Group Medical Visits in Heart Failure (MEDIC-HF)
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Group Medical Visits in Heart Failure for Post-Hospitalization Follow-Up
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SPECIFIC AIMS

The primary goal of this research project is to improve the health status and decrease hospitalization and death for patients discharged with heart failure (HF) via self-management education to patients, disease monitoring and medication titration through shared medical appointments (SMAs).

HF is a complex chronic illness where patients have a significant impairment of health status,[1] with a high burden of morbidity and mortality. Half of Americans who develop HF die within 5 years of diagnosis[2] and more than 1/3 of HF patients require frequent hospitalizations,[3] or placement in long term care.[4] Studies have found patient self-care behaviors in HF (e.g. medication/dietary noncompliance) and health system factors (e.g. care discoordination, limited access, lack of education to patients and caregivers) played important roles in patient outcomes to the extent that 50% of the readmissions were judged to be possibly preventable.[5,6]

Based on an operational model of effective chronic disease management (Chronic Care Model),[7,8] one potential solution to addressing patient and system factors is redesign of care delivery, via SMA's, to provide self-management support to patients (and caregivers when available) while also performing disease monitoring and medication management in an environment of peer support. Our previous successes in conducting SMAs for diabetes[9-11] suggested that these tasks can be accomplished in a coordinated and efficient manner by a multi-disciplinary team of non-physician health care professionals in an SMA setting *to address patient and system factors related to low health status and outcomes surrounding patients with HF.* However, there is a paucity of literature about HF-SMAs in general,[12-14] and none in the *effectiveness* of HF-SMA in improving health status in HF. Given that patients discharged with HF are susceptible to declining health and hospitalization, it would be important to know if*, how and to which groups,* the successes in diabetes SMAs can be translated into HF, a disease with a higher morbidity and mortality. Although both Providence and Phoenix VAMCs have been conducting HF-SMAs for a combined total of 4 years, only 20-30% of eligible patients are referred to HF-SMA. A major barrier for implementation is the lack of *effectiveness* data. Thus, a rigorous assessment of HF-SMA *effectiveness* along with a pre-implementation assessment of potential barriers using a mixed method approach is needed prior to dissemination. This research, while focused at HF, will contribute to advancing implementation of SMAs as a team-based intervention for other chronic complex conditions.

We propose a 2-site randomized-controlled *effectiveness* trial with mixed methods to test a SMA intervention provided by a non-physician team of nurses, nutritionists, health psychologist, and nurse practitioners and/or clinical pharmacists, versus usual care to improve patient's health status and reduce hospitalizations and death in HF after discharge. In this trial, patients within 12 weeks of a HF hospitalization and/or IV diuretic therapy will be randomized to receive either HF-SMA versus usual care. The HF-SMA will consist of four sessions of 2-hour duration that occur every other week for 8 weeks or based on the clinics' appointment availability. The session will start with an assessment of patients and their needs followed by pre-assigned theme-based disease self-management education, followed by patient-initiated disease management discussion, and conclude with break-out sessions of individualized disease monitoring and medication case management. The study duration will be 180 days for all patients from the day of randomization. The specific aims are:

Primary Aim:

Aim 1: To determine whether HF patients who participate in HF-SMA, as compared to usual care, experience better cardiac health status measured by Kansas City Cardiomyopathy Questionnaire[15-17] (primary outcome), and overall health status (EQ-5D, secondary outcome), from baseline to 90 and 180 days.

Hypothesis: HF patients who participate in HF-SMA will experience better cardiac and overall health status than patients who receive usual care from baseline to 90 and 180 days after randomization.

Secondary Aims:

Aim 2: To determine whether HF patients who participate in HF-SMA, as compared to patients who receive usual care, have fewer hospitalization or death, at 90 and 180 days

Hypothesis: HF patients who participate in HF-SMA will have fewer hospitalizations or death than patients who receive usual care from baseline to 90 and 180 days after randomization.

Aim 3: To determine whether HF patients in HF-SMA, as compared to patients in usual care, experience improvement in intermediate outcomes, namely, process (HF Self-Care behaviors) and physiologic (plasma BNP levels) measures from baseline to 90 and 180 days after randomization.

