Overall goal: To study the effectiveness of a symptom management and psychosocial care intervention, Collaborative Care to Alleviate Symptoms and Adjust to Illness (CASA), in patients with chronic heart failure (CHF) at the Denver VA Medical Center, Denver Health, and University of Colorado Hospital. This is a study of behavioral and care strategy interventions and involves no investigational drugs or devices.

Specific Aims:
Aim 1. Assess the effect of a symptom management and psychosocial care intervention on heart failure-specific health status as a primary endpoint, and symptom distress, depression, quality of life, self-care, and spiritual well-being as pre-specified secondary endpoints.

Aim 2. Evaluate whether the intervention influences quality of life indirectly through effects on symptom distress and depression.

Aim 3. Examine the effect of the intervention on informal family caregivers' depression, burden, benefit-finding, social support, perceptions of patients' symptoms, quality of the patient-caregiver relationship, and contributions to patients' heart failure self-care.

Aim 4. Identify valuable core CASA intervention content and processes from the perspectives of patients and intervention team members.

Aim 5. Identify barriers and facilitators to the implementation and sustainability of CASA from the perspectives of providers (i.e., physicians, nurse practitioners) whose patients received the CASA intervention.

Aim 6. Determine interest and capacity of rural clinic settings to adopt CASA's team-based model of outpatient palliative and psychosocial care.

Background and Significance:
Symptom severity in HF prompts health care utilization,[1-3] independently predicts hospitalizations and mortality,[4] and contributes substantially to the high cost of HF care.[5] Furthermore, symptoms increase suffering and reduce quality of life in patients with HF[6] Many patients report the typical HF symptoms of breathlessness (44-85%) and fatigue (66-85%) as well as depression (19-55%), pain (38-58%), and other symptoms that reduce quality of life and persist over time [7-9] A mean of 15 physical and emotional symptoms are experienced concurrently.[6, 7]

Previous HF intervention studies do not measure or improve the large number of symptoms HF patients' experience.[10, 11] Studies focus on treating disease and evaluating hospitalization and mortality outcomes, acute changes in breathlessness with diuretics, and occasionally health status. Furthermore, major trials of telemonitoring[12], disease management,[13] and education[14] have not shown significant improvement in patient-centered outcomes such as symptoms, in part because they are heavily focused on volume management.

Prior palliative care interventions to improve symptoms and quality of life in outpatients with HF are sparse, have mixed results, and did not use high quality randomized study designs.[15-17] Symptoms worsened in the intervention arm of one trial,[16] and in another, common symptoms including depression and pain did not improve.[15] *These previous palliative symptom management interventions did not include effective depression or psychosocial care, although it is known that depression increases the intensity of other symptoms*.[6, 18, 19] Our proposed study addresses key gaps in the fields of HF, palliative care, and nursing research.

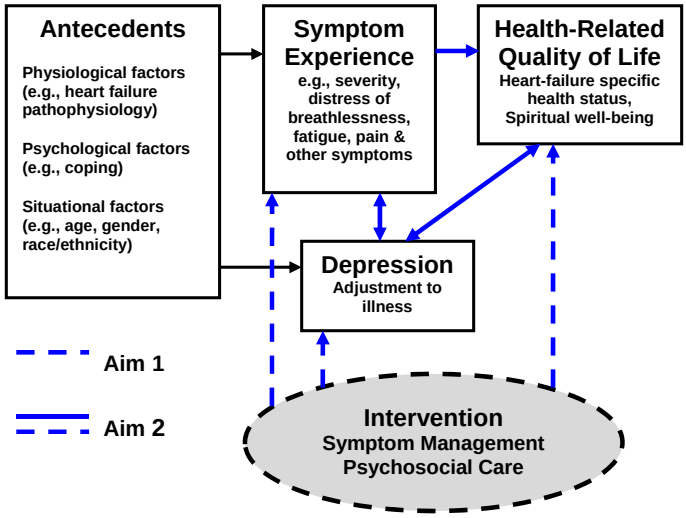
Our study design will further contribute to the design of HF palliative care interventions focused on improving quality of life by examining the relative impact of different predictors of quality of life. While symptoms are strongly related to quality of life in cross-sectional studies, the relative importance of symptoms compared to

factors such as depression and spiritual well-being to quality of life over time is poorly described. *Examining the relative impact of different predictors of quality of life (e.g., spiritual well-being, HF self-care) will enable targeted approaches in subsequent interventions to improve quality of life in advanced HF.* This work will further refine our proposed intervention while informing the next generation of interventions.

Previous HF intervention studies do not measure or improve the large number of symptoms HF patients' experience, and prior palliative care interventions were unsuccessful, in part because of inadequate psychosocial care. We will test the *hypothesis* that an innovative, evidence-based, theory-driven symptom management and psychosocial care intervention will reduce symptom severity and depression in intervention patients compared to patients receiving usual care. We will test this hypothesis using a 3-site, 2-arm randomized, controlled trial (RCT) with outcome assessments at baseline, 3, 6, and 12 months in participants with a primary hospital diagnosis of HF that is advanced. The effect of the intervention on overall symptom severity and depression will be examined using linear mixed-effect models. The *rationale* for this aim is that if the intervention is successful, the research will contribute a patient-centered intervention that can be replicated, implemented, and disseminated in diverse health systems.

We plan to assess the effect of a symptom management and psychosocial care intervention on heart failure-specific health status as a primary endpoint. The study conceptual model and the proposed intervention effects are illustrated in **Figure 1**. The conceptual model is based on integrating elements of Lenz' unpleasant symptom theory[20] into an adaptation of the Wilson and Cleary model of health related quality of life.[21] Antecedent factors, the symptom experience, and depression/anxiety influence health-related quality of life. Heart failure-specific health status and spiritual well-being[22] have been conceptualized as components of quality of life.

Figure 1. Conceptual Model & Proposed Intervention Effects



Additionally, we plan to include and assess the role of informal family caregivers in our intervention. Evidence suggests that relationships heart failure patients have with their caregivers can influence patients' self-care,[23] fatal and non-fatal cardiac events,[24] and survival,[25] where better relationships predict more favorable outcomes and poor relationships predict adverse outcomes. Moreover caregivers' feelings of burden and depression are negatively related to patients' perceptions of relationship quality and self-care,[26] which may influence patient outcomes. There is little understanding of how caregivers influence patient outcomes, and this study will examine the role of caregivers in a symptom management intervention.

Briefly, the intervention is a palliative symptom management and psychosocial care (PSMPC) intervention that includes (a) evidence-based palliative symptom management of breathlessness, fatigue, and pain, provided by a nurse; (2) a 6-8 session structured psychosocial care protocol targeting depression and adjustment to illness,

supplemented by informal (family) caregiver assessment and support, provided by a social worker or psychologist; and (3) brief weekly team meetings with the nurse, social worker/psychologist and a palliative care specialist, cardiologist, and primary care provider.

Preliminary Studies:

The study team has led multiple projects in HF palliative care that support the proposed conceptual model (**Figure 1**) and components of the palliative symptom management and psychosocial care intervention.[6, 27-31] Several studies demonstrated that depression and symptom experience must both be addressed to improve health-related quality of life as they are highly interrelated and are key contributors to quality of life.[6, 27] In a qualitative study of patients with HF and their informal caregivers, participants reported that they desire symptom alleviation and psychosocial support early in illness, integrated with disease-specific care, and coordinated by a provider who understands their heart condition and knows them well.[31]

Each component of the palliative symptom management and psychosocial care intervention and their combination has proven feasible.

(1) The PI, Dr. Bekelman, served as the site investigator at the Denver VA Medical Center for a multi-site HF disease management RCT that successfully recruited an average of 8 HF patients per month and implemented a team-based care delivery approach in HF patients (VA HSR&D CCN 06-068-3/COMIRB #07-0588; Rumsfeld, PI, Bekelman, Co-I). Both this study and the VA Collaborative Cardiovascular Care (C3P) trial (HSR&D IHI 02-062-1)[32] employed team-based collaborative care successfully. For example, in the C3P study (Hattler, Co-I), 90% of medication recommendations written by the collaborative care team were implemented by primary care providers.

(2) The PI has extensive clinical experience with the study population over the last 5 years as Director of HF palliative care programs at the University of Colorado Hospital[33] and the Denver VAMC.

