance strategies for improvements in self-care behavior.

The Other Self-Care component of the TSC intervention will start with education about the role of self-care in HF and motivational interviewing to strengthen self-care motivation and commitment to change.[122;123] HF self-care behavior change strategies that have been tested in previous trials[10] will also be used. A structured monitoring form will be used to track the specific targets of the intervention on a session-by-session basis.

Daily weight checks are necessary in HF to recognize edema[124] and because weight change not due to edema is a serious adverse sign and predictor of poor prognosis.[125] Most patients have bathroom scales that are accurate enough for self-monitoring, but one will be provided for patients who cannot afford one.

Outcome Measures

Beck Depression Inventory[126] (BDI-II): Each BDI-II item assesses an individual symptom on a 0-3 scale, for a total score range of 0-63. The BDI-II total score at 18 weeks is the trial's primary outcome. Remission (total score $\leq$9) and maintenance of gains over the follow-up phase are secondary outcomes.

Patient Health Questionnaire (PHQ-9): Patients in both arms of the trial will complete a PHQ-9 questionnaire every 3 weeks between baseline and Week 24 to track changes in the severity of depression.

Beck Anxiety Inventory (BAI): The BAI is a widely used measure of the self-reported severity of clinical anxiety symptoms. Like the BDI, scores on the BAI range from 0-63. Continuous scores on the BAI will be evaluated as a secondary outcome measure, to determine the degree of change in anxiety.

Hamilton Rating Scale for Depression[127] (HAM-D-17): Total scores on the HAM-D-17 range from 0-50; remission is defined as a score ≤7. The HAM-D will be derived from the Depression Interview and Structured Hamilton (DISH)[128] at baseline, *18, and 24 weeks.* The DISH will also be used to diagnose DSM-5 major depression. Total scores and remission on the HAM-D will be evaluated as secondary outcomes.

Self-Care of Heart Failure Index[113;114] (SCHFI): The SCHFI is a 15-item self-report measure that assesses HF self-care maintenance, confidence, and management. Each item is rated on a 1-4 scale. The Maintenance score is the trial's co-primary outcome and the Confidence score is a secondary outcome. Management scores will be obtained only from the subgroup of patients who have had a recent acute exacerbation of HF.

Kansas City Cardiomyopathy Questionnaire[129] (KCCQ): The KCCQ is a 23-item self-report questionnaire that assesses physical limitations, symptoms, self-efficacy, social interference, and quality of life in HF. Scores range from 0-100, with higher scores representing better health and QOL. It is widely used in clinical trials and is more sensitive to change than other widely-used measures of health-related QOL in heart failure.[130]

NIH Patient-Reported Outcomes Measurement Information System[131] (PROMIS): PROMIS measures are available as short forms and as computerized adaptive tests (CATs) that typically require only 5-7 items to yield an accurate score. Thus, multiple domains can be assessed while minimizing patient burden. The following CATs that assess relevant aspects of functioning will be administered as secondary outcomes: 1) Sleep Disturbance, 2) Sleep-Related Impairment, 3) Fatigue, 4) Satisfaction with Participation in Discretionary Social Activities, and 5) Satisfaction with Participation in Social Roles. This adaptive test battery will include between 25 and 35 items, depending upon the individual patient's pattern of responses.

Actigraphy: *Patients will be asked to wear a wrist actigraph for one week at baseline, 18 weeks, and 24 weeks to measure daily physical activity levels and sleep patterns. Secondary outcomes based on actigraphic data will include the average daily activity level and a sleep efficiency index.*

Assessment Schedule

The baseline, 18-, and 24-week assessments are the most extensive ones and they include an interview, so they will be conducted at our clinical research center. The other assessments will be conducted via the Web or by paper-and-pencil questionnaires, depending upon the patient's preference. Paper-and-pencil PROMIS short forms will be used instead of CATs when necessary. Table 2 presents the assessment schedule.

		Week Number					
Measure	Baseline	6	12	18	24	36	52
Beck Depression Inventory (BDI-II)	X	X	X	X	X	X	X
Beck Anxiety Inventory (BAI)	X	X	X	X	X	X	X
DISH: DSM-5 major depression diagnosis	X			X	*X*		
DISH: Hamilton Rating Scale for Depression (HAM-D-17)	X			X	*X*		
Self-Care of Heart Failure Index (SCHFI)	X			X	X	X	X
Kansas City Cardiomyopathy Questionnaire (KCCQ)	X			X	X		X
PROMIS measures	X			X	X		X
Actigraphy	*X*			*X*	*X*		

Table 2. Assessment schedule.