Hypothesis: HF patients in HF-SMA, as compared to patients in usual care, will experience an increase in HF Self-Care behaviors and decrease in BNP levels from baseline to 90 and 180 days after randomization.
Aim 4: To determine for HF-SMA, perceived benefits, areas in need of improvement, potential obstacles of implementation, and fidelity of the intervention across sites, by conducting (1) face-to-face interviews with a selected sample of patients and (2) telephone interviews with stakeholders (physicians of the patients who underwent HF-SMA and physician administrators).

A. BACKGROUND & SIGNIFICANCE

The primary goal of this research project is to improve the health status and decrease hospitalization and death for patients discharged with heart failure (HF) via self-management education to patients, disease monitoring and medication titration through shared medical appointments (SMAs).

Significance & Scope of the Problem

HF currently affects 5.1 million people in the US and 825,000 new HF cases are being diagnosed annually.[18] HF is a leading cause of cardiovascular disease morbidity and mortality worldwide, costing 1-2% of the total healthcare budget in developed countries.[19] In 2009 alone, 1 in 9 deaths in the US cited HF as a contributing cause.[20] Half of Americans who develop HF die within 5 years of diagnosis[2] and more than one third of HF patients require frequent hospitalizations,[3] or placement in long term care.[4] HF has a particularly higher impact among older people (≥65 years old) and those with multiple co-existing illness,[21,22] with ≥90% of HF-related deaths to occur among people ≥65 years.[21,23,24] With 1 in 10 elderly living with HF[25] and an aging population in the US, HF mortality and morbidity greatly impacts the health of our Veteran population. Indeed, our preliminary data from a random cohort of >100,000 patients admitted with HF at VHA hospitals nationwide, showed the HF veteran population to be elderly (average age = 71 years), and has 30-day and one-year mortality rates of 6 and 30%, respectively, after their hospitalization.[26] Since the main goal of the VHA is to improve health of the veterans, patient-reported health status is an important outcome metric for HF patients that includes symptom burden, functional status and health-related-quality-of-life, and an independent predictor of mortality, cardiovascular events, hospitalization and cost of care.[27] HF patients have a significant impairment of health status,[27] in both physical and mental health,[28,29] in addition to declines in functional status.[30]

Patient and System Factors Related to Patient Outcomes in HF

Studies have found patient and health system factors played an important role in patient's health status and symptoms to the extent that 50% of the readmissions were judged to be possibly/probably preventable.[5,6] Patient factors included behaviors such as medication (15%) or dietary sodium (18%) non-compliance,[31-33] and failure to promptly seek medical attention (20%),[5] and social factors such lack of a social or peer support to call for problems.[5] Behavioral factors were a key component and calls for the need of a structured learning and behavioral modification approach such as the SMA approach. Factors contributing to medication non-adherence included too many medications,[31] dissatisfaction with medicine information provided, and concerns about the potential adverse effects of medicines.[31,34] Barriers related to dietary sodium restrictions include low knowledge about dietary sodium,[35] and the poor taste of food on the low sodium diet.[35] Lack of knowledge in early symptoms of HF decompensation was one of the main reasons for treatment-seeking delays, with a median duration of early symptoms to treatment of 5-7 day delay.[5,6] Hospital factors included inadequate care coordination (discharge planning and/or follow-up), inadequate patient and caregiver education and support (e.g. who to call for problems), and limited access to providers after hospitalization.[5,6] Traditional settings of one-to-one visits are labor intensive and inefficient in addressing these multi-disciplinary needs.[7,36] SMAs, described further below, is poised to fulfill the above needs by providing education and behavioral intervention, medication management and disease monitoring in a group setting of peer support.

