COMIRB Protocol

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Protocol #: **15-1891**
Project Title: **Palliative care to improve quality of life in CHF and COPD**
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I. Hypotheses and Specific Aims:

We will conduct a two site randomized clinical trial (VA Eastern Colorado Health Care System [VA ECHCS] and VA Puget Sound [PSVAHCS]) to determine whether an intervention to improve symptoms and to help Veterans adjust to living with Chronic Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD) and Interstitial Lung Disease (ILD) improves quality of life. The intervention will also help Veterans communicate preferences for treatment with their providers. The intervention involves routine clinical care and no experimental drugs or devices. The results will be directly relevant to Veterans who suffer with these illnesses and their families, as well as to providers, leaders in VA Central Office, and other researchers. Furthermore, this study will generate information that supports the broader dissemination and implementation of the intervention and informs the development of future palliative care and team-based interventions in the VA. Specific aims include:

Aim 1: Determine the effect of the intervention on (a) quality of life as a primary outcome, and (b) depression, symptom burden, advance care planning communication and documentation, disease-specific health status, emergency department visits, hospitalizations, and mortality as secondary outcomes.

Aim 2: Examine the implementation of the intervention.

Aim 2a: Assess the degree, barriers, and facilitators of implementation of various intervention components. Identify which intervention components and processes are most critical from the perspectives of patients, intervention team members, and primary care providers whose patients received the intervention.

Aim 2b. Evaluate the resources (e.g., personnel time and other costs) associated with the intervention, and estimate the resources needed for implementation and maintenance of the intervention in other VA settings.

The brief study title is Advancing Symptom Alleviation with Palliative Treatment (ADAPT) and will be used with participants as it provides a simple acronym.

II. Background and Significance:

Among Veterans, CHF and COPD are top causes of poor quality of life, hospitalizations, mortality, and health care costs. While not as common, ILD also leads to poor quality of life, has few effective treatments, and has a poor prognosis. While palliative care is effective in advanced cancer, it has not been adequately studied in CHF, ILD, or COPD. Commonalities in CHF, ILD, and COPD make them priorities for a palliative care intervention to improve quality of life in both populations. CHF and COPD commonly co-occur: there is a 20% chance a patient with COPD will have CHF, and a 30% chance a patient with heart failure will have COPD.[1] Despite disease-specific treatments CHF, ILD, and COPD, Veterans with these illnesses still suffer from the burdens of persistent, diverse symptoms and depression that reduce quality of life. These burdens are remarkably similar in CHF, ILD, and COPD despite different organ systems and pathophysiology.

Palliative care need #1: Poor quality of life in CHF, ILD and COPD is due to similar persistent, diverse symptoms and depression. This is illustrated in the study conceptual model (**Figure 1**), which is based on

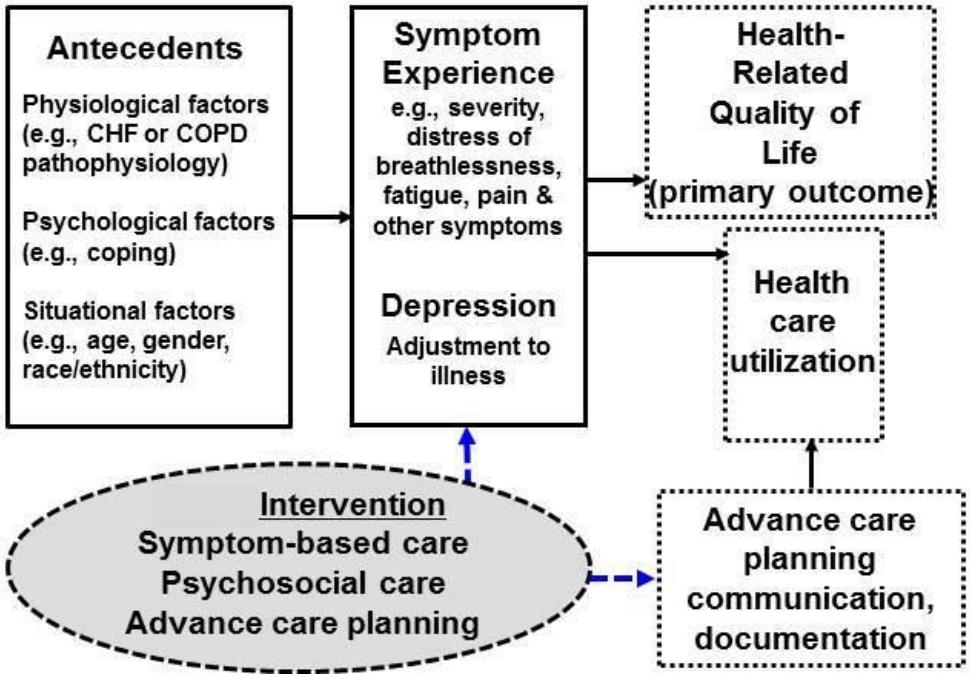
integrating elements of Lenz' unpleasant symptom theory[2] into an adaptation of the Wilson and Cleary model of health related quality of life.[3] As illustrated in the conceptual model, in CHF, ILD, and COPD, the symptom experience and depression exert major influences on health-related quality of life.

1. **Symptom experience: persistent, diverse symptoms**. Patients who have CHF, ILD or COPD are burdened by the same disease-related symptoms of breathlessness (44-85%) and fatigue (66-85%) as well as pain (38-58%) and other non-disease related symptoms that reduce quality of life and persist over time.[4-11] In CHF, a mean of 15 physical and emotional symptoms are experienced concurrently.[12] Diverse symptoms reduce quality of life in patients with CHF,[12] ILD,[10, 13] COPD.[7]

2. **Depression**. Depression in CHF, ILD and COPD is a key determinant of the experience of symptoms[12, 14-16] and quality of life.[14, 17, 18] Between 20-30% of patients with CHF,[19] ILD[16] or COPD[20] have depressive disorders. Between 50-60% have clinically significant depressive symptoms.[19, 21] VA studies demonstrate that the prevalence and severity of depression in Veterans with CHF and COPD increases with disease severity.[20, 22, 23]

Combining palliative symptom management with psychosocial care to reduce depression and help patients adjust to illness is an innovative approach. This approach is based on the strong correlation between depression and symptoms[12] and evidence showing that combined treatment of depression and pain is the most effective approach for both.[24]

Figure 1. Conceptual Model & Proposed Intervention Effects



Diverse symptoms and depression are not only major contributors to quality of life in Veterans, but they are also associated with numerous other adverse outcomes (**Figure 1**). In both HF and COPD, symptom severity and depression independently predict health care utilization (e.g., emergency department visits and hospitalizations) and mortality[19, 25-29] and contribute substantially to high care costs.[30]