(3) The psychosocial care component of the intervention was developed by Carolyn Turvey, PhD through grants from the NIMH (R34MH73566) and the American Heart Association (AHA 0555699Z). It is a fully manualized intervention that uses behavioral and interpersonal techniques and is delivered primarily by telephone visits in 6-8 biweekly sessions. In a randomized pilot study of the intervention (n=37), the mean Beck Depression Inventory-II (BDI-II, scale range 0-63) scores for the intervention patients dropped from 21.1 to 11.8, while those in the usual care remained approximately the same, 17.8 to 16.2 (mixed effects model, treatment assignment by time interaction $F=5.45$, $df=2, 30.5$, $p=0.009$). Defining treatment response as a 50% or greater decline in BDI-II score, 9/19 (47%) responded in the intervention group as compared with 1/18 (5.5%) in the usual care group.

(4) The combination of these components has been tested in our pilot study designed to test the feasibility of palliative symptom management and psychosocial care intervention (PSMPC). In our initial piloting, we randomized patients to receive PSMPC, a mail-based psychospiritual intervention, or both. Patients at the VA were overwhelmed with both interventions and therefore we changed the randomization to be one intervention compared to the other. We found that both interventions could be feasibility implemented at the VA. We expanded our recruitment to Denver Health and University of Colorado Hospital and have tested the feasibility of the PSMPC intervention at these other two sites.

Experimental Design and Methods:

Study Design:
The study design is being modified based on findings from initial pilot testing and receipt of funding for a multi-site efficacy trial (1R01NR013422-01, Bekelman, PI The study is a 3-site, 2 arm randomized controlled trial of the PSMPC intervention vs. usual care control.

Study Sites: The Denver VA Medical Center, the University of Colorado Hospital, and Denver Heath

Study Duration: Four years.

Study Population: We will recruit patients (n=400; 45 for initial pilot testing and 355 effectiveness trial screening, with a goal of enrolling 312 patients into the RCT) with CHF who meet the eligibility criteria described in **Table 1**. The eligibility criteria were chosen so that participants are likely to be symptomatic and have a poor quality of life, both of which are targeted with the interventions. The eligibility criteria define a cohort with chronic disease (previous HF diagnosis) that is symptomatic based ONE OR MORE of five previously established criteria: previous hospitalization for HF,[34, 35] high diuretic use,[36] high BNP,[37] low ejection fraction and low Kansas City Cardiomyopathy (KCCQ, a self-report measure of HF health status, see "Measures") score.[38]

Table 1. Eligibility Criteria

Inclusion Criteria
- Age 18 years of age or older
- Able to read and understand English
- Consistent access to a telephone
- Patients need to have a primary care provider who is willing to facilitate intervention medical recommendations
- Current diagnosis of heart failure with at least one of the following:
  - - Hospitalization primarily for heart failure (including current)
  - Taking at least 20 mg oral furosemide (or equivalent) daily in a single or divided dose
  - BNP ≥ 100 or NT-proBNP ≥ 500
  - EF ≤40%
- KCCQ-SF≤70
- Bothered by at least one of the following symptoms recently
  - -Pain
  - -Depression
  - -Fatigue
  - -Breathlessness

Exclusion Criteria
- Previous diagnosis of dementia
- Active substance abuse or dependence, defined by either a diagnosis of abuse or dependence, an AUDIT-C ≥ 8, or self-reported substance abuse in the past 3 months
- Diagnosis of schizophrenia or bipolar disorder
- Comorbid metastatic cancer
- Nursing home resident
- Heart Transplant Recipient
- Recipient of left ventricular assist device (LVAD)

The rationale for enrolling patients age 18 years or older who are able to read and understand English is that the intervention was developed in English for adults and the majority of the study instruments have been validated only in English. VA patients need to have a primary care provider within the Eastern Colorado Health Care System (ECHCS) so that orders and consults can be made within the medical record that the primary care provider (PCP) can sign. Subjects who have a previous diagnosis of dementia will be excluded because the intervention requires participation in counseling that was not developed for people with dementia, and most of the questionnaires were not validated in persons with dementia. Subjects who have problems with active substance abuse, defined as an AUDIT-C score ≥ 8[39], a diagnosis of substance abuse or dependence or positive response on a substance abuse screening question, are unlikely to participate in the regular follow up phone calls or respond to the intervention and will be excluded. Subjects with comorbid metastatic cancer are excluded because this study focuses on heart failure rather than cancer palliative care. Additionally, patients with diagnoses of bipolar affective disorder or schizophrenia will be excluded because the counseling components of the intervention were not designed for these patient populations. Patient who have received heart transplants or left ventricular assist devices (LVAD) will be excluded because their care is heavily focused on post-transplant and LVAD management and they rarely see their primary care providers, making it difficult to implement this intervention. Finally, nursing home residents, except those undergoing rehabilitation in the VA Community Living Center, will be excluded since

this study is focused on outpatient care. Competence for study participation will be evaluated by potential participants' ability to explain to study personnel the goals of the study, requirements of study participation, and potential risks and benefits.

Enrolled patients (n=312) will be asked to identify an informal (family) caregiver 18 years of age or older who is "the one person (besides a health care provider) who helps you the most with your medical conditions." Informal caregivers must be at least 18 years of age, able to read or understand English, and not be a paid caregiver. If the informal caregiver is interested in participation and provides informed consent, they will also participate in the study (Aim 3).

We will conduct brief (15min) interviews with patients that participated in the intervention to get their feedback on the effectiveness of the intervention. We will also host focus groups with intervention staff to discuss effectiveness of intervention (Aim 4). There will be separate focus groups for physician and non-physician intervention staff to reduce power differentials between physician and non-physician personnel.

Providers (i.e., physicians, nurse practitioners) that have had patients participate in the intervention will be asked to complete a brief survey regarding their perspective on the usefulness of the CASA intervention and how it might be implemented in actual clinical practice (Aim 5). This will be done after their patients complete the intervention. We anticipate sending surveys to up to 100 care providers.

We will also explore potential implementation of CASA in rural areas (Aim 6). We will perform site visits to rural clinics to meet with up to 20 health care leaders and providers. We will use structured interviews and survey data to explore challenges unique to rural areas, such as resource scarcity (personnel, technological, etc.). This phase of the project will begin Spring 2015 so as to incorporate what we have learned from patient, staff and care provider qualitative data.

Recruitment Process We will request a waiver of HIPAA authorization to allow us to conduct eligibility screening by evaluating medical records of outpatients seen in primary care and cardiology and of hospitalized inpatients to identify potentially eligible patients. We believe the waiver is justified because of the high percentage of heart failure patients who might not be eligible for this study. Potential patients will be approached in the hospital, given a brief overview of the study, and, if they are interested, will be asked to consent to screening. Research assistants will administer a screening questionnaire that includes some general "warm up" questions that don't affect eligibility, the AUDIT-C[39], a substance abuse screening question, and the Kansas City Cardiomyopathy Questionnaire (KCCQ)[40] to potentially eligible patients. This strategy was approved by COMIRB and was successful in the nearly completed HF disease management trial (PCDM trial, COMIRB #07-0588; VA HSR&D CCN 06-068-3, Rumsfeld, PI, Bekelman, Co-I).

Approaching Potentially Eligible Patients

1. VA. We will contact potential research subjects to conduct eligibility screening using two methods: (1) Using a research database of veterans who consented to be contacted for future research studies as part of the VA PCDM trial (COMIRB #07-0588); (2) Using our clinical relationship with patients: VA inpatients (Dr. Robert Burke, Hospitalist Attending Physician); primary care patients (Dr. Connor McBryde, Primary Care Attending Physician); and cardiology patients (Dr. Brack Hattler, Cardiology Attending Physician). A research assistant will call (patients from the research database) or contact (via letter or approached in-person) potentially eligible patients identified through the medical record review with whom we have a clinical relationship and ask permission to describe the study verbally.

2. Denver Health. Patients with whom Dr. Ed Havranek (Attending Cardiologist),Dr. Henry Fischer (Internal Medicine Attending Physician), or Lauren DeAlleaume (Family Medicine) have a clinical/treatment relationship will be contacted by study personnel to determine eligibility and to discuss the study. Thus patients will be

contacted (via letter or approached in-person) who are (1) hospitalized with heart failure or (2) being seen in the outpatient cardiology clinic for heart failure, or (3) seen in internal or family medicine clinics who have heart failure.

3. University of Colorado Hospital. Patients with whom Dr. Larry Allen, Dr. Daniel Matlock, or Dr. David Nowels have a clinical/treatment relationship will be contacted (via letter or approached in-person) by study personnel to determine eligibility and to discuss the study. Dr. Allen is a cardiologist at the University of Colorado Hospital and has a clinical/treatment relationship with inpatients and outpatients on the University of Colorado Hospital cardiology and heart failure services. Dr. Daniel Matlock is an Internal Medicine Attending Physician, and Dr. David Nowels is a Family Medicine Attending Physician.