SMA for Chronic Disease Management in HF and Gaps in the Evidence

Based on an operational model of effective chronic disease management (Chronic Care Model),[7,8] one potential solution to addressing both patient and health system factors is redesign of care delivery, via "SMA's" to educate patients (*and caregivers if available*) about HF self-care thereby enabling behavioral modification while also performing disease state monitoring and medication management. **Group medical visits or SMAs** are defined as visits in which several patients meet with one or more provider(s) at the same time,[37] and typically involve a multidisciplinary team of a health psychologist, a prescribing provider, and a documenter.[38] *An important distinction is that SMAs are not 'classes' because they provide individualized medication prescribing and clinical monitoring of patient health status. SMA also distinguishes itself from the traditional case management or disease management models, which is usually provided by one provider to one patient at a time.*[39,40] As such, SMA is a comprehensive disease management program, where several patients with the same disease can meet with multidisciplinary health professionals in the same setting, in a coordinated fashion, for efficiency and improved access, and where behavioral change can be facilitated through education and group peer support (details below under behavioral change).[9-11] *Thus, we postulate that the change in self-care behaviors, and individualized medication prescribing and clinical monitoring in HF-SMA will lead to improvement of patient's health status, decrease in symptoms and BNP levels (a biological measure of the severity of HF)[41-43] and subsequent decrease in hospitalizations and possibly mortality for HF.*

Although studies have shown that some disease management programs may improve patient outcomes in HF,[39] the effect and complexity of disease management programs are highly heterogeneous.[44] Some interventions did not improve patient outcomes,[45] including an intensive model that involved close follow-up by their primary care provider, beginning before discharge and continuing for six months.[46] These findings call for the need of additional models that could potentially account for both efficacy and efficiency, such as SMAs in HF. Our previous successes in SMAs for diabetes,[9-11] and those of others,[47,48] suggest that this approach to be an ideal setting to empower patients with HF self-care skills and induce change in self-care behaviors in HF in addition to medication management and disease monitoring to improve their symptoms and health status. However, ***effectiveness*** of SMAs in HF management is unknown, and ***unlike patients with diabetes, a mostly asymptomatic disease in its initial stages,*** HF patients are vulnerable, especially after hospitalization, with a constant risk of further decline in health status or death.[49] Indeed the national VHA data showed that ~20% of these patients are readmitted within 30 days of their discharge.[50]

As stated by a systematic review commissioned by the VHA QUERI on SMAs, ***there is little evidence on the effectiveness of SMAs in disease conditions other than diabetes and there are uncertain effects of SMAs on physiological variables other than HbA1c.***[48] A key gap noted in this recent meta-analysis of SMAs was the lack of evidence for SMAs in patients with HF.[48] In our literature survey, there are only 3 small studies of SMAs in HF reported, and 1 RCT (n=198) that is single-center, in a non-VHA setting, education-focused (without disease monitoring or medication titration), and not targeted to the recently hospitalized population.[51] Three small studies addressed different mechanisms at which HF-SMA may improve outcomes. An observational HF-SMA study (n=39) from the Naval Medical Center, San Diego, reported that HF-SMA resulted in improvements in self-care after 6 months.[14] Another study (n=52) of HF-SMA found improvements in the HF knowledge in patients randomized to HF SMA.[12] A pilot of 20 patients showed that satisfaction with SMA was high among patients and office staff. [52] But, none of these studies reported significant differences in health status or hard endpoints. The single-center RCT showed trend toward improvement in hospitalization or death that support potential for HF-SMA in improving hard outcomes in this proposal.[51] ***Because SMAs are not a pharmacotherapy, the precise elements of the intervention will differ by health condition and need to be elucidated and refined for HF, which will be effected in this proposal.*** Preliminary data from Providence VAMC and Phoenix VAMCs indicated that hospital readmission rates for HF patients enrolled in SMAs are lower than secular controls (details under pilot), but only 20-30% of patients are referred to HF-SMAs. A major barrier for increased local implementation is the lack of rigorous ***effectiveness*** data. Thus, there is a need for a rigorous assessment *of* ***effectiveness*** prior to being able to transfer the successes from diabetes SMAs to HF.