Statistical Analysis Plan

Data Management: The Research Electronic Data Capture (REDCap) system[132] hosted by the Washington University Biostatistics Division will be used for secure data management, quality assurance, and questionnaire administration. Redcap data will be integrated into SAS 9.3 for all analyses and quality control reports, including evaluation of model variable distributions, identification of outliers and invalid values, and examination of missing data patterns to build efficient multiple imputation models for the intent-to-treat (ITT) analyses. All hypothesis tests will be two-tailed with a Type I error rate of 0.05.

Hypothesis 1a (severity of depression) will be tested by fitting 18-week BDI-II scores to a linear mixed model (LMM). Depression scores (Y_{BDI}) will be regressed on a within-time factor (β_{TIME}), treatment (β_{TRT}), antidepressant stratum (β_{AD}), baseline depression severity (β_{BDI}), and the treatment x time interaction (β_{INT}). The hypothesis will be tested by a treatment contrast at 18 weeks (H_0: $\mu_{SCD}=\mu_{UC}$ vs. H_1: $\mu_{SCD}\neq\mu_{UC}$).

Hypothesis 1b (remission) will be tested by a binary logistic regression model of the conditional probability of remission (Y) given treatment assignment (β_{TRT}). The treatment effect odds ratio ($\theta_{TRT}=\exp(\beta_{TRT})$) hypothesis test takes the form of H_0: $\theta_{TRT}=1$ (no relationship) vs. H_1: $\theta_{TRT}\neq1$. The model includes treatment (β_{trt}), antidepressant stratum (β_{AD}), and baseline depression severity (β_{BDI}). Model validity will be evaluated by residual analyses, restrictions on overfitting, goodness-of-fit assessment via Nagelkerke, Cox-Snell pseudo-R^2, and Hosmer-Lemeshow tests, as well as by multicollinearity and overdispersion diagnostics.

Hypotheses 2a (superior TSC outcomes after SCD than after UC) and 2b (improvement in depression is associated with better self-care outcomes regardless of group assignment) will be tested in a single LMM. SCHFI Maintenance and Confidence scores at 24 weeks (Y_{SC}) will be regressed on time (β_{TIME}), treatment (β_{TRT}), BDI-II change between baseline and 18 weeks ($\beta_{\Delta dep}$), SCHFI scores at baseline ($\beta_{sc(b)}$) and 18 weeks ($\beta_{sc(18)}$), and antidepressant stratum (β_{AD}). The 24-week treatment contrast tests Hypothesis 2a (H_0: $\mu_{SCD}=\mu_{UC}$ vs. H_1: $\mu_{SCD}\neq\mu_{UC}$), while a test of $\beta_{\Delta dep}$ tests Hypothesis 2b. Group differences in self-care trajectories will also be tested in a secondary LMM with a treatment x time interaction term.

Hypotheses 3a-*f* are that SCD will be superior to UC on post-treatment scores: a) Beck Anxiety, b) PROMIS Sleep Disturbance and Sleep-Related Impairment, c) PROMIS Fatigue, d) KCCQ, e) PROMIS Social Activities and Roles, *and f) activity level on actigraphy*. Treatment contrasts at 18 weeks of the form $C_k=(H_{0k}$: $\mu_{SCD}=\mu_{UC}$ vs. H_{1k}: $\mu_{SCD}\neq\mu_{UC}$) will be tested for the k^{th} outcome measure fitted to LMMs. KCCQ and PROMIS scores at other occasions will be fitted to secondary LMMs to test for treatment differences over time.

Hypothesis 3*g* is that the one-year hospitalization rate will be lower in the SCD than in the UC arm. A Poisson regression model will be fitted to test the hypothesized treatment effect, with antidepressant stratum, baseline BDI-II, and baseline SCHFI Maintenance scores as covariates.