Patients at all three sites who are interested in the study will be asked to consent to screening [see recruitment scripts: patients contacted through our research relationship with them; patients contacted though our clinical relationship with them]. Patients who are eligible after screening will be asked to provide informed consent (CASA study and evaluation interview) and to complete HIPAA B forms. Informed consent will be conducted in-person, whenever possible. If geographic distance prohibits an in-person visit, the patient will be mailed the consent forms and a member of the study team will contact the patient via telephone to conduct the informed consent process. If amenable, the patient will sign the consent form and return it to the study team. Patients will be offered Three $25 gift certificates as incentives for participation, provided at the baseline, 6m and final study visits. Patients will be assigned a study identifier, a number unrelated to any personal identifying information. Data will be kept on a secured server (see Protocol Application for details). No surveys will be labeled with the subject's name or identifying information. The surveys will be coded with the patient's study identification number.

Enrolled patients (n = 312) will be asked to "identify a family member or person who helps you the most with your medical condition, besides your health care provider" as part of the informed consent process. We will explain that part of this intervention is to involve informal (family) caregivers in care. Patients unable to identify an informal caregiver will not be excluded from the study. If the informal caregiver is not present with the patient, we will ask the patient for permission to contact the person they identified as a caregiver so that we may explain the study, address any questions and facilitate their participation. If the patient prefers, we will ask them to give this informal (family) caregiver a recruitment letter and/or our contact information so that they may contact us. When we establish contact with the informal caregiver, we will obtain verbal informed consent (see Attachment M, Request for Waiver of Caregiver Written Consent). Caregivers will be offered two $15 gift certificates as incentives for participation, provided at the baseline and final study visits.

Prior to the start of the study, all research staff will be trained and will practice the consent process. The training will include the process of fully explaining the study and consent procedures, explaining the possible risks and inconveniences, answering patient questions and assessment of the patient's understanding of the study and consent process.

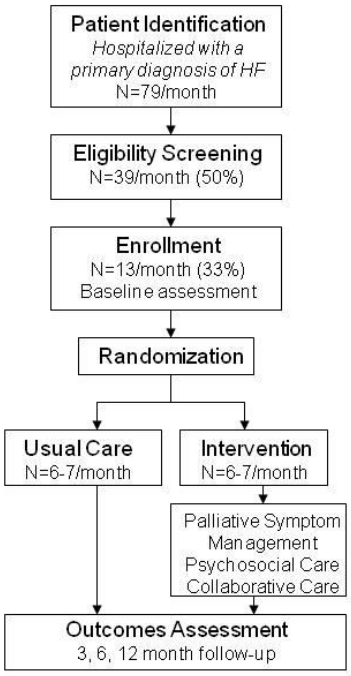
Intervention personnel who participate in the focused group discussions will be asked to provide verbal consent at the beginning of all focus group. The consent will include:

- Full disclosure that the session will be digitally recorded and detailed notes taken;
- Statement that responses will be kept confidential and names will not be linked with responses in the summary;
- An opportunity for them to excuse themselves

Providers and leaders will be approached by phone, email, or in person (Aims 5 and 6). We will request a waiver of written consent for providers who participate in the interview (Aim 5) because the interviews may be done via telephone, are minimal risk, and it is impractical to obtain written consent from busy health care

providers. We will request full informed consent from rural providers and leaders (Aim 6). Informed consent will be obtained in conformation with the policies established by the COMIRB in accordance with the Department of Health and Human Services Code of Federal Regulations regarding the protection of human subjects (45 CFR 46.116). A written consent form that includes the elements listed in 45 CFR 46.116 will be used as documentation of informed consent (45 CFR 46.117). After the consent process, the study subject will keep a copy of the consent, and another copy will be maintained in separate locked file in a locked office of the study coordinator/research assistant.

Figure 2. Study Design and Population Flow



Recruitment Targets

Aims 1-3: The estimated flow of patients and accrual goals are displayed in **Figure 2**. These estimates are based on the investigators' prior experience recruiting similar HF patients,[28, 41] our Preliminary Studies, and account for readmission of the same patients. The accrual goals are displayed in **Table 2**. Patients who refuse study participation will be asked why they refused, and if they consent, we will obtain their baseline demographic and clinical characteristics. The study coordinator will meet by conference call with the recruitment research assistants every week and with the study physicians once monthly until accrual goals are met for each site.

Aim 4: We anticipate at least 120 of the 150 (80%) eligible patients will participate, as they have already participated in the intervention and would be likely to offer feedback.

Aim 5: We expect approximately 100 providers will complete the brief survey.

Aim 6: We expect to enroll 20 leaders and/or providers from rural sites in the VA Eastern Colorado Health Care System for interviews.

Table 2. Study Participants' Accrual by Site

	HF hospitalizations per month	Patients randomized per month
VA	18	5
UCH	40	6
DH	21	2
Total	79	13

Randomization

During a recruitment period of two years, 312 patients (13/month x 24 months) will be randomized to receive either the intervention or usual care. Randomization will occur at the patient level. The random allocation sequence will be computer generated using block sizes of 2-4, an allocation ratio of 1:1, and stratification by recruitment hospital. The allocation sequence will be concealed until after the last subject has completed the 12-month follow up and all of the data have been entered, re-checked, and finalized. Diane Fairclough, DrPH, study statistician, will generate the allocation sequence and assign participants to the intervention and usual care groups.

Description of the Intervention and Control Groups

Palliative symptom management and psychosocial care (PSMPC)

The intervention is patient-centered, multidisciplinary, addresses palliative care and psychosocial issues, and integrates with primary care provider (PCP) care. It is designed to support the emerging Patient Aligned Care

Teams (PACTs), the VA version of the Patient-Centered Medical Home.

A nurse (Registered Nurse, RN) and a social worker or psychologist (at least a Master's level, e.g., MSW or MA) will be the primary intervention personnel. The nurse will provide evidence-based palliative symptom management based on physician recommendations, and the social worker will provide psychosocial care that targets depression and adjustment to illness using an evidence-based, manualized psychotherapy supplemented with care for informal (family) caregivers. They will meet weekly for one hour with a collaborative care team (CCTeam) including a cardiologist (Dr. Hattler, Co-I), palliative care specialist (Dr. Bekelman, PI), and primary care provider (Dr. McBryde, Co-I). The CCTeam will both provide care and write orders for treatments for PCPs to sign. This is exactly the same process as the VA HF clinical trial (COMIRB #07-0588).

Table 3. Sample Fatigue Evaluation

CAUSE	EVALUATION
Decompensated HF	History, vital signs, volume status, BNP
Poor sleep hygiene	Discuss sleep hygiene handout
Sleep-disordered breathing	Epworth questionnaire[53]
Anemia	Complete blood count
Hypogonadism	Testosterone
Hypothyroidism	Thyroid-stimulating hormone
Depression	Screen for depression (PHQ-9)[54]
Anxiety	Screen for anxiety (GAD-7)[55]
Pain	Brief Pain Inventory[56]
Medications	Review medication list
Deconditioning	Exercise < 15-30 minutes 3x per week
Malnutrition	Albumin, prealbumin, cholesterol
Delirium/cognitive dysfunction	Confusion assessment method, brief cognitive assessment
Liver dysfunction	Hepatic function panel

Collaborative care: The CCTeam will provide evidenced-based symptom management[42-46] integrated with a HF care plan[47] based on the nurse and social worker interviews/evaluations of patients and medical record review within 1 week of enrollment. The nurse will record the Team's recommendations in a progress note in the patient's electronic medical record. The psychosocial care and other non-pharmacological recommendations will be implemented immediately by the social worker and nurse, respectively. Orders for medications or tests will be written for PCPs to review & sign at their discretion. The team will re-review patients if their symptoms are not improving based on monthly nurse phone calls or at a minimum of 1 and 2 months after enrollment.

Visits: The nurse and social worker will make an initial in-hospital or clinic-based visit with patients. At the initial visit, a history and examination will be conducted and the patient will be asked to choose an initial symptom (fatigue, breathlessness, pain) on which to focus. Follow-up visits will be by phone, and the number and duration will be tracked. The nurse will provide approximately 4 visits (one phone call every 2-3 weeks) to check on symptoms, and the social worker will provide 6 visits approximately weekly to complete the psychosocial intervention. This will be allowed to vary dependent on patient needs.