HF-SMA, Patient-Centered Care and Patient Aligned Care Teams (PACT)

HF-SMA is in alignment with the current VHA PACT principles,[53] where access (currently a primary concern VHA wide) will be enhanced through SMAs (allows for up to 6 HF patients per session, with their caregivers if present), and patients will be exposed to a team of multi-disciplinary health care professionals, where they will receive more quantity of care but also quality of care due to providers of diverse expertise,[48] in a single coordinated care program. Given that patients often have concerns that span several clinical disciplines (e.g. dietary, medications, lack of social support [who to call for problems], worsening health status), the opportunity of having a provider with needed expertise to help a given patient's problem is greater in this HF-SMA setting as opposed to the traditional one-provider clinic setting alone. Available evidence suggests that approaches targeting patient's needs for self-care and case management, such as the proposed HF-SMA, are likely the most clinically relevant and effective intervention for HF.[54-56] This approach is also concordant with the Patient-Centered Medical Home model (which are also VHA PACT principles),[53] characterized by: whole-person orientation, coordinated and integrated care, quality and safety [57-59] and enhanced access. The Chronic Care Model (mapped in Figure 1 below) can help explain how the SMA approach can align the needs of the patients with existing hospital resources.[7,36]

HF-SMA and Alignment of Health System Resources with Patient-Centered Care, the Chronic Care Model

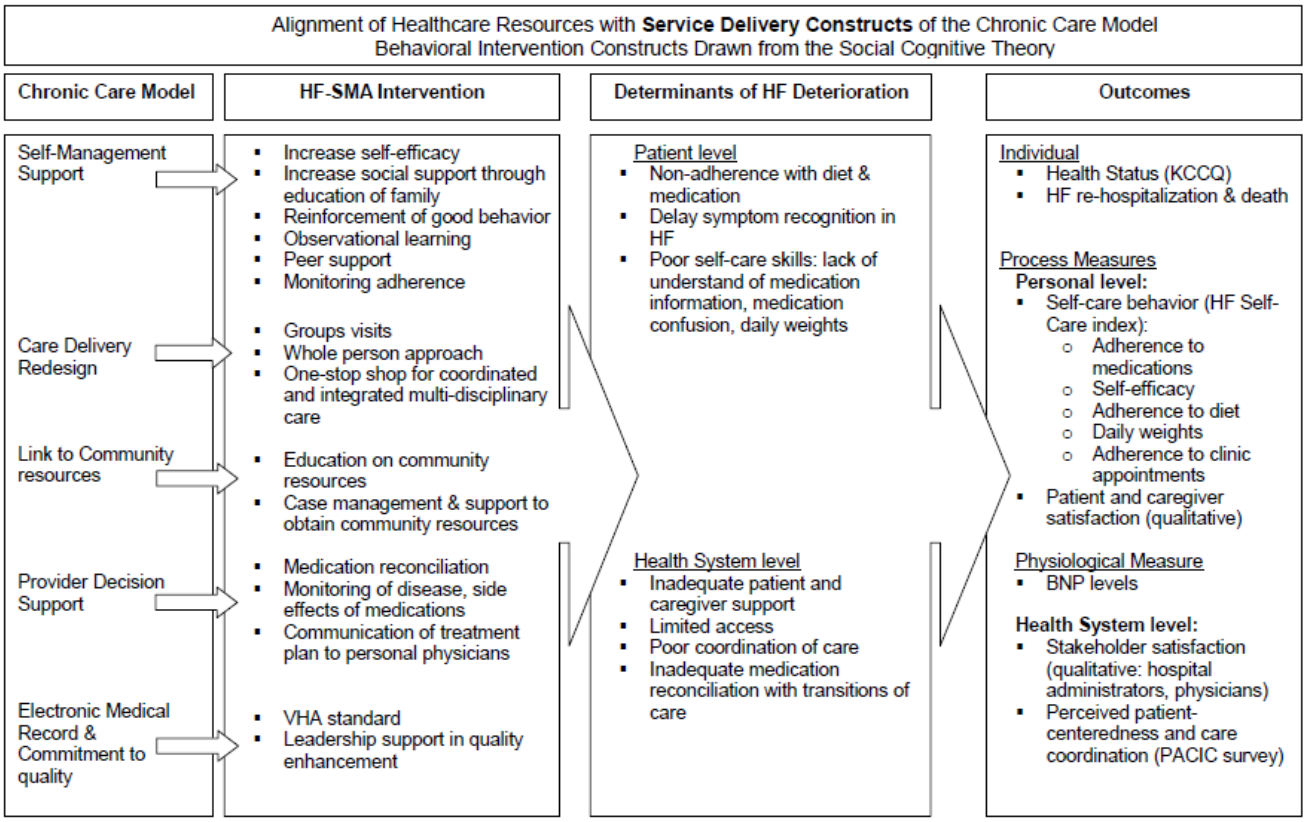
The Chronic Care Model is a disease management approach comprised of 6 components: 1) care delivery system re-design (e.g. SMAs), 2) linking the patient to community resources (exposure to available community and VHA resources), 3) self-management support (e.g. education toward behavioral modification), 4) provider decision support, 5) use of electronic medical record system and 6) a system-wide commitment to quality.[7,36] Both electronic medical record system and organizational commitment to quality are both VHA standards. Our proposed HF-SMA will build upon the pre-existing infrastructure to complete the components of the Chronic Care Model. The use of non-physician health care professionals in a group approach to