Palliative care need #2: Few Veterans with CHF, ILD or COPD engage in advance care planning. Advance care planning is the process of considering and communicating healthcare values and goals.[31] An advance directive is a legal document describing preferences for future care and appointing a surrogate to make health care decisions in the event of incapacity. While the benefits of completing an advance directive are controversial,[32, 33] recent studies demonstrate advance care planning can reduce health care costs; increase the likelihood of dying at home and receiving care aligned with one's wishes; decrease rates of hospital admission; and increase rates of hospice admission.[34, 35] Advance care planning also improves patient and family satisfaction and reduces stress, anxiety, and depression in surviving relatives.[36] Despite these benefits and professional heart and lung organization recommendations,[37-40] few Veterans with CHF, ILD or COPD engage in advance care planning.[41] In addition, patients with CHF, ILD and COPD are often hospitalized at the end of life, although many say they would prefer to die at home.[42, 43]

By addressing diverse symptoms and depression to improve quality of life, and implementing a successful advance care planning intervention, this study will overcome limitations of prior studies
Despite disease-specific care in CHF, ILD, and COPD, patients experience poor quality of life. Disease management interventions in either illness have not consistently improved quality of life because they have not simultaneously addressed diverse symptoms and depression (**Figure 1**). In COPD, intensive pulmonary rehabilitation improves quality of life, but has limited reach as most veterans cannot access or receive pulmonary rehabilitation.

Prior palliative care interventions to improve quality of life in CHF, ILD, or COPD are sparse, have mixed results, and did not use high quality randomized study designs.[44-46] Furthermore, these studies did not evaluate advance care planning outcomes, a key component of palliative care. In the most promising study, common symptoms including depression and pain did not improve because providers often did not follow the palliative care consult recommendations.[44] By using a collaborative care model that integrates palliative care into primary care, our intervention will address this barrier.

By complementing disease-specific care with the addition of palliative and psychosocial care to address diverse symptoms and depression simultaneously, we hypothesize the proposed intervention will succeed in improving quality of life. In addition, the intervention will implement an advance care planning intervention that successfully improved advance care planning communication in COPD (see Preliminary Studies). Because both CHF, ILD and COPD have common barriers to advance care planning,[47-50] our advance care planning intervention is likely to succeed.

Limitations of palliative care delivery models will be addressed in this proposal to increase the reach and potential for dissemination of palliative care

1. Need to integrate palliative care into primary care. The predominant care delivery model in palliative care is inpatient, consultative care focused on the end of life. However, both patients with CHF and providers believe palliative care should be provided earlier in CHF and integrated into chronic outpatient care.[51, 52] Most of the care of Veterans with CHF or COPD takes place in primary care, and both primary care providers (PCPs) and specialists believe palliative care should be provided through primary care.[53] The intervention integrates palliative care into primary care through (1) a nurse who provides palliative care and collaborates with the Veteran's PCP, and (2) once a palliative care plan is approved by the PCP, palliative care orders are written for the PCP to review and sign
2. Specialist, consultative model of palliative care cannot be scaled-up to CHF and COPD. Given the difficulty assessing when end of life is near and talking to patients about palliative care, as well as concerns about professional control, providers avoid referring patients for palliative care.[53] Furthermore, there is an inadequate palliative care workforce to provide care for the large numbers of Veterans with advanced CHF or COPD.[54] Patients with advanced CHF prefer not to see additional providers for their care, including palliative care specialists.[52] Rather than using a consultative model, the study uses population-based identification of patients. A nurse and social worker are trained to provide basic palliative care and are supervised by a palliative care specialist.
3. Prior palliative care interventions are not structured and thus are difficult to replicate or disseminate. The proposed palliative care intervention is structured and operationalized in a treatment manual which will facilitate replication and dissemination.

Study innovation and rationale for Aim 2: within the context of an effectiveness trial, examine implementation issues
Blending the efficacy and effectiveness stages of intervention testing can (1) reduce the time delay between the discovery of health care innovations and their implementation;[55] (2) produce additional knowledge for researchers; and (3) increase the operations and policy relevance of clinical research.[56] VA researchers have emphasized the importance of understanding challenges to implementation early in intervention studies.[57] In the context of an effectiveness trial, VA QUERI has recommended blending by testing the effects of a clinical intervention while simultaneously observing and gathering information on implementation. QUERI has termed this a "hybrid effectiveness-implementation" (type 1) study design.[56]

The proposed study is innovative in that it is a "pragmatic" or "practical" (i.e., "effectiveness") clinical trial[58] that uses a type 1 hybrid design to generate information on implementation of team-based and palliative care interventions. It is an effectiveness trial because (1) population-based sampling is used to identify a "real world" population of veterans; (2) the intervention "dose" is allowed to vary with Veteran needs as would occur in the clinical setting; and (3) the analysis includes all patients regardless of compliance with the intervention and missing data. As a type 1 hybrid, the study will include collection of data on valuable intervention content and processes from the perspectives of patients, intervention team members, and PCPs whose patients received the intervention (**Aim 2a**). This data will yield information about barriers and facilitators of intervention delivery that will be important to plan subsequent implementation if the intervention is successful. If the intervention is not successful, this aim will inform subsequent implementation of other team-based, palliative care, or specialty/primary care interventions.

The operational partners contributing to this study recommended we determine the personnel time and other costs to implement and maintain the intervention (**Aim 2b**). This information, combined with an understanding of whether the intervention improves quality of life or advance care planning outcomes, was most important to them in considering intervention implementation and dissemination.

Research staff at VA ECHCS will assist PSVAHCS in some aspects of recruitment, follow-up data collection and the process evaluation. The Intervention SW and RN at each site will interact with participants at both sites.

III. Preliminary Studies:

Preliminary studies demonstrate study and intervention feasibility and likelihood of success:

1) The Principal Investigator (PI, Bekelman) developed and conducted initial pilot-testing of the CASA palliative symptom management component, which includes evaluations and treatments for fatigue, breathlessness, and pain, as Director of outpatient CHF palliative care programs at the University of Colorado Hospital (published sample of patients)[59] and the Denver VAMC.

2) The psychosocial care component of the intervention was developed by Carolyn Turvey, PhD (see letter of support) through grants from the NIMH (R34MH73566) and the American Heart Association (AHA 0555699Z).[60] 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 improved 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, 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.

3) In a single arm pilot study of 15 patients with advanced stage (GOLD III/IV) COPD, depression (Patient Health Questionnaire-9), anxiety (Generalized Anxiety Disorder-7), and overall quality of life (St. George Respiratory Questionnaire) improved with CASA over three months (effect sizes of 0.64, 0.54, and 0.22 respectively). The nurse was able to continue the intervention after the study concluded, and 10 patients (67%) elected to continue the intervention.