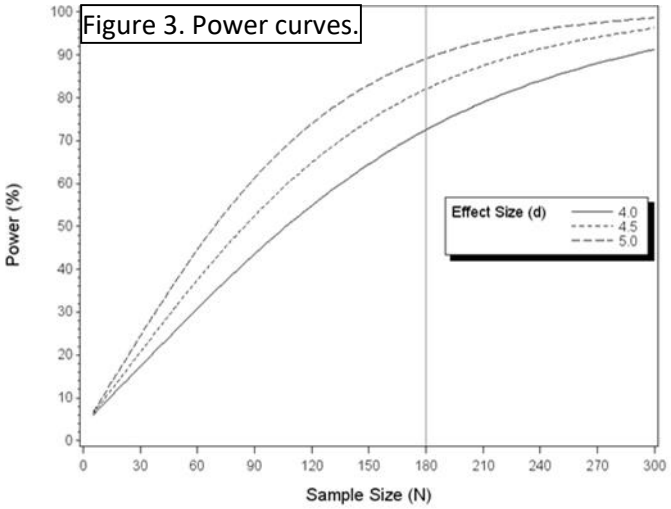
Consideration of Relevant Biological Variables: Planned moderator and subgroup analyses will augment the models discussed above to determine whether the effects of treatment differ by sex, race, or age, as well as by baseline severity of depression and antidepressant use. In addition, baseline levels of HF self-care Maintenance and Confidence will be examined as moderators of the TSC outcomes.

Power Analysis and Sample Size

The analyses will follow the intention-to-treat (ITT) principle[133], and multiple imputation (MI) will be used for data that are missing at random (MAR). The MI model will include auxiliary correlates[134;135] of the ITT model variables, and tipping point analysis[136] will be used to assess the assumptions of the missingness mechanism.

Primary Hypothesis 1a: The target sample size is based on the Type 1 error rate (α), power, treatment effect size ($d=\mu_{SCD}-\mu_{UC}$), and variance (σ^2_{BSL}, σ^2_{6mo}, $\sigma_{(BSL,6mo)}$) from an unstructured covariance structure, estimated from a linear mixed-effects ANCOVA model fitted to BDI-II scores from our previous HF trial. With α=0.05, $\sigma^2_{BSL}=72.4$, $\sigma^2_{6mo}=108.9$, and $\sigma_{(BSL,6mo)}=37.6$, a MIXED model simulation[137] was used to create Figure 3, with power estimates plotted against N for d=4.0, 4.5, and 5.0. We are predicting a larger treatment effect than the 4.5-point difference observed in our previous trial. With 90% power and up to 18% attrition[138;139], 180 patients permit detection of a treatment effect of d≥5.0 BDI-II points. For Hypothesis 1b (remission of depression), this target sample size allows us to detect a ≥25% remission rate difference between SCD and UC.

Figure 3. Power curves.



Secondary Hypotheses: We applied the same power procedures and assumptions (N=180 and up to 18% attrition) to estimate the smallest detectable difference (SDD) for the other outcomes. Table 3 presents estimates of the variance components (σ^2_{BSL}, σ^2_{6mo}, $\sigma_{(BSL,6mo)}$) along with the SDD for the continuously distributed secondary

outcomes at 80% and 90% power. For Hypothesis 3g, the Poisson model has 80% and 90% power to detect 55% and 60% decreases in hospitalization rates, respectively, in SCD relative to UC.

	Covariance Estimates			SDD	
				Power	
Outcome Measure	σ^2_{BSL}	σ^2_{6mo}	$\sigma_{(BSL,6mo)}$	0.80	0.90
Beck Anxiety Inventory (BAI)	115.0	97.9	57.6	4.2	4.8
Hamilton Rating Scale for Depression (HAM-D-17)	30.7	31.2	8.9	2.4	2.7
Self-Care of Heart Failure Index (SCHFI)					
Maintenance	253.9	241.6	184.0	6.5	7.6
Confidence	467.6	364.3	217.6	8.0	9.2
Kansas City Cardiomyopathy Questionnaire (KCCQ)	443.6	512.0	338.9	9.5	11.0
PROMIS measures					
Sleep Disturbance	25.0	49.0	14.0	3.0	3.4
Sleep-Related Impairment	30.3	56.3	16.5	3.2	3.7
Fatigue	47.4	78.8	29.7	3.7	4.3
Satisfaction with Discretionary Social Activities	40.7	65.3	26.6	3.4	4.0
Satisfaction with Social Role Participation	41.8	51.1	14.6	3.0	3.5
Actigraphy (average daily total activity count / minute)	*2683*	*3015*	*1894*	*23.0*	*26.6*

Table 3. Smallest detectable differences (SDDs) on the continuously distributed secondary outcome measures.