complement traditional physician care is another example of the system re-design. The medication reconciliation during HF-SMAs is a good example of provider decision support and preserves quality and safety of care by coordinating care from different multi-disciplinary providers, and should increase stakeholder (treating physician) satisfaction. The patient and care-giver education (self-management support) followed principles of patient-centeredness for patient empowerment and engagement and should enhance patient satisfaction. Additional HF-related care including disease monitoring, medication effect monitoring, and referrals into additional support programs (link to resources) addresses the patient-centered medical home principles of enhanced access, whole-person orientation, quality and safety, and integrated care.

Potential for HF-SMA to promote behavioral change

In addition to disease state monitoring and medication management, HF patients require intense training in self-care, such as weight monitoring and adherence to diet and medications, and early symptom recognition,[60] which is difficult and time-consuming to provide in the traditional one-on-one visit setting. Based on the self-management support and system re-design constructs of the chronic care model, HF-SMA has the potential to address the self-care needs of these patients in a coordinated and efficient manner. The mechanisms at which the self-management support in HF-SMA could lead to behavioral modification can be explained, at least in part by the Social Cognitive Theory (Figure 1). Based on the Social Cognitive Theory, promotion of healthy self-care behaviors in the SMA setting such as sodium restriction, weight-monitoring and medication adherence can be explained by determinants at the personal and environmental levels.[61-64] At the personal level, the SMA providers will use interactive discussions to shape expectations (anticipatory outcomes of a behavior) in an environment of peer support and use the group dynamic (environmental factor) to promote observational learning (behavioral acquisition that occurs by watching the actions and outcomes of other's behavior which include credible role models). The SMA provider will provide reinforcement for healthy behavior (both direct and vicarious); and will foster self-control (regulation of goal-directed behavior performance, self-monitoring, goal setting, problem solving and self-reward) through self-reinforcement and promotion of self-efficacy,[65] to increase healthy behaviors stated above. In addition, social support is also increased through education of family and support members when present. Our previous studies of SMAs in diabetes have shown positive results in improvement in self-care behaviors and glycemic control.[9,11]

Figure 1. Theoretical Underpinning of HF-SMA Intervention



Significance of HF-SMA:

Given the impact of HF to the US population and to the VHA, this proposal is significant because SMA is an innovative and potentially transformative care model to improve health status, and reduce hospitalization or death, for veterans with HF. The current proposal is also responsive to the VHA HSRD Research Priorities of "Assess innovative approaches to improve access…for a vulnerable veteran population," such as the one studied, with multiple comorbid illnesses. The challenge of providing patient-centered care for veterans with HF is an urgent problem due to an increasing limited access to health care providers,[66] an increased HF prevalence due to an aging population and improved heart disease survival,[20] and an acute care-focused health system. HF-SMA is a tool of system re-design that has the potential to provide patient-centered care in a resource-constrained system while enhancing patient access. Given the potential benefits and evidence of its efficacy in diabetes, use of SMA's have become a quality metric within the VA National Primary Care strategic plan,[67] but steps of its use in HF is still unknown. Thus, this project will help determine whether SMAs should be deployed and how they can be used in HF care. The alignment of HF-SMA with PACT principles and the VA National Primary Care strategic plan will facilitate implementation if proven ***effective***. Our qualitative assessment will also help VHA in the understanding of potential barriers to implement HF SMAs. Given the impact and the potential contributions to the VHA, we have the support from CHF QUERI (Dr. Heidenreich), National Pact Coordinator (Dr. Kirsh) and the National Director for Cardiology (Dr. Rumsfeld) to help us disseminate our findings and design of wide implementation if proven ***effective*** (support letters attached).

B. INNOVATION

The innovations are: 1) a rigorous and well-powered experiment to test the ***effectiveness*** of SMAs in HF is much needed to fill the knowledge gap on HF-SMA and its effects on outcomes meaningful to the patient, the provider and the VHA (aims 1-4). Given the 2-site design (East and West regions), we will be able to perform an assessment of *heterogeneity of treatment effects*, if any, and select out system factors (hospital/provider) if any, and patient subgroups that favored SMA intervention, even when the overall trial shows a non-significant result. 2) Our mixed method approach and the planned pre-implementation assessment will help understand potential mechanisms of benefit, if any, thereby, streamline and refine the intervention in the next iteration, in preparation for broader implementation. 3) Given the poor health status of patients with HF, traditional treatment settings required intensive physician involvement to show clinical efficacy, especially after hospitalization.[68] Therefore, our study will address whether the addition of non-physician health professionals, via SMA approach, may improve patient outcomes. 4) If proven ***effective***, our intervention will add another care delivery model to treat HF and possibly other complex chronic diseases alike that have frequent exacerbations. **The importance of developing a new and robust intervention to improve patient outcomes in HF cannot be overemphasized, especially given recent literature that showed not all interventions in HF work as planned.** Examples of such ineffective interventions are regular follow-up calls after discharge[45] or close follow-up by primary care,[46] which did not improve patient outcomes despite better patient satisfaction. Because experimental interventions can have a neutral or even negative effect on outcomes, we have chosen a neutral comparator (usual care) rather than an active comparator.

Thus, *this randomized-controlled trial to test the effectiveness of HF-SMA in improving patient outcomes after hospital discharge is timely and critically needed to create an innovative approach to HF management, and support patients with symptomatic HF. Currently, patients with HF may have limited options in traditional care models which strain system resources and fail to comprehensively address patient needs.*

C. PRELIMINARY WORK ON SMA

1. Group Visits for Diabetes: Multidisciplinary Education and Intervention for Cardiac Risk Reduction (intervention duration 4 weeks, PI: Wu): We have shown in a general population with diabetes and HbA1c >7% that the addition of multi-disciplinary educational-behavioral interventions and medication titration in a group visit setting to primary care are feasible and effective after 4 weekly sessions vs. usual primary care. HbA1cs improved from 8.1±1.6 to 7.3±1.1 (Cases) vs. 7.8±1.1 to 7.7±1.2 (controls); P<0.05).[10]

2. Multi-targeted intervention in diabetes group visits (intervention duration 6 months, PI: Wu): We extended our weekly group visit intervention of 4 weeks to be followed by 5 monthly booster sessions to treat diabetes patients with multiple cardiac risk factors. After 6 months, more diabetes self-care behaviors improved in the SMA arm and the mean 10-year cardiac risk estimated by UKPDS calculator decreased significantly for SMA arm (28.4% to 20.3% p<0.01), but not usual care (27.0% to 23.4%, P=1.0).[11]

3. Pharmacist-led Group Visits in Depression (intervention duration 6 months, PIs: Taveira, Wu): SMAs for uncontrolled diabetes and co-morbid depression. After 6 months, 10-year UKPDS risk scores

decreased significantly for SMA arm (20.6 to 15.7%, p<0.01), whereas there was no significant change in usual care (22.7 to 20.4, p=.21). There was also trend towards improvement in depression symptoms.[9]