4) In a single arm pilot study of 17 patients with CHF (15 Veterans at the Denver VAMC), 16 completed the study, and symptom distress, depression, anxiety, and quality of life improved with CASA over three months (using the same measures as in the proposed IIR study, effect sizes of 0.64, 0.12, 0.57, and 0.27 respectively).[61] This study was funded by VA QUERI RRP 11-239 (PI: Bekelman). As planned in the intervention protocol, the CASA intervention team met weekly, and the nurse and social worker each provided a mean of 6 phone visits per patient.

5) In a RCT of 376 Veterans with COPD conducted by Co-I David Au (VA HSR&D IIR 02-292), advance care planning communication increased from 11% to 30% using the patient-completed preference form.[62]

6) For the proposed study, collaborating with the VA Office of Analytics and Business Intelligence, we electronically identified the number of potentially eligible patients with CHF and COPD. There were a total of 10,860 Veterans with CHF or COPD (Denver VAMC, n=5301; Seattle VAMC, n=5550). Of these, we identified 5,951 who were at high risk of hospitalization and death (see Table 1, Eligibility).

7) Drs. Bekelman (PI) and Au (Co-I) have expertise conducting multi-site behavioral and health delivery clinical trials.

IV. Research Methods

A. Outcome Measure(s):

Aim 1: The measures were chosen to reflect domains of the conceptual model (Figure 1) as follows (instrument abbreviations defined below):

- **Antecedents**: Demographics; CHF factors (e.g., left ventricular ejection fraction); COPD factors (e.g., spirometry)
- **Symptom Experience**: GSDS (symptom distress), Symptom assessments
- **Depression**: PHQ
- **Health-Related Quality of Life**: FACT-G (primary outcome measure), QUAL-E, KCCQ-12, CCQ, K-BILD
- **Health Care Utilization**: Hospitalizations
- **Advance care planning communication, documentation**: patient-reported advance care planning communication, advance directive documentation in Electronic medical record review

1. FACT-G (primary outcome): The Function Assessment of Chronic Illness Therapy-General is a widely used, valid, reliable (alpha range, 0.88-0.92), and responsive 27 item self-report measure of health-related quality of life that includes domains of physical, social/family, emotional, and functional well-being.[35, 63-65] Norms for the general population allow FACT-G scores to be measured and compared across study populations.[66] Validity in CHF and COPD has been demonstrated through FACT-G correlations with disease severity.[64]
2. 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.[67]
3. GSDS: The General Symptom Distress Scale is a single item measure of overall symptom distress that is reliable and valid[68] and asks, "In general, how distressing are all of your symptoms to you?" It is rated on 0 ("not at all distressing") to 10 ("extremely distressing") on a numeric rating scale.
4. PHQ-8: The Patient Health Questionnaire-8 is an 8-item valid and reliable instrument that provides a continuous measure of depressive symptoms and is sensitive and specific for a diagnosis of major depressive disorder.[69]
5. GAD-7: The Generalized Anxiety Disorder-7 is an 7-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.
6. 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").
7. PROMIS Fatigue: The Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale is a 4-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").
8. ISI: The Insomnia Severity Index is a 7 item reliable and valid instrument to quantify perceived insomnia severity.[72]
9. Constipation and Numbness/Tingling: These symptoms will each be assessed by one question asking how much the symptom distressed or bothered the respondent in the last week using a 6 point Likert-type scale from no symptom to very bothersome.
10. KCCQ-12: The Kansas City Cardiomyopathy Questionnaire is a 12-item self-administered validated questionnaire (administration time 5-10 minutes) that measures CHF-specific health status.[73] it is a shortened version of the KCCQ 23 item measure which is reliable, sensitive to clinical change, and predicts hospitalization and mortality.[74, 75] Additionally, we will ask two questions assessing how bothersome symptoms are. It will be administered to Veterans with CHF.
11. CCQ: The Clinical COPD Questionnaire is a self-administered 10-item measure of COPD symptoms, functioning, and emotional well-being. It is well-validated, reliable, and responsive.[76, 77] It will be administered to Veterans with COPD.

12. K-BILD: The King's Brief Interstitial Lung Disease is a 15-item self-completed health status measure for ILD. It is validated and can be used to assess ILD from the patient's perspective. It will be administered to Veterans with ILD[78].
12. 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. For example, spirometry results (COPD), NYHA classification (CHF), etiology of CHF or COPD, most recent ejection fraction (CHF), and BNP or NT-pro BNP (CHF) will be documented. Medical history (including comorbidities), current medications, number of hospitalizations in the previous year will also be collected at the time of the enrollment visit. Patients' current care, including palliative care, mental health, cardiology, pulmonology, hospice and specialist pain care will be ascertained at baseline and 6 months. At the 6 and12 month study visit, patients will be asked to relate interim events, including hospitalizations, the reasons for them, and for permission to obtain medical records relevant to such events from VA and non-VA facilities. Medications from the medical record will be documented again at the six month visit.
13. Advance care planning communication will be measured using patient report questions at the baseline and 6 month study visits. Advance directive documentation will be defined by the presence of any of the following notes in the electronic medical record at baseline and 6 months: advance directive discussion; scanned advance directive (either a living will or durable power of attorney for health care); or medical orders for life-sustaining treatment.
14. Hospitalizations/emergency room visits, mortality and risk of hospitalization and/or death: The following events will be assessed during the study period through VA and non-VA facility medical record review to supplement patient report: hospitalization (with cause) and mortality. We will also review medical records for intensive care use and end of life care patterns. We will also assess risk of hospitalization and/or death for participants during the study. Vital status will also be ascertained via the VA Vital Status File and the National Death Index.
15.Telephone Interview for Cognitive Status (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[79] and has demonstrated good sensitivity and specificity when discriminating between normals and individuals with mild cognitive impairment.[80] The TICS will be used as a covariate in the analyses.
16. Satisfaction surveys: Satisfaction with health care and the study will be assessed. Questions were adapted from the CANHELP Questionnaire.[81]

Aim 2a: We will conduct a mixed method (i.e., combination of quantitative and qualitative) evaluation to assess intervention implementation.

Intervention database: The intervention database will be used to track intervention content and processes.

Brief patient interviews: After the 6 month outcome measurement, we will conduct interviews with Veterans randomized to the intervention arm to ask for their feedback on the intervention.

Intervention Close Out Summary: The intervention team will complete an Intervention Team Intervention Close Out Summary on each Veteran once they complete the intervention.

Focused Group Discussion with Intervention Team: We will conduct structured group discussions with intervention team members at the completion of the project intervention period to debrief about how the intervention was implemented.

Surveys of PCPs: We will administer a brief survey to all PCPs who have patients who have completed the intervention.

Aim 2b: We will evaluate the resources and costs to implement and maintain the intervention. Data for the *costs to implement* (i.e., start-up costs) and the *cost to maintain* the intervention will be collected separately. At a minimum, the costs to implement will include personnel training, database development; the costs to maintain will include identification of eligible Veterans and personnel time to provide the intervention (e.g., patient visits/phone calls; team meetings; communication/coordination with PCPs).