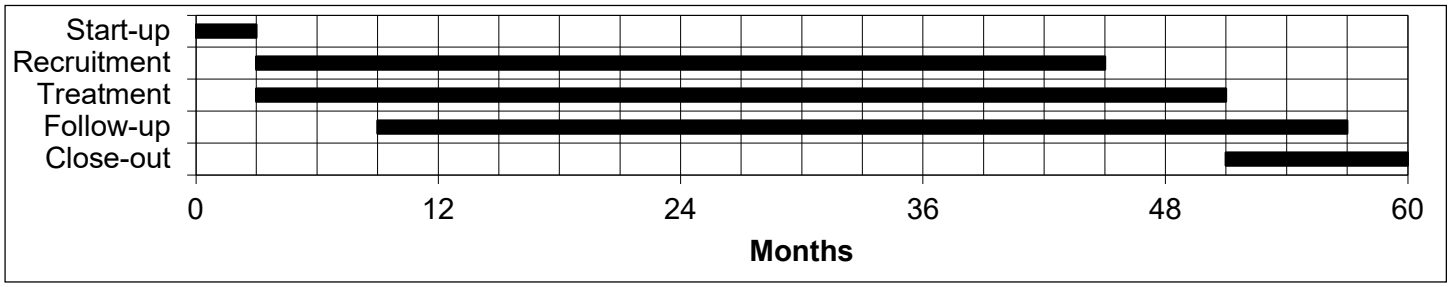


Figure 4. Study Timeline

POST-FUNDING PROTOCOL REVISIONS APPROVED BY DSMB

Note: This section describes the protocol revisions that were made during the start-up phase of the study, before any patients were enrolled. It also includes revisions related to the decision to suspend the psychiatric component of the intervention as of September 2018, due to underutilization. Following this decision, patients were referred to their own (nonstudy) physicians to discuss antidepressant medication options.

Revised Intervention Schedule

This revision supersedes Table 1 and the associated descriptive information in the Intervention section of the original Research Plan.

In the original study design, the active CBT phase lasted up to 18 weeks, and in both arms, the initiation of the Tailored Self Care (TSC) intervention was based on improvement in depression scores. In the revised schedule, the active CBT phase lasts up to 16 weeks and the TSC intervention starts at 8 weeks regardless of the patient's depression score. This revision will make the protocol simpler, more predictable, and less burdensome, and it will also facilitate the primary statistical analyses. Figure 1 (below) displays the revised schedules for the Stepped Care for Depression (SCD) and Enhanced Usual Care (EUC) arms.

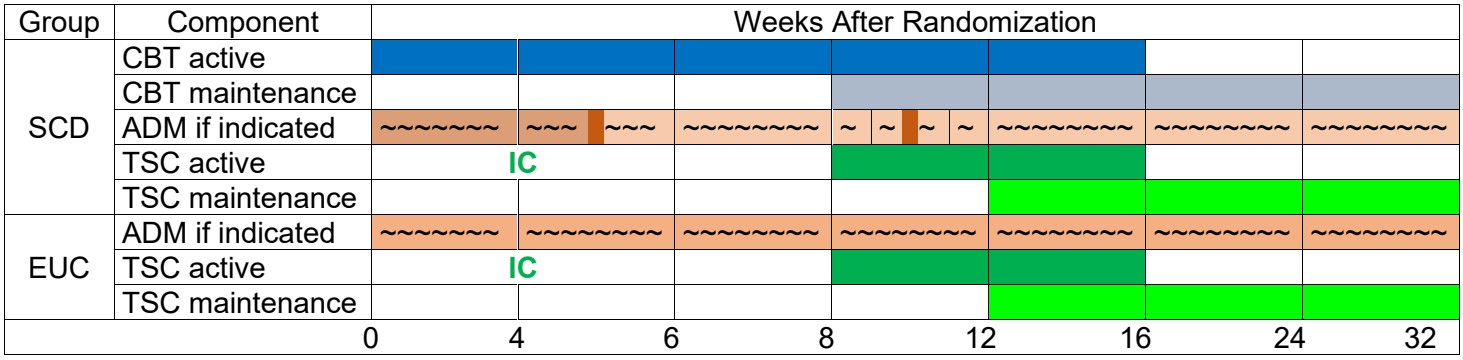


Table R1. Revised Intervention Schedule. The red bars are points when patients may be referred to their primary care physician to discuss antidepressant medication options. The "~" marks are non-study antidepressant prescriptions (if indicated). Note that some patients may already be taking a nonstudy antidepressant at enrollment, and others may start during the trial.