Table 4. Sample Fatigue Treatments

(Cause-specific treatments from Table 1)
Bupropion SR 150 mg daily x 1 week, then 150 mg AM and noon
Energy pacing (see Table 4, #4)
Physical therapy
Behavioral activation; counseling to help veteran & informal caregiver adjust to fatigue (see Table 4, #1-3)
Increase function/reduce impairment from fatigue: wheelchair, walker, other adaptive devices
Try to reduce or eliminate antihistamines, anticholinergics, benzodiazepines, opioids, antipsychotics, central alpha blockers, tricyclics, anticonvulsants, muscle relaxants, alcohol.

Symptom Management: To facilitate patient commitment and activation, we will suggest patients choose an initial symptom, pain, fatigue, or breathlessness, to work on. These symptoms are targeted because they are common, burdensome, and substantially affect quality of life in patients with HF.[6, 9]

Patients will have the option of choosing other symptoms in subsequent visits (e.g., constipation). In our previous studies, the overwhelming majority seek help for one of these three symptoms or

depression,[31, 33] which will be addressed through the psychosocial care. The nurse will conduct a nursing evaluation of the symptom and discuss management with the CCTeam. The CCTeam will implement evidenced-based management of the symptom, based on the *Clinical Practice Guidelines for Quality Palliative Care.*[63] Example evidence-based management for the evaluation and treatment of one of the symptoms, fatigue, is described in **Tables 3 and 4**.

Psychosocial Care: The social worker will contact the patient, conduct a psychosocial assessment,[48] and offer 6 phone-based counseling sessions (outlined in **Table 5** and detailed in counseling treatment manual and patient materials. This counseling was specifically developed and tested in patients with HF to improve depression.[49] The purpose is to help veterans adjust to living with HF and to activate/empower them to discuss issues related to their illness with their care providers. The social worker will also contact the patient's informal (family) caregiver to assess their needs and offer support in accordance with National Consensus Project for Quality Palliative Care[50] and National Association of Social Workers[48] guidelines. Dr. Turvey, co-investigator, will provide (1) a 2-day in-person training to the social worker or psychologist who will be conducting the counseling, (2) ongoing consultation and supervision through video-teleconferencing, and (3) review of audio-recordings of sessions to help with problems and to assure treatment integrity. The counseling will be supplemented with antidepressant medication if the collaborative care team agrees this is an appropriate, evidenced-based recommendation.[51]

Table 5. Psychosocial Care
Brief psychotherapy
1. Thinking about the future
2. Loss/grief/acceptance: adapting to change
3. Changing circumstances, change roles
4. Getting active (behavioral activation)
5. Pacing yourself
6. Rumination
Caregiver assessment and involvement

Control Group (treatment as usual)

Patients in the control group will continue to receive care at the discretion of their providers, which may include referral to cardiology, palliative care, or mental health. They will also have the same amount of interaction with research assistants as the intervention patients, completing questionnaires and participating in study visits at the same frequency. Patients' providers will be given the results of all baseline data surveys, and patients will be given an information sheet that outlines self-care for HF. For example, patients in the usual care arm who have significant depressive symptoms will be notified of this and their providers will also be contacted. Referring providers will then assume responsibility for depression care at their discretion, with no constraints on treatment or referrals. Therefore, the usual care patients may benefit from the feedback of screening instruments to their referring providers. This sets a high but appropriate standard by which to judge the effectiveness of the intervention. Budgetary constraints prohibit giving usual care patients additional time with a nurse or social worker to match the intervention patients' time. If the intervention is successful, we will plan for this in a subsequent study.

Study Procedures for Positive Depression Screening

The Patient Health Questionnaire-9 will be used to evaluate depression symptoms (see page 11). For study participants who have a positive screen for depression (a score equal to or over 10 on the PHQ survey), a research note documenting this will be entered into the electronic medical record and the PCP will be notified as a co-signer on this note. If a study participant scores greater to or equal to 1 on question 9 of the PHQ, which asks about thoughts of dying or self-harm, three procedures will occur: (1) the PCP will be contacted through an electronic medical record note; (2) the PI will be notified; and (2) the CCTeam nurse or social worker or psychologist will ask the participant to discuss their response to this question. If the study participant expresses active suicidal thoughts and is felt to be at imminent risk, the study participant will be transferred the patient to the emergency or mental health department.

Data Collection, Measures, and Analysis

Data will be collected and analyzed to assess the intervention effects on patients (Aim 1), conduct the mediation analysis (Aim 2), the intervention effects on informal caregivers (Aim 3),evaluate intervention content and process (Aims 4-5) and determine interest in program and implementation capacity of rural providers (Aim 6) utilizing the following methods.

Patient Outcome Measures and Planned Study Visits (Aims 1-4)

Research assistants will administer measures to patients during four study visits: enrollment (baseline), 3. 6, and 12 months (**Table 6**). The estimated completion time is 45-50 minutes with an additional 15 minutes for intervention patients who complete the evaluative interview. The measures were chosen to reflect domains of the conceptual model (Figure 1) as follows (instrument abbreviations defined below):

- **Antecedents**: Left ventricular ejection fraction, brain natriuretic peptide (BNP), demographics, cognitive status (TICS)
- **Symptom Experience**: MSAS† (symptom severity), GSDS† (symptom distress), PEG, PROMIS fatigue, dyspnea assessment
- **Depression**: PHQ-9†
- **Health-Related Quality of Life**: KCCQ quality of life subscale*, QUAL-E§, EQ-5D†; FACIT-Sp†
- **Other**: SCHFI†, Mutuality Scale¥, ESSI¥, Satisfaction†

* Primary endpoint measure (Aim 1)

† Secondary endpoint measure (Aim 1)

§ Measure used in Aim 2 mediational model

¥ Measure used in Aim 3

Table 6. Study Visits and Assessments for Aims 1-4	**Baseline**	**3-Month**	**6-Month**	**12-month**
Assessment				
Questionnaires/surveys	X	X	X	X
Demographics/Study Form	X			X
Medications	X	X	X	X
Hospitalizations/mortality		X	X	X
Program evaluation (intervention only)			X	

Table 7. Study measures to be completed by patient participants for Aims 1-4.

Conceptual Model Domain (**Figure 1**)	Measure	Number of Items	Completion Time
Antecedents			
Situational, sociodemographic, and physiological factors	Demographics	10	5 minutes
Cognitive Status	TICS	11	4 minutes
Decision Making	Control Preferences Scale	1	< 1 minute
Symptom Experience			
Symptom distress	MSAS-SF	13	3 minutes
Symptom Distress	GSDS	1	< 1 minute
Pain intensity and interference	PEG	3	1 minute
Fatigue intensity and interference	PROMIS Fatigue	8	2 minutes
Breathlessness intensity and interference	Dyspnea Assessment	3	1 minute
Depression/Anxiety			
Depression	PHQ-9	10	3 minutes
Anxiety	GAD-7	7	2 minutes
Health-related Quality of Life			
Health Status	KCCQ	23	8-10 minutes
Spiritual Well-Being	FACIT-Sp	12	5 minutes
Quality of Life	QUAL-E	16	8 minutes
Health Status	EQ-5D-5L	6	3 minutes
Disability	Sheehan Disability Scale	5	2 minutes
Other			
Self-care	SCHFI	22	8-10 minutes
Relationship Quality	Mutuality Scale **(for patients with informal, family caregivers only)**	15	5 minutes
Satisfaction with Healthcare	Recommend Healthcare to Others	3	< 1 minute
Program evaluation (Intervention only)	Qualitative evaluation questions	7	15 min

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1. KCCQ (Primary endpoint): The Kansas City Cardiomyopathy Questionnaire is a 23-item self-administered questionnaire (administration time 5-10 minutes) that measures HF-specific health status. Validated subscales measure HF symptom burden and quality of life. The KCCQ is reliable, sensitive to clinical change, and predicts hospitalization and mortality.[38, 40, 72] The single depression item will be removed from analysis of the quality of life subscale given measurement overlap with the PHQ-9.

2. MSAS-SF: The Memorial Symptom Assessment Scale is a valid and reliable self-report measure of symptom distress.[63] Patients check off which of 10 symptoms (e.g., pain) they have had over the past week. Patients who have had the symptom rate how much that symptom distressed or bothered them from 0 ("not at all") to 4 ("very much") on a numeric rating scale. The primary endpoint will be the sum of the three symptoms the trial is targeting (pain, lack of energy, and shortness of breath) and a secondary endpoint will be the sum of the other symptoms, because the intervention will most likely affect them but they are not directly targeted.