B. Description of Population to be Enrolled:

Settings

The study will be conducted at the VA Eastern Colorado Health Care System (VA ECHCS) and Puget Sound VA Health Care (PSVAHCS) systems. Each health care system includes a tertiary care medical center and seven community-based outpatient clinics (CBOCs).

Study population:

Aim 1: A total of 400 adult subjects will be randomized in a 1:1 ratio to one of 2 treatment arms: 1) enhanced usual care or 2) team-based palliative care intervention plus usual care. A component of the study intervention involves speaking to study subjects' informal (family) caregivers. The eligibility criteria (**Table 1**) aim to enroll Veterans with a diagnosis of CHF, ILD, or COPD who are at risk of hospitalizations or death, have poor quality of life, and are able to participate in the intervention.

Table 1. Eligibility Criteria

Inclusion Criteria	Definition
• CHF: Diagnosis of CHF in 2 years prior to enrollment	• Inpatient hospital diagnosis or ≥2 outpatient visits*
• COPD: Diagnosis of COPD in 2 years prior to enrollment	• Inpatient hospital diagnosis or ≥2 outpatient visits*
• ILD: Diagnosis of ILD in 2 years prior to enrollment	• Inpatient hospital diagnosis or ≥ 2 outpatient pulmonary visits **
• Among those with CHF or COPD, high risk for hospitalization and death	• Care Assessment Need score ≥ 80
• Poor quality of life	• FACT-G score ≤ 70
• Symptomatic	• Bothered by at least one of the target symptoms: pain, fatigue, depression, shortness of breath, trouble sleeping
• Primary care or other provider who is willing to facilitate intervention medical recommendations	• PCP listed in Electronic medical record review or self-report
• Able to read and understand English	• Self-report
• Consistent access to and able to use a standard telephone	• Self-report
Exclusion Criteria	
• Previous diagnosis of dementia	• Inpatient or outpatient diagnostic code†
• Active substance abuse	• Electronic medical record review for substance abuse in the previous 6 months
• Comorbid metastatic cancer	• Electronic medical record review
• Diagnosis of obesity hypoventilation syndrome	• Inpatient or outpatient diagnostic code (ICD9 278.03, ICD10 E66.2) or (BMI >=45 and diagnostic codes for COPD)
• Nursing home resident	• Electronic medical record review or self-report
• Heart or lung transplant or LVAD	• Electronic medical record review or self-report
• Participation in the intervention arm of the CASA trial, COMIRB 11-0969	• Electronic medical record review
• Enrolled in palliative care, hospice or home based primary care	• Electronic medical record review or self-report
• Prisoner	• Electronic medical record
• Pregnant	• Electronic medical record or self-report

* ICD-9 code definitions for CHF (428.XX) validated in Go et al[82]; ICD-9 code definitions for COPD (491.XX, 492.XX, 493.2, 496.XX) validated in Au et al[83] and the corresponding ICD-10 codes

**ICD-9 code definitions for ILD: 515, 516.30, 516.31, 516.32, 516.34, 516.37 and the corresponding ICD-10 codes

† ICD-9 codes for dementia (290.0-290.43, 291.2. 046.1, 294.0, 294.1x, 294.2x, 294.8, 331.0, 331.1x, 331.2, 331.6, 331.7, 331.82, 331.89, 331.9) from Taylor et al[84] and Bharmal et al[85] and the corresponding ICD-10 codes

Patients with CHF, ILD, or COPD in both the PSVAHCS and VA ECHCS will be identified electronically by staff at the VA ECHCS site using validated combinations of diagnostic codes.[82, 83] The Care Assessment Need

(CAN) score will be used to define a population at increased risk for hospitalizations or death that is likely to need the palliative care intervention because of increased illness severity.[86] The CAN is a VA-developed prognostic tool that was created to help primary care proactively identify and manage at risk Veterans on a population level. We will collect the CAN score on all potential subjects with a diagnosis of CHF, COPD, or ILD as defined in Table 1. A CAN score of ≥ 80 for those with CHF or COPD was chosen in consultation with the VA Central Offices of Primary Care and Palliative Care. Preliminary studies identified 5,951 Veterans total at both sites with CHF or COPD and a CAN score of ≥ 80. The CAN score may not be as valid for the small number of patients with ILD, thus we will not use it as an eligibility criterion.

To enroll a sample with poor quality of life who is appropriate for the intervention, potential participants will need to report a Functional Assessment of Chronic Illness Therapy-General (FACT-G) score ≤ 70 and be bothered by one of the intervention target symptoms. The FACT-G is a widely-used, valid, reliable quality of life measure that is the primary outcome in this study. It measures physical, social/family, emotional, and functional well-being. A score of ≤ 70 identifies poor quality of life as validated by declining performance status and increasing disease burden.[87]

Given the intervention delivery model whose purpose is to integrate palliative care into chronic care, a provider (ideally the PCP) must be willing to work with the intervention team. In prior studies,[61,72] all PCPs were willing to work with the team. The intervention was developed in English for adults and the majority of the study instruments have been validated only in English. As the intervention is provided by phone, participants must have phone access. Potential participants 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 a substance abuse documented in EMR in the previous 6 months (cannabis will be allowed) 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 CHF, ILD, and COPD rather than cancer palliative care. Those with a diagnosis of obesity hypoventilation syndrome, or those at high risk for obesity hypoventilation syndrome (BMI >= 45 and diagnostic codes for COPD), are excluded as we do not think this intervention will be helpful to them. Those with a heart or lung transplant or left ventricular assist device (LVAD) will be excluded because they already receive substantial psychosocial care and resources. Those receiving palliative care, hospice and home-based primary care will be excluded as they are likely to be receiving services similar to what is provided in the intervention. We will exclude those who participated in the intervention arm of the CASA trial (COMIRB #11-0969) as they have received some components of the intervention in this trial. Finally, nursing home residents 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.

Patient interviews: After the outcome measurement at 6 months, we will conduct interviews with Veterans randomized to the intervention arm to ask their opinions on the helpfulness of the intervention. We will interview a subset of patients completing the intervention every 6 months in order to account for potential differences over time (e.g., intervention provider experience).

Intervention personnel: All intervention personnel will be invited to participate.

Primary care providers whose patients have received the intervention: Providers who have patients who have completed the intervention will be invited to complete a brief survey.