Stepped Care for Depression: In the **SCD** arm, the active (weekly) CBT phase will last at least 8 weeks. It will end when the participant meets the study's clinical improvement criteria (i.e., PHQ-9 total score <5 and ENRICHD CBT Performance Criteria Scale [CBT-PCS] score = 12) OR at Week 16. The CBT maintenance phase will begin when the patient has met the study's clinical improvement criteria OR at Week 16, but no sooner than Week 8. The CBT maintenance phase will end at Week 32.

The original proposal called for a brief CBT for Insomnia (CBT-I) phase to be "tacked on" to the end of the active CBT phase for patients with residual insomnia. The revised protocol eliminates the CBT-I phase. Therapists will instead incorporate CBT-I techniques into the treatment plan as needed, at any point during the active CBT phase for patients with insomnia. This gives the therapists greater flexibility to address depression-related insomnia, when indicated, as a collaborative treatment goal.

If a patient in the SCD arm has not improved ≥25% on the PHQ-9 by Week 5, the therapist will refer the patient to his or her primary care physician for evaluation and antidepressant medication, if indicated. Referral to the PCP may also occur at Week 10 if the patient has not improved ≥50% by then. (The original plan was to refer SCD participants at Week 5 or 10 to the study psychiatrist for evaluation and a study-provided antidepressant medication if needed. This part of the plan was dropped as of September 2018 due to underutilization.)
Enhanced Usual Care: Patients randomized to **EUC** will be asked to call or schedule an appointment with their personal physician as soon as possible to discuss nonstudy depression treatment options.

Tailored Self-Care (TSC): For all participants in both arms of the trial, the weekly (active) **TSC** intervention phase will start at Week 8 and end between Week 12 and Week 16, depending upon the "dosage" of intervention that the patient needs to address his or her HF self-care deficits and goals. Starting at Week 12, the active TSC phase will end when the patient achieves all self-care goals OR at Week 16. The TSC maintenance phase will start no sooner than Week 12, and it will run through Week 32.

The original Research plan divided the TSC intervention into two phases (Exercise and Other). The revised protocol combines these phases. Exercise will still be one of the first self-care goals, but work on other self-care goals can now begin concurrently with exercise, depending on the participant's needs and goals.
Adaptive CBT and Medication Milestones

This revision supersedes the improvement criteria listed in Table 1 of the original Research Plan.

Based on a literature review including studies published after the grant submission, and a secondary analysis of DASH-1 data, we now know that rapid progress in CBT predicts successful depression outcomes and, conversely, that lack of early progress predicts poor outcomes. We examined the DASH-1 data to refine the progress milestones for the SCD arm in DASH-2. The following table displays the milestones and shows the steps that will be taken if a participant in the SCD arm misses a milestone. Note: the baseline PHQ-9 score (not the Initial Clinical Evaluation [ICE] score) is the denominator for the improvement milestone percentages.

Week	PHQ-9 Improvement Milestone	CBT	PHQ-9 Improvement Milestone	Antidepressant Medication
2	≥10%	Implement adaptive strategy		
4	≥20%	Implement adaptive strategy		
5	≥25%	Implement adaptive strategy	≥25%	If on nonstudy ADM: evaluate, possibly recommend change. If not on an ADM: evaluate, possibly refer for nonstudy ADM
6	≥30%	Implement adaptive strategy		
8	≥40%	Implement adaptive strategy		
10	≥50%	Implement adaptive strategy	≥50%	If on nonstudy ADM: evaluate, possibly recommend change. If not on an ADM: evaluate, possibly refer for nonstudy ADM
12	≥60%	Implement adaptive strategy		
14	≥70%	Implement adaptive strategy		
16		Start maintenance phase if it hasn't already started, regardless of PHQ-9 score		Recommend antidepressant evaluation by personal physician if clinically indicated.
24				
32		End CBT maintenance phase		

Table R2. Revised Improvement Milestones for the CBT Arm

Note: Adaptive strategies for CBT are described in the next section.