This is also because improvements in one symptom could lead to improvements in other symptoms as a result of symptom clustering.[64-66]

3. PHQ-9: The Patient Health Questionnaire-9 is a 10-item valid and reliable instrument that provides a continuous measure of depressive symptoms and is 88% sensitive and specific for a diagnosis of major depressive disorder (administration time 3 minutes).[67, 68] The PHQ-9 was developed in medically-ill outpatients, including patients with HF.

4. GSDS: The General Symptom Distress Scale includes a measure of overall symptom distress that is reliable and valid[69] and asks, "In general, how distressing are all of your symptoms to you?" and is rated on 0 ("not at all distressing") to 10 ("extremely distressing") on a numeric rating scale. Patients rank the symptoms into the first, second, and third most distressing, and also rate how well they can manage those symptoms.

5. PEG: The PEG is a reliable and valid 3-item scale of pain intensity and interference.[70] Patients rate the pain's intensity and interferences with their enjoyment of life and general activity on a numeric rating scale ranging from 0 ("no pain" or "does not interfere") to 10 ("pain as bad as you can imagine" or "completely interferes").

6. PROMIS Fatigue: The Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale is an 8-item scale that measures fatigue impact and fatigue experience.[71] Patients rate how much fatigue they have experienced and how much fatigue has bothered them on a 5-point Likert-type scale ranging from 0 ("not at all") to 5 ("very much").

7. Dyspnea Assessment: The Dyspnea Assessment is a 3-item measure that asks patients to rate the intensity of their shortness of breath over the past week and how that interferes with their day-to-day activities and enjoyment of life. Two of these questions are items from the validated Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M)[72] and the third item was adapted from the PEG.[70]

8. SCHFI: The Self-care of Heart Failure Index is a valid and reliable 22-item self-report measure (administration time, 8-10 minutes) of self-care that includes three self-care scales: maintenance, management, and confidence.[73]

9. FACIT-Sp: The Functional Assessment of Chronic Illness Therapy - Spiritual well-being scale (12 items; admin time 5 minutes) is a self-report measure that assesses overall spiritual well-being and includes subscales of meaning/peace and faith. It was developed and validated in a large sample of medically ill patients, many of whom had cancer,[74] and has good psychometric characteristics in HF patients.[27]

10. QUAL-E: The Quality of Life at the End of Life is a valid and reliable self-report measure of several domains, each scored separately, of quality of life in advanced illness.[75] We will use the relationship with health care system, preparation, life completion, and global quality of life sub-scales (16 items total, administration time 8-10 minutes).

11. TICS: The Telephone Interview for Cognitive Status is an 11-item verbally administered test of cognitive status. The TICS takes approximately 4 minutes to administer and assesses memory and other cognitive functions. The TICS was originally developed to discriminate between cognitive normals and dementia patients[76] and has demonstrated good sensitivity and specificity when discriminating between normals and individuals with mild cognitive impairment.[76] The TICS will be used as a covariate in the analyses.

12. Control Preferences Scale: The Control Preferences scale is a one-item measure of patient preferences regarding participation in health-care decisions. Using a 5-point Likert-type scale ranging from patient-only decision-making to provider-only decision-making, patients rate the extent to which they want to be involved in their care.[78]

13. GAD-7: The Generalized Anxiety Disorder-7 is an 8-item valid and reliable screening instrument for four common anxiety disorders in primary care (post-traumatic stress disorder, generalized anxiety disorder, panic disorder, and social anxiety disorder.[79,80] It provides a continuous measure of anxiety symptoms.

14. Mutuality Scale: The Mutuality Scale of the Family Caregiving Inventory is a 15-item scale (5 minute administration) that assesses the extent to which a relationship is characterized by emotional investment and the individual feels as if the relationship is gratifying and mutually supportive. Evidence suggests the Mutuality Scale is reliable and valid measure of relationship quality.[81]

15. EQ-5D-5L: The EQ-5D-5L is a measure of health status in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients rate these dimensions on 5-point scales ranging from no problems to extreme problems. A sixth item assesses how good patients think their health is today from 0 ("worst health you can imagine") to 100 ("best health you can imagine").[82]

16. Satisfaction with Healthcare: Patients will rate their Satisfaction with their Healthcare using three items that ask how satisfied they are with the care they have received for their heart failure, symptoms, and dealing with stress, depression, or mood problems. Patients will rate their satisfaction using a 7-point scale ranging from 1 ("very dissatisfied") to 7 ("very satisfied"). Similar questions have been used in effectiveness trials of collaborative care.[83]

17. Sheehan Disability Scale: The Sheehan Disability Scale is a 5-item measure of functional disability in work, social, and family life. Patients rate how much their symptoms have disrupted their lives on an 11-point scale ranging 0 ("not at all") to 10 ("extremely"). This measure has been shown to be a valid and reliable measure of disability that is sensitive to treatment effects in a variety of outcome studies.[84]

18. Demographics/Study Form: Age, gender, race and ethnicity, education level, and clinical variables will be determined at the enrollment visit from the electronic medical record and patient self-report. NYHA classification, etiology of HF, most recent ejection fraction, and BNP or NT-pro BNP will be documented. Medical history (including comorbidities), current medications, and number/reasons for hospitalizations in the previous two years will also be collected at the enrollment visit. At the final study visit, patients will be asked to relate *interim events* at follow-up visits, including hospitalizations with cause and emergency department (ED) visits, the reasons for them, and for permission to obtain medical records relevant to such events. Medications will be documented again.

19. Interim events: Over the 12-month study period for each patient, the following events will be assessed through medical record review to supplement patient report: hospitalization (with cause), outpatient/ED visits, and mortality. Vital status will also be ascertained via the VA Vital Status File and the National Death Index.

20. Program Evaluation: Participants in the intervention group will be asked for their feedback regarding the helpfulness of the intervention portion of the study after all of the outcome measures have been completed.

Process measurement

We will document study processes to facilitate replication and incorporation in dissemination manuals if the intervention is successful and to provide insights for future interventions if not successful. Process measurement will also generate insight into which aspects of the intervention were most effective, and will allow accounting intervention resource use. Process measurement will include: (1) tracking of nurse and social worker contacts with patients, including number, time spent, and reason; (2) tracking of adherence to the intervention protocol using a study form that examines whether or not study protocol actions were completed, as measured by medical record review; and (2) accounting of medication and testing recommendations by the collaborative care team and proportion executed.

Caregiver Outcomes and Planned Study Visits

Caregivers will complete measures caregivers at three times during the study: enrollment (baseline), 6 months, and 12 months. Caregivers will be given the option of completing the surveys online through a secure web-based survey system (REDCap) or through mailed paper surveys. The estimated completion time is 45-50 minutes for baseline and end of study surveys and 15-20 minutes for 6-month surveys. The measures were chosen to reflect domains of the caregiving experience:

- **Perceptions of Patient Symptom Experience**: MSAS-SF, PHQ-2
- **Caregiver Benefits and Burdens**: Benefit Finding Scale, ZBI-SF, DOBI
- **Depression**: PHQ-8
- **Other**: CC-SCHFI, Mutuality Scale , ESSI

1. MSAS-SF: The MSAS-SF, as described above, will be given to caregivers to assess their perceptions' of the patients' symptoms. Thus, the initial survey prompt will be modified to have caregivers identify which symptoms "the person [they] help" has had over the past week.

2. PHQ-2: Perceptions of patients' depressive symptoms will be assessed with the PHQ-2, a two-item screen derived from the PHQ-9.[85] Caregivers will rate the extent to which their patients have experienced little interest or pleasure in doing things and feelings of sadness or depression over the past two weeks.

3. Benefit-Finding Scale: This 17-item scale measures the experience of caregiving, particularly positive experiences.[86]

4. ZBI-SF: The Zarit Burden Inventory-Short Form (ZBI-SF) is a 12-item measure of the extent to which caregivers feel overwhelmed by their caregiving responsibilities. The ZBI-SF takes approximately 4 minutes to administer and has been shown to be a reliable and valid measure of subjective caregiver burden.[87]

5. DOBI: The Dutch Objective Burden Inventory (DOBI) measures the number and frequency of caregiving tasks the caregiver performed over the past three months. The scale includes 38 tasks and takes approximately 8-10 minutes to administer. The scale has been validated for use in heart failure caregivers and has good evidence for reliability and validity.[88]

6. PHQ-8: The Patient Health Questionnaire-8 is a form of the PHQ-9 (described above) that does not ask about thoughts of death or suicide. It is recommended to use this version of the PHQ when assessing from a distance and when the goal is to assess relationships among variables rather than to screen for depression.[85]

7. CC-SCHFI: The Caregiver Contributions to The Self-care of Heart Failure Index is a valid and reliable 22-item self-report measure (administration time, 8-10 minutes) of caregivers' contributions to patient self-care that includes three self-care scales: maintenance, management, and confidence.[89]

8. Mutuality Scale: Same as above.

9. ESSI: The ENRICHD Social Support Inventory (ESSI) measures social support. This 7-item scale takes approximately 3 minutes to complete and assesses the extent to which an individual has sources of structural (e.g., a partner), instrumental (tangible), and emotional (caring) support. This measure was developed for use in a population with cardiovascular disease and has demonstrated good reliability and validity.[90]

10. Demographics: Caregivers will self-report age, gender, race, ethnicity, marital status, and relationship to patient.

Table 8. Study measures to be completed by caregiver participants.