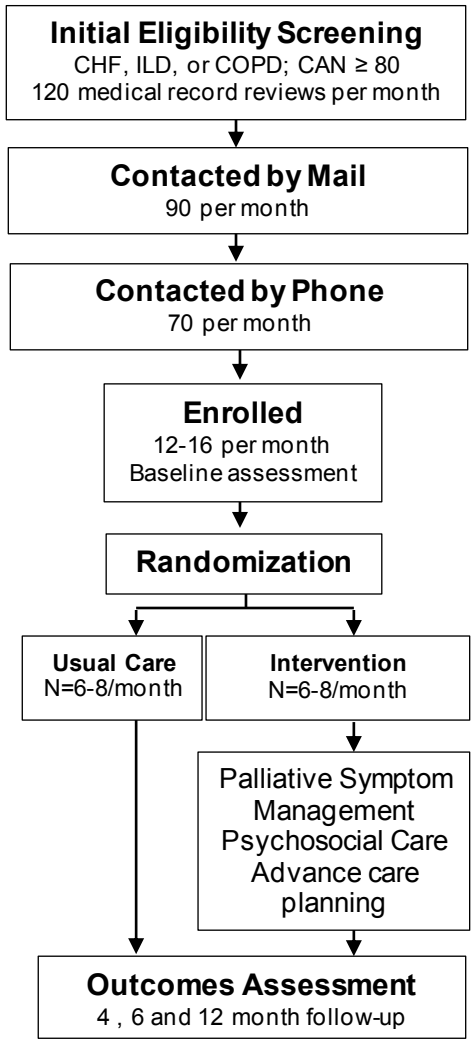
C. Study Design and Research Methods.

Timeline

Table 2. Timeline	Year							
Activity	1		2		3		4	
Study start-up	x							
Patient recruitment		x	x	x	x			
Outcomes measurement, implementation data collection		x	x	x	x	x	x	
Analysis and write-up								x

The proposed study will be completed within a 4 year timeline (**Table 2**). Collection and analysis of medical record information will continue for up to ten years after a patient's active study participation concludes.
The table illustrates timing for completion of the main study tasks using 6-month increments. We will try to complete recruitment over a 19 month period, but have budgeted for completing recruitment over 25 months.

Figure 2. Study Population Flow



Recruitment Targets and Tracking

Aim 1:
The estimated flow of patients and overall accrual goals are displayed in **Figure 2**. We will aim to randomize 8 patients per month at each site (16 total) over a 19 month period. This will yield one intervention patient per week per site on average. If enrollment is slower than anticipated, we will still be able to complete the study on time if 6 Veterans per month are randomized at each site over a 25 month period.

Aim 2a:

Patient interviews: We anticipate at most 120 eligible patients of the 200 receiving the intervention will participate, as they have already participated in the intervention and would be likely to offer feedback.

Intervention personnel: We expect all intervention team members to participate as they are invested in the intervention and would be likely to want to provide feedback.

Primary care providers whose patients have received the intervention: We expect approximately 100 providers will participate.

Recruitment Process
Aim 1:

1. We are requesting a HIPAA waiver to allow us to screen administrative databases and review medical records of Veterans seen at each study site to identify Veterans who may be appropriate for the study. Data sources for screening include CDW Production, CDW Raw, CAN Score, PACT Implementation Index, Real SSN, Scrambled SSN, CAPRI, and VSSC web reporting.
2. Administrative data will be pulled according to the inclusion/exclusion criteria outlined in section "Study population." We will also use a research database of veterans who consented to be contacted for future research studies as part of the VA CASA trial (COMIRB #11-0969) and meet eligibility requirements. Providers within the VA system can also choose to tell potential study participants about the study and provide them with a flyer for the patient to write in patient contact information and either return to study staff or call study staff directly for more information about the study.
3. Study staff will review medical records to confirm eligibility criteria.
4. Veterans who meet initial eligibility screening will be mailed a letter that describes the study and gives them the opportunity to call the recruitment team if they are interested or decline by returning a postage paid letter and envelope. The letter will also say that the Veteran will be contacted by phone if the study team does not receive communication from the Veteran. Veterans can also opt out during the phone call.
5. Interested Veterans will be asked to verbally consent to further phone screening to verify eligibility (see included script).

6. Patients who are eligible after screening will be asked to provide informed consent (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 a $10 incentive for participation, provided at the baseline, 4m and 12 month visits and $15 at the 6 month visit. Participants may decline payment.

   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.

VA providers may refer their patients to the study.

The research coordinator, research assistant, study social worker and the study nurse may contact and conduct study procedures with patients according to the protocol at both sites.

Prior to the start of the study, all research staff will be trained and will practice the screening and 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.

Randomization - Aim 1:
Randomization will occur at the patient level with 1:1 randomization of patients to intervention or control groups. Randomization will be computer generated using random block sizes and stratified by site and disease CHF, ILD, or COPD, or both CHF and COPD.

Sample Size
The sample size was planned to detect a clinically significant change on the primary outcome, quality of life. We plan to enroll 400 Veterans and anticipate 5% will die and 15-20% will have missing outcome data because they did not complete surveys or dropped out. Thus approximately 115 Veterans per arm will complete the study. With this sample size, we will have 85% power to detect a moderate effect size of 0.4 (two-sided test, alpha=0.05). The minimal clinically important difference on the FACT-G is 4-6 points,[88] and with a standard deviation of 15, a Cohen's d effect size of 0.4 will be on the high end of clinical significance. We believe this is appropriate as this is a personnel-intensive intervention. **Table 3** illustrates a range of sample sizes per study arm with different power and effect size assumptions.

Table 3. Sample sizes per study arm for different assumptions

	Power		
Effect size	**80%**	**85%**	**90%**
0.35	130	148	173
0.40	100	114	133
0.45	79	90	105

Aim 2a:
Patient interviews: Patients will consent to participant in interviews when they provide informed consent for Aim 1.

Intervention personnel: All intervention personnel will be asked to participate in the focused group discussion. Recruitment and consent: Those who agree will be asked to provide verbal consent to the following at the beginning of all focus group:

- 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

Primary care providers whose patients have received the intervention: Providers will be invited to complete the survey via email, phone or in-person. By completing in the survey, they will provide consent for this portion of the study. We will request a waiver of written consent for providers who complete the survey because the surveys are minimal risk, and it is impractical to obtain written consent from busy health care providers.

Table 4. Intervention Overview

Intervention Component	Personnel
Algorithm-guided symptom management: breathlessness, fatigue, pain, trouble sleeping	Registered Nurse (RN)
Structured psychosocial care, targeting depression and adjustment to illness; advance care planning	Social Worker
Team collaborative care model: 30-60 minute weekly team meetings	RN, LCSW, palliative and primary care providers

Description of the Intervention

Overview: The intervention is Veteran-centered, multidisciplinary, addresses palliative and psychosocial issues, and integrates with PCP care (**Table 4**). A nurse (Registered Nurse, RN) and a social worker (Master's level, e.g., MSW) will be the primary intervention personnel. The nurse and social worker will meet weekly for approximately 60 minutes with a collaborative care team ("Team") including a representative PCP and palliative care specialist. Each site (VA ECHCS, PSVAHCS) will have a Team. The Team will provide caseload supervision and write notes and orders for patient's clinical providers to sign.