The intensive (weekly) phase of CBT will end when the criteria for successful completion have been met (PHQ<5 and CBT-PCS=12), or at 16 weeks, whichever comes first. If the successful completion criteria are met between Weeks 8 and 16, the frequency and duration of CBT sessions will be tapered and the focus will shift to maintenance of gains and relapse prevention.

If the patient has not met the criteria for successful completion by Week 16, the frequency and duration of CBT sessions will be gradually tapered but will continue to focus on achievement of remission until the depression is in remission OR at Week 24, whichever comes first. After this point, the focus will shift to self-therapy skills, maintenance of gains, and relapse prevention.

The therapist will determine whether the ADM milestones have been met at Weeks 5 and 10. If a milestone is missed either time, the therapist will refer the patient to his or her primary care physician to discuss antidepressant medication options, in addition to continuing CBT.

Adaptive CBT Strategies

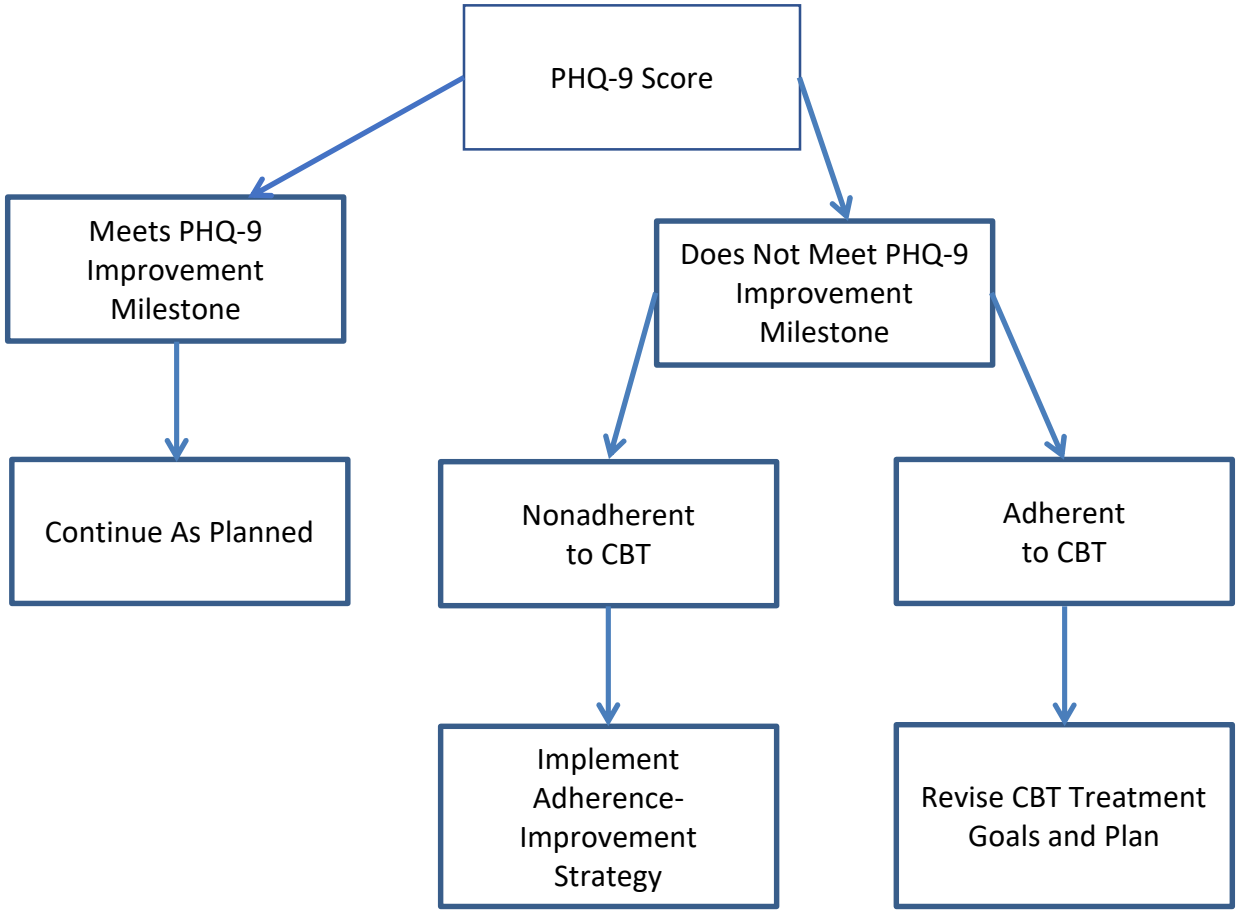
At each "milestone" week (e.g, Weeks 2, 4, 5, 6, etc. in Table R2, above), the therapist will determine whether the patient has met the PHQ-9 improvement milestone. If the milestone has been achieved, the therapist will continue with the original CBT treatment plan.