Conceptual Model Domain	Measure	Number of Items	Completion Time
Antecedents			
Situational, sociodemographic, and relationship factors	Demographics	15	5 minutes
Contributions to Patient Self-Care			
Caregiver contributions to self-care	CC-SCHFI	22	8-10 minutes
Patient Symptom Experience			
Symptom prevalence and distress	MSAS-SF (Perceptions of Patients' Symptoms)	23	5 minutes
Depression	PHQ-2 (Perceptions of Patients' Depression)	2	1 minute
Depression/Burden			
Depression	PHQ-8	9	3 minutes
Subjective Caregiver Burden	ZBI-SF	12	4 minutes
Objective Caregiver Burden	DOBI	38	8-10 minutes
Quality of Life			
Relationship Quality	Mutuality Scale	15	5 minutes
Social Support	ESSI	7	3 minutes
Quality of Life	Benefit-Finding Scale	17	7 minutes

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Data collection and management (Aims 1-3)

To ensure data integrity, the study protocol manual will include a section on data collection with descriptions of each data element or measure and instructions for its accurate collection or acceptable source. Several strategies will be used to avoid missing data and dropout, such as follow-up phone calls and letters. The study will use REDCap, a secure, HIPAA compliant, web-based application for building and managing online databases which is provided free of charge by the UCD CCTSI. All patients who are screened will be entered into one REDCap database that will store names, last four SSN (VA only) or medical record number (UCH and DH), eligibility and screening data, and contact information (phone numbers and addresses). There they will be assigned a study ID number that will link their information to the rest of their responses if they enroll in the study. A second REDCap database will contain patient and caregiver survey data and patient medical information. This database will not have any personal identifying information and will only be linked by study ID number. A third clinical database will be created in Microsoft Access that will be stored on secure VA servers with limited access. Only patients randomized to the intervention will be entered into this database, and it will store medical and visit data to track the process of the intervention. The data analyst will construct the study databases.

Monitoring plan

Monitoring will focus on recruitment, baseline comparability of treatment groups, protocol adherence, completeness of data, accrual of primary endpoint data, safety, and follow-up rates. This monitoring will provide the basis for reporting to a DSMB and quarterly review by the study investigators.

Data Collection for Aims 4-6.

Please refer to table 9 for a summary of data collection and analyses for Aims 4-6.

Table 9:

Study Aim	Data Source	Sample Size	Analytic Framework
AIM 4. Identify valuable core CASA intervention content and processes	Brief Patient Interviews	120	Qualitative analysis of patient and team member experiences on intervention content and structure (e.g., nurse, psychosocial care, care coordination with primary care provider), allowing for emergence of new codes/ideas
	CASA Patient Close Out Summary (one page each, data already collected as part of the CASA trial)	150	
	Focused Group Discussions with Intervention Team*	4-6	
AIM 5. Identify barriers and facilitators of CASA implementation and sustainability	Email Survey of Primary Care Providers Whose Patients Have Received CASA intervention	100	Qualitative analysis of data from multiple sites using the following **CFIR Domains**, *Constructs*, allowing for emergence of new codes/ideas **Intervention Characteristics** *Relative advantage, complexity, cost, design quality and packaging* **Characteristics of Individuals** *Knowledge & beliefs about Intervention* **Outer Setting** *Patients Needs and Resources* **Inner Setting** *Implementation climate, relative priority, readiness for implementation*
	Focused Group Discussions with Intervention Team*	4-6	
AIM 6. Determine interest and capacity of rural clinics to implement CASA's team-based model of outpatient palliative care	Interviews with Rural Health System Leaders and Providers	20	

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Intervention evaluation data collection (Aims 4 & 5)

Brief Interviews with Patients: We will conduct brief in-person interviews with all willing patients in the CASA intervention arm who are completing endpoint measurement. Interviews will be conducted to elicit patient views about different parts of the intervention (e.g., nurse vs. social worker); how to improve the content and value of the intervention; communication and coordination; and whether and to what extent they continue to

sustain their use of CASA after the study. Value as defined by CHF patients is critical for ensuring CASA's patient centeredness. Interviews will be recorded with patient's consent.

CASA Intervention Patient Close Out Summary: As part of the CASA trial, the nurse and social worker complete a final "close out summary" on each patient once they complete the intervention. This 1-page summary form captures information on what worked well and not so well with components of CASA, what was missing, whether the patient engaged in and followed up with a goal (goal setting), and the likelihood that goal setting would continue. There will be approximately 150 close-out summaries to analyze.

Interviews of Primary Care Providers: We will administer a brief interview to select primary care providers who have patients who have completed the CASA intervention. Using a combination of rating scales and a few open-ended questions, the goal of these interviews is to efficiently identify strong positive or negative opinions about the usefulness of different CASA components, integration of CASA into work flow, and CASA's impact on quality of care. We will also ask for their insights into ways to sustain and spread CASA to other urban and rural sites.

Focused Group Discussion with Intervention Team Members: We will conduct several (2-3) structured group discussions with intervention team members to debrief about CASA implementation. The goal of these feedback sessions is to elicit intervention team views about what is and is not working well; what parts of CASA could be streamlined, dropped or enhanced; their views about patient, family caregiver, and primary care provider receptivity and responsiveness. Finally, we will ask team members about what it would take to scale-up and sustain a program like CASA as a regular service for patients with CHF within the current site and in rural sites and what should be included in an implementation toolkit. Dr. Main will lead these focused group discussions which will be audiotaped and transcribed.

Rural feasibility data collection (Aim 6)

Site Visits and Interviews with Rural Health System Leaders and Providers: Drs. Bekelman and Main will conduct site visits at rural clinics to explore their capacity to adapt, implement and sustain CASA. During the site visits, we will tour facilities and interview approximately four key leaders and providers at participating sites who have a role in decision making and planning for CASA implementation. Leaders and providers will be identified by key personnel at existing sites. Interview guides will use a combination of broad, open-ended questions to elicit leader/provider perceptions of CASA, using questions/probes guided by CFIR constructs. The questions are designed to improve our understanding of the facilitators and barriers to scaling up use of the CASA in rural areas, learning about their infrastructure and resources, current arrangements for palliative and psychosocial care, and how the CASA care model could be organized and implemented to improve quality of CHF care. We will learn how CASA fits within their organizational mission and priorities, meets a clear patient need, and might help them improve the quality of patient care. We will identify preferences around implementation processes to inform an implementation strategy. These interviews will be audiotaped and transcribed.

Data Analysis Plan

Aim 1: Assess the effect of a symptom management and psychosocial care intervention on heart failure-specific health status, measured by the KCCQ overall score, as a primary endpoint, and symptom distress, depression, quality of life, self-care, and spiritual well-being as pre-specified secondary endpoints.

Descriptive Statistics and Basic Comparisons
All analysis variables, both predictors and outcomes, will be examined carefully prior to any formal statistical analysis. Standard graphical methods, including histograms and boxplots, will be used to examine overall distributions and identify potential outliers, which will be confirmed prior to inclusion in analysis. Internal consistency of multi-item scales will be examined, and whenever possible, items and scales will be compared

to existing data to ensure appropriate performance within our HF population. Data transformations will be considered if indicated, such as log transformations for highly skewed data, to meet model assumptions. Each measure will be summarized using standard descriptive statistics, including means and standard deviations, medians, and ranges for continuous measures and proportions for categorical measures. Baseline characteristics will be compared between groups using appropriate exact nonparametric tests, such as Fisher's exact tests and Wilcoxon rank-sum tests.