Team collaborative care model: The Team will provide symptom-based care by integrating palliative symptom management with CHF, ILD, and/or COPD disease-specific care plans[37, 38] based on the intervention team interviews/evaluations of patients and medical record review. Study staff will record the Team's recommendations in a progress note in the Veteran's electronic medical record. The psychosocial care and other non-pharmacological recommendations (e.g., pacing) will be implemented immediately by the intervention team. Orders for medications or tests will be written for patient's clinical providers to review & sign at their discretion. This integration into ongoing primary care both informs patient's clinical providers of the intervention care plan and provides an extra level of safety for patients by asking clinical providers to sign medical orders. The team will have phone access to a cardiologist and pulmonologist for specialist support and will re-review patients if their symptoms are not improving as assessed by the study staff.

Visits: The intervention team will make an initial in-person, phone or VA telehealth equipment visit with patients and informal caregivers. At the initial visit, a history and examination will be conducted and the patient will be offered the option of choosing which initial symptom (fatigue, breathlessness, pain, depression, trouble sleeping) on which to focus. With participants' permission, these visits may be audiorecorded. If an informal (family) caregiver is present, s/he will be invited to participate in the discussion. Follow-up visits will be by phone or in-person to accommodate patient preferences, and the number and duration will be tracked. The nurse will provide approximately 6 visits (2/month) to check on symptoms and provide education, and the social worker will provide approximately 6 visits (2/month) to complete the psychosocial intervention. This will be allowed to vary dependent on patient and staffing needs. In the unexpected situation that study nurse or social worker are unavailable to contact participants, study physicians will contact study participants to administer the intervention as needed.

Algorithm-guided symptom management: The nurse will assess patients' symptoms and, based on the symptom algorithms, discuss an initial management plan with the collaborative care team. Algorithms for breathlessness, fatigue, and pain have been previously developed and studied. An algorithm for trouble sleeping was developed for this study. To facilitate patient commitment and activation, we will suggest patients choose one of the symptoms to work on initially, although they will have the option of choosing other symptoms in subsequent visits (e.g., constipation). In our previous studies, the overwhelming majority seek help for fatigue, breathlessness, pain or depression,[52, 61] which will be addressed by the social worker. The nurse is responsible for following up on medical orders, disease and health care system navigation education, advance care planning discussions, assessing changes in patients' symptoms and progress on behavioral changes (e.g., increased physical activity), and communicating with patients' PCPs. The social worker will assist the nurse as needed for this part of the intervention.

Structured psychosocial care: The social worker will conduct a psychosocial assessment,[89] and provide 6 phone-based counseling sessions. This counseling was specifically developed and tested in patients with CHF or COPD to improve depression[60] (see Preliminary Studies). The purpose is to help veterans adjust to living

with CHF, ILD, or COPD and to activate/empower them to discuss issues related to their illness with their care providers. The counseling will be supplemented with antidepressant medication if the Team agrees providing antidepressant medication is an appropriate, evidenced-based recommendation. The social worker will also follow up on the patient-completed advance care planning preference form to help patients clarify health care goals and complete written advance directives. The nurse will assist the social worker as needed for this part of the intervention.

Advance Care Planning: The intervention team will meet with the patient one time to discuss care goals. Using a structured guideline,[90] participants understanding of their illness will be assessed. Questions about what is important, goals, concerns and fears will be asked. If a caregiver is present, s/he will be invited to participate in the discussion. The discussion will be documented in the medical record.

Control Group (treatment as usual plus information from baseline surveys and self-care materials)
Patients in the control group will continue to receive care at the discretion of their providers, which may include referrals to and ongoing care from cardiology, pulmonary, 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 depression surveys if screen positive for depression. 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 self-care materials or 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. We considered a control group that included time with a nurse or social worker to match the intervention patients' time ("attention control"). However, this is not feasible as the intervention "dose" of nursing and social work care varies according to patient needs and symptoms. It would not be possible to match the "dose" of provider time in both groups.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Aim 1: Study personnel will administer measures four times: enrollment (baseline), 4 months, 6 months and 12 months (**Table 5**). The baseline and 6-month measures which are comprised of approximately 120 questions and are expected to last 45 minutes, will be obtained during an in-person visit, by mail and phone or by video teleconference. We will allow patients to complete 4 month and 12 month measures by mail or phone if they prefer Veterans will be offered an incentive for completing each of the 4 study visits ($10 at baseline, $10 at 4 months, $15 at 6 months, $10 at 12 months). Patient reported survey data is necessary to achieve study aims as the primary outcome is quality of life which is patient perceived. Demographic data and information from medical record review is necessary to determine secondary outcomes. We have implemented the following protections:

Table 5. Study Visits and Assessments	**Baseline**	**Month 4**	**Month 6**	**Month 12**
Demographics/study form	X			
FACT-G (primary outcome)	X	X	X	X
PHQ-8, GAD-7	X	X	X	
KCCQ-12, CCQ, K-BILD	X	X	X	
QUAL-E,Symptom Assessment, GSDS	X		X	
Advance care planning communication, assess for advance directive documentation	X		X	
Medications	X		X	
Heath care utilization, vital status, risk of hospitalization/death			X	X
Use of other medical services	X		X	

Satisfaction	X		X	

Medical record data will be gathered for up to ten years after each participant concludes active study participation. The purpose of this is to determine the effect of the intervention on long-term health and health care use. This could include but is not limited to hospital discharge summaries, progress notes, operative notes, laboratory results, and diagnostic tests.

Protection against loss of confidentiality.
To protect against loss of confidentiality, all research materials will be inaccessible to anyone other than the investigators and research staff. All source documents will be identified by study identification (ID) number, and the key to that ID will be kept in a locked file cabinet in a locked office of the site PI, study coordinator, or research assistant. All personally identifiable information also will be kept separately from data forms and in a locked file cabinet. No results will be entered into our data collection system or reported in a personally identifiable manner. Any non-VA healthcare records will be faxed to a fax machine in a restricted access room.

We will use the Research Electronic Data Capture (REDCap) system for electronic entry of deidentified outcome data. All tracking system data will be password-protected with several levels of protection. The first will allow access to the operating system of the computer. The second will allow access to the basic menus of the integrated system; within certain menu options, such as database browsing, a third password will be required. All user interaction with the web-based system, from transmission of access passwords to sensitive patient data, is done via 128-bit encryption using the secure HTTPS protocol. REDCap is also HIPAA-compliant. Data will be downloaded from VINCI REDCap to the local VA Server for analysis. Data for intervention patients will be stored on VA secure research servers designated for storage of protected health and identifiable information.