If the milestone has not been achieved, the therapist will determine whether the patient is adherent to the CBT protocol. This will entail clinical evaluation of several factors including understanding and acceptance of the cognitive-behavioral model, session attendance, and completion of "homework" assignments, among others.

If adherence is not satisfactory, a strategy to improve adherence will be devised and implemented. Alternatively, if the patient is not making sufficient progress despite satisfactory adherence, the CBT treatment plan will be revised. The revision will usually involve addressing barriers to improvement and/or shifting the focus of treatment to therapeutic goals that the patient is more likely to be able to achieve.

The adaptive strategies will be based on the approaches presented in *Strategic Decision-Making in Cognitive Behavioral Therapy* (Wenzel, 2013) and in *Cognitive Therapy for Challenging Problems: What to Do When the Basics Don't Work* (J.S. Beck, 2005). The adaptive CBT algorithm is displayed in Figure R1, below.

Figure R1. Adaptive CBT Algorithm.



Revised Assessment Schedule

This section supersedes Table 2 and some of the details of the Outcome Measures section of the original Research Plan.

The assessment schedule was revised to ensure compatibility with the revised intervention schedule and to reduce participant and staff burden. This included dropping the PROMIS measures which were originally included as exploratory outcomes, and dropping some nonessential assessment points.

Measure	Baseline	Weeks After Randomization				
		8	16	32	40	52
Beck Depression Inventory (BDI-II)	X	X	X	X	X	X
Beck Anxiety Inventory (BAI)	X	X	X	X	X	X
DISH: DSM-5 major depression diagnosis	X		X			
DISH: Hamilton Rating Scale for Depression (HAM-D-17)	X		X			
Self-Care of Heart Failure Index (SCHFI)	X	X	X	X		X
Kansas City Cardiomyopathy Questionnaire (KCCQ)	X	X	X	X		X
Actigraphy	X	X	X			
Patient Health Questionnaire (PHQ-9)	X					
Generalized Anxiety Disorder Questionnaire (GAD-7)	X					

Table R3. Revised Assessment Schedule.

Primary Outcomes

The revised primary **depression** outcome is the BDI-II total score at Week 16. In the original Research Plan, it was the BDI-II score at Week 18.

The revised primary **HF Self-Care** outcome is the Maintenance Scale score from the Self-Care of Heart Failure Index (SCHFI) at Week 16. In the original research plan, it was the Maintenance score at Week 24.

Interpretation of Co-Primary Outcomes

If the BDI-II score is significantly lower in the SCD than the EUC arm at Week 16, this will be interpreted as showing that stepped care for depression is superior to enhanced usual care for depression, regardless of the self-care outcomes.

If the SCHFI Maintenance score is significantly higher in the SCD than the EUC arm at Week 16, this will be interpreted as showing that self-care outcomes can be improved in patients with major depression by pre-treating their depression with a stepped care intervention. However, this interpretation is contingent on the superiority of SCD to EUC for depression on the BDI-II at Week 16. If the SCD intervention does not yield superior depression outcomes, pre-treatment with SCD will not be recommended for depressed patients who are going to receive a tailored HF self-care intervention.

It should be noted that Hypothesis 2b under Specific Aim #2 is that regardless of group assignment, improvement in depression prior to initiating the TSC intervention will predict better self-care outcomes. If improvement in depression does predict better self-care outcomes, but the SCD intervention is not superior to EUC, the interpretation will be that it is helpful to treat depression before intervening in HF self-care BUT that stepped care for depression is not superior to usual care for depression in patients with HF.