Primary Analysis

Data from all participants will be included regardless of level of participation using an intent-to-treat approach**.** All outcome measures will be analyzed as continuous variables. Analyses of the repeated measures, including primary and secondary endpoints, will be performed using maximum likelihood estimation (MLE) for incomplete data (SAS Proc Mixed). This approach has several advantages: 1) all available data on eligible subjects can be included in the analysis even when there are missing data at follow-up, 2) MLE estimates the correlation between related measures and adjusts test statistics appropriately, 3) time varying covariates can be incorporated into the model, and 4) the assumptions about missing data are relaxed from Missing Completely at Random (MCAR) to Missing at Random (MAR).[91] The primary analyses will not explicitly consider the pre-randomization variables unless there is a strong imbalance across the two groups, but the effect of these variables on outcome will be investigated as secondary analyses. Because missing data may occur as a result of morbidity or mortality, we will also perform sensitivity analyses utilizing auxiliary information such as BNP, hospitalization (with cause), outpatient/ED visits, and mortality to convert the missing data problem to a setting that is more likely to be MAR conditional on the auxiliary information.

Additional Exploratory Analyses

We also propose several exploratory analyses that will investigate how relationships between the symptom experience, depression, and health-related quality of life change over time. These analyses will guide subsequent applications of our intervention. For example, an understanding of the time course by which symptoms and depression effect quality of life will help target assessments and treatments focused on quality of life outcomes to this time frame. The exploratory analyses will address two questions:

Question 1: How much do changes in potentially modifiable factors, such as symptom severity and burden and depression, explain variation in quality of life? We hypothesize that changes in modifiable factors over time explain the largest amount of variance in quality of life over time. The analysis (SAS Proc Mixed) will utilize the change from baseline in quality of life (as measured by the KCCQ quality of life subscale) at 3, 6 and 12 months as the outcome. We will estimate the proportion of the variance explained by baseline demographic variables (e.g. age, gender); baseline measures of disease severity (e.g. ejection fraction, BNP); and changes in modifiable factors (symptom distress and severity, depression, attitudes about impairment and spiritual well-being).

Question 2: How does the strength of the association between changes in quality of life and changes in the modifiable and unmodifiable factors vary over time? We hypothesize that the modifiable (particularly the psychological) associations will increase and the unmodifiable will decrease over time. These hypotheses will be tested by adding interactions with time to the models employed to answer question 1.

Aim 2. Evaluate whether the intervention influences quality of life indirectly through effects on symptom severity and depression. This aim will examine our conceptual model using a mediation analysis. The data gathered in the clinical trial described in Aim 1 will be used to complete this aim.

Overview

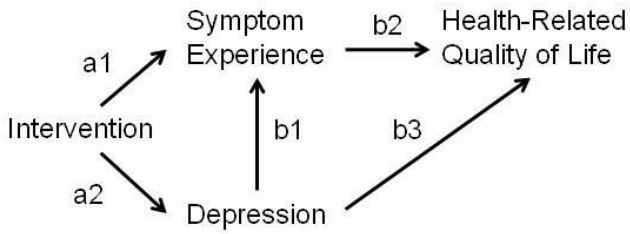
Previous observational studies demonstrate aspects of the conceptual model[19] (Figure 1), but no intervention studies have examined these relationships. The *objective* of this aim is to understand longitudinal relationships between symptoms, depression, and quality of life. *We are not powered to examine direct intervention effects*

on quality of life, but, as supported by a vast literature on mediation analysis,[92] we are adequately powered to examine mediational pathways by which the intervention influences quality of life (see "power analysis" below). We will test the *hypothesis* that symptom experience, measured as symptom severity using the ESAS total score, and the number of depressive symptoms, measured by the PHQ-9 score, mediate the relationship between the intervention and health-related quality of life, measured by the KCCQ quality of life subscale. This hypothesis will be tested using a structural equation modeling framework because the variables are measured longitudinally, and we are interested in testing mediation pathways and using multiple dependent variables. The *rationale* for this aim is that a fundamental understanding of the relationships between symptoms, depression, and quality of life is critical to the further refinement of therapeutic strategies to improve symptoms and quality of life. For example, we will understand the relative importance of each path of intervention effect, and consider strengthening or diminishing the palliative symptom management or psychosocial care components. If the intervention is not successful, a deeper understanding of the relationships between these variables will guide the content of future interventions to improve symptoms and quality of life. Furthermore, examining these variables in a longitudinal study will provide much stronger evidence for their relationships.

Data Analysis Plan

The analyses for this aim will be carried out using Mplus[93] following well-established statistical methods for testing the mediated effect with longitudinal data[94] and multiple mediators.[95] The general structure of the proposed model is depicted in **Figure 3**. This model is a simplified version of the overall conceptual model (Figure 1). The model will be estimated in a parallel process growth modeling framework where the change in symptom severity over time will be estimated simultaneously with the change in the number of depression symptoms over time, each of which will be captured by latent initial status and slope factors. The a1 path from the intervention to symptom severity will measure the impact of the intervention on changes in symptom severity (the symptom severity slope factor) and the a2 path will test the impact of the intervention on changes in the number of depression symptoms (the depression slope factor). The b1 path from depression to symptom severity is included to test the hypothesis that some of the impact of depression on quality of life will occur through reduced symptom severity. The b2 and b3 paths capture the effects of the symptom severity and depression slope factors on health-related quality of life measured at the end of the study. The overall fit of the proposed model, the significance of the individual paths, and the significance of the mediated effects will be assessed. The mediated effects will be calculated using the product of coefficients method and will be evaluated for statistical significance by a bias-corrected bootstrapped standard error estimate.[96] Three specific indirect effects will be estimated: (1) the indirect effect of the intervention on health-related quality of life through symptom severity (a1*b2), (2) the indirect effect on quality of life through depression (a2*b3), and (3) the indirect effect on health-related quality of life in a multiple mediator framework through the intervention's impact on depression and the impact of depression on symptom severity (a2*b1*b2).

Figure 3. Structure of the mediational model



Through exploratory analyses, we will examine the same model using our alternative measures of the symptom experience (symptom distress, GSDS) and health-related quality of life (QUAL-E subscales).

Aim 2 Power Analysis

Power calculations were based on the magnitude of the individual paths, as well as the power to test each of the three proposed specific indirect effects. Power was calculated in Mplus using a Monte Carlo simulation.[97,

[98] The population model followed the structure of Figure 3, but was estimated as a parallel process growth model. For consistency with the power estimates under Aim 1, moderate-sized effects from the intervention to symptom severity and depression were specified (i.e., 13% of the variance in symptom severity and depression accounted for by the intervention). Based on an earlier cross-sectional study showing large correlations (>.50) between symptoms, depression, and quality of life,[6] large effects (26% of the variance in outcomes) were specified for the paths from depression to symptom severity, from depression to health-related quality of life, and from symptom severity to quality of life. Assuming a two-sided $\alpha = .05$, power was sufficient (>=.80) to detect significant differences in each of the paths and in the three mediated effects. Power estimates may be considered conservative because Monte Carlo simulations do not calculate power using bootstrapped estimates, although this method has been shown to be the most powerful method for testing the significance of the mediated effect[99] and will be used in this analysis.

Aim 3. Examine the effect of the intervention on informal family caregivers' depression, burden, benefit-finding, social support, perceptions of patients' symptoms, quality of the patient-caregiver relationship, and contributions to patients' heart failure self-care.

Similar to Aim 1, analyses of the repeated measures will be performed using maximum likelihood estimation (MLE) for incomplete data (SAS Proc Mixed) to examine the differences between caregivers of patients in the intervention compared to caregivers of patients in the control group over time on caregivers' depression, burden, benefit-finding, perceptions of patients' symptoms, quality of the caregiver-patient relationship, and contributions to patients' heart failure self-care.

Data Analysis for Aims 4-6

The qualitative data collection and analysis is designed to be flexible and iterative in nature. Using the Consolidated Framework for Implementation Science (CFIR), we will analyze project data to address each specific aim, then conduct a final, more comprehensive analysis to examine differences and similarities of CFIR and other implementation influences that emerge within the current implementation context (Denver Metro Area health care systems) compared to the planned implementation contexts (rural health systems). This approach is informed by the CFIR, which reinforces the importance of understanding implementation barriers and facilitators within the context that an intervention or innovation is planned, implemented, and sustained. By focusing our analysis within each implementation context – current and planned –we are able to describe and disentangle the importance of these different contexts and their influence on perceived facilitators and barriers of CASA implementation and scale-up.

Aim 4. Identify valuable core CASA intervention content and processes from the perspectives of patients and intervention team members.