Protection against loss of privacy.
The majority of the interactions with study subjects will occur over the phone. Study personnel will make these phone calls from a private office or cubicle. At the beginning of any phone calls, study personnel will ask subjects if it is an acceptable time to talk and if privacy can be assured. We will accommodate study subjects by calling on different dates or times. For the recruitment visit and initial study visit that takes place in the hospital or clinic setting, we will also attempt to enhance privacy as much as possible if study subjects do not have a private room. For example, we will use a family conference room on the hospital unit or clinic and close curtains or doors.

Table 6. Intervention implementation (Aim 2a) objectives, data collection, and analytic frameworks

Objective	Data Source	Sample Size	Analytic Framework
Assess intervention component implementation	Intervention database	150	Quantitative: descriptive statistics by site and illness of the variability in "dose" and content of the delivered intervention
Identify critical intervention components and processes and facilitators/barriers to intervention implementation	Brief patient interviews	100	Qualitative analysis of data 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*
	Intervention close out summary	150	
	Focused group discussion with intervention team	1-2	
	Survey of PCPs whose patients have received the intervention	150	

*CFIR, Consolidated Framework for Implementation Research

Staff Training, Supervision and Quality Assurance.
The intervention manual and protocol, procedures for medical or psychological emergencies, procedures for protection of human subjects, and HIPAA requirements will be reviewed in detail in a pre-study meeting. The importance of adherence to intervention protocol will be stressed. The social workers will be trained in the intervention and how to provide psychosocial care. This will include training to review the theory underlying the counseling, a review of the treatment manual and patient materials, and role-playing to show the appropriate application of the counseling. Study training will also include training for the study nurse who is conducting the palliative symptom management algorithms and coordinating the collaborative care team. This training will review the symptom management algorithms and procedures for unanticipated events (e.g., a subject complains of chest pain while on the phone). Day-to-day supervision and study fidelity and quality assurance will be maintained by the PIs.

Data management/Data quality
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 VA research servers for building and managing online 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 Data Safety and Monitoring Board and quarterly review by the study investigators.

In the event we discover a serious medical or psychological problem in the usual care group, a referral will be made to appropriate medical and/or psychological professionals. Participants will be encouraged to access resources provided by their personal health team as well as community resources.

Study Procedures for Positive Depression Screening:
The outcome measures administered to all subjects include a screen for depression (a score of greater than 10 on the PHQ-8[69]). Because the intervention focuses on depression, these issues will be addressed in intervention subjects as part of the intervention. Subjects in the *usual care* group who score above the screening cutoff for moderate depression will be advised of this and given resources for depression care, including advice to discuss these results with a health care professional. In addition, the results will be forwarded to their health care professional.

Aim 2a: To understand why particular intervention components and processes were most critical from the perspectives of patients, intervention team members, and PCPs, we used the Consolidated Framework for Implementation Research (CFIR) to guide data collection (**Table 6**). CFIR, which is well-established in VA, was chosen as it provides a useful framework for considering contextual facilitators and barriers to intervention implementation.[91] Specific domains and constructs from CFIR were chosen to reflect the areas that were important to patients, intervention team members, and providers in the CASA pilot study.[61] The following data sources will be used for Aim 2a:

Intervention database: The following data will be collected: (1) team meeting duration, number of patients discussed and time spent per patient, medical orders (e.g., tests, medications) written and completed; (2) nurse and social worker visit duration, number, and content (using a brief checklist) for each patient.

Brief patient interviews: After the outcome measurement at 6 months, we will conduct brief in-person or telephone interviews with Veterans randomized to the intervention arm. 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 to what extent they continue to sustain their use of the intervention after the study. We will continue to interview as staff time permits or until no new information emerges from continuing interviews, a principle known in qualitative research as "saturation."[92] We will interview a subset of patients completing the intervention every 6 months in order to account for potential

differences over time (e.g., intervention provider experience). We will seek variability in the sample we interview (e.g., by sampling from both study sites and sampling patients who benefit the most and least from the intervention based on changes in the FACT-G score at 6 months or participant ratings of helpfulness). Interviews will be audio-recorded using a secure recording mechanism or an audio recording device. Detailed notes will be taken during the interviews. Interviews will be transcribed verbatim by VA contracted transcription service or a member of the study team. All interviews will be de-identified and all PHI/PII will be removed before transcribed.

Intervention Close Out Summary: This 1-page summary form will capture information from intervention providers on what worked well and not so well with components of the intervention, what was missing, and whether the patient engaged in and followed up with behavioral changes.

Focused Group Discussion with Intervention Team: The goal of this discussion is to elicit intervention team views about what worked well; what parts of the intervention might be streamlined, dropped or enhanced; and their views about patient, family caregiver, and PCP receptivity and responsiveness. A qualitative researcher will lead these focused group discussions which will be recorded and transcribed

Surveys of PCPs: Using a combination of rating scales and a few open-ended questions, the goal of these surveys is to efficiently identify strong positive or negative opinions about the usefulness of different intervention components, integration of the intervention into work flow, and the perceived impact of the intervention on quality of care. We will also ask for their insights into ways to sustain and spread the intervention to other urban and rural VA sites. The questions were selected to explore specific CFIR constructs of importance. Providers will complete the survey via phone, in-person, or via e-mail.

Aim 2b: In addition to the above data collected for Aim 2a that are associated with the intervention content and processes, we will also use methods and instruments described in Ritzwoller et al 2009[93] to evaluate the resources and costs to implement and maintain the intervention. These resources and costs will be measured from the perspective of each VA health care system site. The rationale for this perspective is that each health care system (ECHCS and PSVAHCS) has budgetary and administrative authority over implementing programs such as the proposed intervention. Resources associated with the program will be classified as labor (e.g., nurse intervention time) or non-labor (e.g., supplies, printing of patient materials) and recorded using Excel spreadsheets. Costs for research (e.g., grant administration, IRB approvals, informed consent, analysis) will not be included.

E. Potential Scientific Problems:

1. *Recruitment problems*. The recruitment goals are modest, reasonable for each site, and were planned based on the investigators experience with similar prior trials. If necessary, resources can be diverted to increase efforts at one of the recruitment sites. We can also add recruitment of inpatients at the sites' VAMCs using the same enrollment criteria and conduct a sensitivity analysis to determine if outcomes are different for those recruited in this setting.

2. *Limits of administrative data for the diagnosis of CHF, ILD, or COPD*. While the administrative codes used to identify patients with CHF or COPD have been validated, they are not perfect and some Veterans will be enrolled who do not have these illnesses. However, all enrolled Veterans will be appropriate for the intervention because they will (1) be at high risk of hospitalization and death, (2) have poor quality of life, and (3) be symptomatic. The team will recommend appropriate evaluation and management for all Veterans. For example, this may include a spirometry test to evaluate for COPD if it was not previously done.

3. *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. In addition, social workers have basic spiritual assessment and management skills. If spiritual distress is identified, for example, the team can enlist assistance from a chaplain or the Veteran's religious community.

4. *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. The process monitoring will inform future interventions.

5. *This is a personnel intensive intervention.* Compared to a traditional palliative care consultation in which a specialist palliative care team (physician, nurse, social worker, chaplain) all provide direct patient care, the intervention was designed to use much less personnel time. Most of the intervention is delivered by phone. We will track the personnel time and other costs associated with the intervention (Aim 2b).

F. Data Analysis Plan:

Aim 1 Data Analysis

Descriptive Statistics and Basic Comparisons. All analysis variables, including predictors, covariates, 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 using Cronbach's alpha, and whenever possible, items and scales will be compared to existing findings on their psychometric properties to ensure appropriate performance. Data transformations will be considered, 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 tests, such as Chi-square and t-tests.

Primary/Secondary Analyses. Data from all participants will be included regardless of level of participation using an intent-to-treat approach**.** The primary outcome measure, FACT-G, will be analyzed as a continuous variable, while the secondary outcomes will be either continuous (disease-specific health status, depression, symptom burden, emergency department visits, hospitalizations) or binary (advance care planning communication and documentation; mortality). Due to the short follow-up period, time-to-event analyses will not be used. Analyses of the repeated measures, including primary and secondary endpoints, will be performed with SAS 9.4 using maximum likelihood estimation (MLE) for incomplete data using linear mixed models for continuous outcomes and generalized linear mixed models with a logit link for binary endpoints. 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, if desired, and 4) the assumptions about missing data are relaxed from missing completely at random to missing at random.[94] The primary analyses will not consider the pre-randomization variables, but the effect of these variables on outcomes will be investigated as secondary analyses. We will add a random intercept for PCP to the analytic models to account for clustering of outcomes by practice patterns.

The primary outcome will be the difference in FACT-G score at 6 months. Because of the anticipated high correlation of baseline FACT-G with follow-up FACT-G ($r>0.5$), we will include the baseline FACT-G as a precision variable in the mixed model.[95] To describe the treatment by disease interaction, we will estimate the treatment effect and its confidence interval within each of the disease groups (CHF, ILD, COPD) using disease-specific health status measures (KCCQ, K-BILD, CCQ) at the 6 month endpoint. In exploratory analyses, we will estimate treatment effect within illness subgroups (CHF, ILD, and COPD) on the primary outcome, and within subgroups of illness, including CHF (preserved vs. reduced ejection fraction) and COPD (defined by spirometry and imaging). Missing data will be reviewed to identify potential patterns and examined to assess how these patterns impact our results. Specifically, we will examine plots of group means over time stratified by the time of the last completed observation to determine if biases are evident due to missing data. When data are missing at random, unbiased results can still be obtained from the likelihood method used in the analysis. To account for the possibility of data missing not at random, sensitivity analyses will be performed using pattern mixture models[96] and results will be presented to assess the impact of missing data on the reported conclusions. Among those who were hospitalized or died, we will examine for differences in

intensive care utilization and patterns of care at the end of life. We will also examine for intervention effect on longer term health care utilization (e.g., hospitalization, intensive care utilization).

Aim 2a Data Analysis

The quantitative data on intervention component implementation will be examined using descriptive statistics. For example, for team meetings, the number and type of medical orders written and completed will be summarized. For social worker visits, the median, range, interquartile range, and types of modules completed will be displayed. This type of analysis was completed for the pilot study[61] and will show what components of the intervention were actually done. It will characterize the true "dose" and content of the intervention that was provided. This will contribute information about what may have led to intervention success or failure.

The data on intervention components and processes will be analyzed 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. A qualitative analyst and the research assistant will serve as primary coders for qualitative data, and PI 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 a qualitative analyst, the PI, and the research assistant to review and refine codes, code definitions and conceptual boundaries for our analysis.[97] The iterative analysis will begin by using the a-priori codes based on the CFIR model (Table 6), supplemented by codes reflecting intervention content and structure and questions used for data collection. Codes will be refined and new codes added as new insights emerge. Through systematic coding we will quickly develop working themes and hypotheses about critical intervention components and processes that will be examined (and inform any minor changes in data collection interview guides/survey). These themes will also describe facilitators and barriers to intervention implementation. We will both audio-record 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.

We will use several recommended strategies to enhance the validity or credibility of qualitative findings:[92] (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.

In addition to analyzing and summarizing quantitative (implementation tracking database and provider surveys) and qualitative (patient interviews and intervention team focus groups) findings separately, we will also merge findings to draw overarching lessons learned from multiple methods used. In this process, findings will be summarized in a table placing qualitative themes side by side with the quantitative findings to show the extent to which the data converges. Merging these findings will provide "triangulation": findings from each data source will be used to validate and confirm findings from the other data sources. With the combination of qualitative and quantitative data, we expect to provide a more complete explanation of why certain intervention components and processes are more critical than others, as well as facilitators and barriers to the implementation of the intervention.

Aim 2b Data Analysis

We will first calculate the resources (personnel hours or FTE, and other costs) to implement and maintain the intervention during the study. Personnel costs associated with the program will be calculated based on actual VA nurse (and other staff) wage and benefit rates. Total intervention costs and costs per intervention participant at each site will be calculated. Actual salaries and benefits will be used when calculating personnel costs. Second, we will estimate the resources and costs to implement and maintain the program in a variety of VA settings.

Several sensitivity analyses will estimate the range of intervention costs using alternative assumptions for costs that may vary in different implementation contexts. Three sensitivity analyses are planned: (1) variable labor costs with more or less experienced nurses or physicians; (2) variable efficiency of the nurse and social

worker in part-time vs. full-time intervention roles; this will be done using actual data that reflect the range of time spent per patient early in the study vs. later in the study; (3) variable patient case mix using the range of time spent per patient. In exploratory analyses, we will estimate which patient-level predictors (e.g., cardiac ejection fraction, spirometry, quality of life) are associated with time spent per patient (outcome) using linear regression models.

G. Summarize Knowledge to be Gained

The proposed study is significant because it aims to improve quality of life and provision of care according to Veterans' goals and preferences in common, burdensome illnesses. The study is innovative because it (1) tests the effectiveness of palliative care in CHF, ILD, and COPD, leading causes of death among Veterans; (2) combines palliative and disease-specific care for symptoms with psychosocial treatment for depression to improve quality of life; and (3) leverages the skills of affiliate health providers (nurses, social workers) to provide basic palliative care, with physician supervision; and (4) uses an hybrid effectiveness/implementation design to increase the relevance to operations leaders and future research. The research team has expertise in behavioral and health care delivery clinical trials, CHF, ILD and COPD, and implementation science.

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