Using a combination of inductive and deductive methods, we will create an evolving set of codes linked to units of text (fragments, sentences or paragraphs) using the Atlas.ti software package. Dr. Main and the research assistant will serve as primary coders for qualitative data, and Dr. Bekelman will review coding and codebooks as they are developed. We will follow a systematic process to enhance coder agreement in assigning codes and a peer debriefing process that requires regular meetings with Drs. Main, Bekelman, and the research assistant to review and refine codes, code definitions and conceptual boundaries for our analysis.[43, 44] The iterative analysis will begin by using the a-priori codes based on intervention content and structures and questions used for data collection, with continual refinement of codes and adding new codes as new insights emerge. Through systematic coding we will quickly develop working themes and hypotheses that will be examined (and inform any minor changes in data collection interview/survey guides). We will both audiotape and take detailed notes during all data analysis meetings in order to document proposed codes and code revisions, proposed themes and their descriptions, and other decisions made during these working meetings.

Aim 5 Identify barriers and facilitators of CASA implementation and sustainability from the perspectives of providers whose patients have received the CASA intervention and intervention team members (interpretive-focused formative evaluation), and

Aim 6: Determine interest and capacity of providers in rural settings to adopt CASA's team-based model of outpatient palliative and psychosocial care (developmental formative evaluation)

Although we will primarily analyze qualitative data for Aim 5 and Aim 6 separately, our data collection methods and analytic approaches are designed so we can apply an overlapping set of CFIR constructs as a-priori codes for addressing both study aims. Using overlapping CFIR codes will both allow us to develop contextually grounded understandings of CASA implementation and sustainability and explore important similarities and differences within and across settings. For the proposed evaluation, our analysis will focus on those selected CFIR constructs related to provider and organizational influences on CASA implementation and sustainability, including factors related to organizational context itself. Specifically, we will use codes reflecting the CFIR domain of "Inner Setting" to help us understand organizational context with which CASA is or will be implemented, and a-priori codes for the "Outer Setting," which will help us understand more about, for example, different patient and resource needs and health system expectations and pressures that influence implementing a team-based palliative care intervention like CASA in urban and rural environments. For the analysis of rural interviews, we are particularly interested in understanding the Inner Setting construct of Readiness for Implementation. Understanding this construct will help us describe organizational capacity, resources, and infrastructure that will influence decisions about CASA implementation and sustainability.

Using a combination of inductive and deductive methods, we will create an evolving set of codes linked to units of text (fragments, sentences or paragraphs). This iterative analysis will begin by using the a-priori CFIR constructs as codes, with continual refinement of codes and adding new codes as new insights emerge. Through systematic coding and rating of constructs as either a positive (facilitator) or negative (barrier) influence, we will quickly develop working themes that will be examined within each aim. We will both audiotape and take detailed notes during all data analysis meetings in order to document proposed codes and code revisions, proposed themes and their descriptions, and other decisions made during these detailed working meetings. We will use several recommended strategies to enhance the validity or credibility of qualitative findings:[45-47] (1) structured interview guides administered by well-trained interviewers, (2) coding templates and detailed descriptions of codes, coding decisions and analysis strategies to document all phases of the data analysis (audit trail); and (3) team approaches (at least two analysts) to develop coding templates and independently code subsets of transcripts/notes to determine their agreement and application of codes and code definitions.

Sample Size

Aims 1-3
We plan to accrue 312 patients and anticipate 15% of the participants will die due to progression of their HF and an additional 10% will dropout due to miscellaneous reasons. Thus, approximately 117 participants per arm will have all four assessments. With this sample size, we have 86% power to detect a moderate effect of 0.4 SD (two-sided test, alpha=0.05). This corresponds to a change in KCCQ score of 6-8, depending on the standard deviation in our sample (prior standard deviations of the KCCQ overall score range from 15-20). A change is KCCQ score of 6-8 is above the clinically meaningful change in KCCQ score.[62]

Aims 4-6

The sample sizes are described in Table 9.

Limitations and Considerations

1. *Given the multi-faceted intervention, it will be unclear which components are essential.* The intervention was specifically designed to have multiple components because symptoms and quality of life are complex phenomena. Multicomponent care interventions need to be tested as a whole. The quality improvement literature is rife with evidence that unimodal interventions have a low likelihood of success and interventions that have been shown to be effective in some studies usually have modest effects unless they are combined.[100,101] The analyses in Aim 2 will contribute to understanding the relative importance of intervention components.

2. *If the intervention is not successful in showing improvements in any of the outcome measures,* this will be an important, if undesired result, but study will still contribute to the evidence base regarding models of palliative care delivery and specifically HF palliative care. The process monitoring will inform future interventions.

3. *What is the potential for contamination?* It is possible that a provider may have patients in both the intervention and control arms. However, this is unlikely to have a significant effect because: a) these patients will represent a very small percentage of the patient panels of a given provider; b) providers will not know whether care recommended for a given intervention patient would be appropriate for a given control patient; and c) there is no clear evidence that specific recommendations for a given patient by a specialist or collaborative team are carried over to other patients by providers; and d) changing provider behavior is notoriously difficult. If any contamination did take place, it would bias results toward the null and would not invalidate any differences detected in outcomes.

4. *Recruitment problems*. The recruitment goals are modest and reasonable for each site. If necessary, resources can be diverted to increase efforts at one of the recruitment sites. We can also add recruitment of outpatients using the same enrollment criteria and conduct a sensitivity analysis to evaluate if outcomes are different for those recruited in this setting.

5. *Informal caregiver outcomes are not measured.* This is a patient-focused intervention; caregiver issues are not the primary focus. Prior work has shown the importance of caregivers in HF care, and caregiver involvement is part of quality palliative care. However, caregiver outcomes are beyond the scope of this study.

6. *Key palliative care elements, such as spiritual care, are not explicitly mentioned.* The palliative care specialist is on the team to bring all aspects of palliative care to patient care. If spiritual distress is identified, for example, the team can enlist a chaplain's assistance. The role of spiritual well-being in quality of life will be examined in Aim 3 and the intervention can be modified to formally include spiritual care if necessary.

7. Even if the intervention is not successful, we will still be able to conduct analyses examining the proposed relationships among depression, symptoms, and quality of life, and these analyses will inform the focus of future interventions designed to improve quality of life. In fact, if intervention and control patients are combined in the analysis, we will have adequate power to include functional status in the model in order to make inferences about relationships between symptom distress/severity, depression, and functional status.

8. If the correlations assumed in the power calculation are too high and the analysis is underpowered, the model will still be useful for examining the hypothesized relationships among variables. We would still examine the magnitude and significance of the individual paths, but perhaps not expect that the indirect effects will be significant.

Knowledge to be gained and Future Directions

Collectively, the proposed studies will *impact* clinical care for patients with HF by testing an innovative, evidence-based, theory-driven palliative symptom management and psychosocial care intervention and informing continued development of targeted interventions to improve outcomes. The core components of the intervention are structured to ease replication, implementation, and dissemination, and we plan subsequent studies to conduct an economic analysis of the intervention and to determine if the intervention has an effect on health care utilization and survival. The mediation analyses will inform subsequent interventions by identifying strengths and weaknesses of the proposed intervention. This study will contribute to a key gap in HF and palliative care research. If the intervention is successful, we plan future studies to conduct an economic analysis of the intervention and to determine if the intervention has an effect on utilization (outpatient and emergency department visits and hospitalizations) and survival. Because symptoms and depression are associated with utilization and survival, we will use the data collected on this study to estimate the sample size required to detect intervention effects on these outcomes. The analyses from Aims 2 and 3 will inform a decision to modify the content of the intervention in subsequent studies. If the intervention in this study improves outcomes, we will plan a larger and more rigorous study in diverse geographic locations using a control group that has the same contact time with the nurse and social worker, but that includes HF education or general support rather than palliative symptom management and structured psychosocial care. Ultimately, if the intervention is successful, we would focus on implementation and dissemination, in part using our immediately-available networks. Furthermore, the intervention could be adapted and studied in patients with other chronic illnesses, such as COPD, increasing its potential significance and utility. Similar to patients with HF, patients with COPD have many burdensome symptoms, comorbid depression, and poor quality of life. Finally, if the intervention is not successful, the process monitoring and the analyses in Aims 2 and 3 will guide our efforts in subsequent intervention modification and testing.

By understanding patient, provider, and organizational issues involved in implementation and sustainability, this proposed research will inform how to make available a team-based program to help address these problems and improve quality of life for the many veterans living with CHF. The research will help expand the reach of this program so it can impact a wide range of veterans, including veterans in rural areas.

Timeline

The proposed projects will be completed within a 5-year timeline (Table 10). The table illustrates timing for completion of the main study tasks using 6-month increments during the 5-year timeline.

Table 10. Timeline	Year									
Activity	1		2		3		4		5	
Study start-up										
Patient recruitment										
Outcomes measurement										
Program evaluation										
Site visits to rural clinics										
Analysis and write-up										

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