4. Group Intervention for DM Guideline Implementation" (intervention duration 1 year, PI: Wu): Multi-center trial (VA Providence, VA West Haven, VA Honolulu) comparing pharmacist-led SMAs vs. usual care to lower cardiovascular risk in patients with type 2 diabetes. After 13 months, both groups had significant improvement in blood pressure and lipids, but only participants in the group visits have significant reductions in hemoglobin A1c (0.31±1.31, p=0.02). Compared to 13 months prior, VA healthcare costs in the 13 months after the study decreased by 9.8% for the SMA arm but increased by 47.4% for usual care (p<0.001).[69]

5. HF-SMA at Providence VA Hospital: The Providence VA instituted multi-disciplinary HF-SMA in 2011. Patients are referred from inpatient and outpatient setting by their physicians. Dr. Wu oversees the HF-SMA in case of difficult patient scenarios. In preparation for this proposal, we abstracted data on 70 patients referred to this program: Mean age: 75±12 years, Caucasian (93%), 99% male, NYHA class 3 or 4 at baseline visit (66%), mean left ventricular ejection fraction of 42%, and 50% of patients takes >10 prescribed medications. There was a mean of 41± 64 days delay from hospital discharge to attendance of HF SMA. For care coordination, referral into telehealth occurred in 22% and for home care was 4%. Medication changes and dose titration occurred in 62% of patients. Preliminary results showed a 30-day readmission rate of 6% and a 180-day readmission rate of 25% for all patients enrolled in HF SMA. In contrast, data from the VA Inpatient Evaluation Center showed a HF readmission rate for Providence VA at 22% for 2013[50] and pilot data from a national sample of discharged HF patients ejection fraction <40% showed a 180-day readmission rate of 40%,[70] suggesting a possible reduction in rehospitalization rate by HF-SMAs.

Interview of patients showed that most patients would agree that HF-SMAs are helpful: "*I find it informational..different people have different ideas..last time I came in, one of the gentlemen that was having trouble with his ankles..socks a little too tight..then somebody says, then cut the top of the socks off…*" Medication reconciliation and adherence as well as diet counseling are two most frequently mentioned themes: "*Especially the medications, which I found out the hard way...'cause I had stopped it…it got confusing to me, all the medications…*"; " *learn a lot about diet such as fat, salt and ice cream intake,… Send a cook-I don't know how to cook!*" We also learned that sometimes we give too much information to patients: "…*too much actually...I haven't read a book in like forty years…*" We also found out that at times we did not explain clearly why the patients are attending the HF SMAs: "*I don't remember it at all, so, that's why they ought to let people know what they're doing, exactly what they're there for, because I really wasn't sure why I was there.*." We also learned that patients within 1-2 weeks of hospital discharge are often too frail to want to attend SMAs and not eager to interact, so they often delay their appointment until 3-4 weeks out. These lessons helped us designed the current study to open the window of enrollment up to 12 weeks after their discharge.

Interview of physician stakeholders suggested that many physicians did not know about HF-SMAs or their patients attended HF-SMAs when referred by another provider. These observations taught us that communication with patient's physicians is important after the HF-SMAs for care coordination.

6. HF-SMA at Phoenix VA Hospital: The Phoenix VA instituted weekly HF-SMA in 2013 with capacity to see 4-6 patients in each session. Dr. Dev oversees the HF-SMA in case of difficult patient scenarios. Data on 54 patients referred to this program showed a patient population with a median age of 66 years, 82% White, 100% male, with a mean left ventricular ejection fraction of 35%, and the median number of medications = 10. Preliminary results after SMA showed a 90-day readmission rate of 7% and mortality of 4%, which is in contrast to the 25% 30-day readmission rate for Phoenix patients with a recent HF discharge (FY2014).

Focus groups conducted with patients after HF SMA suggested that the patients liked the open forum format and they believed SMA helped because it addressed a broad spectrum of concerns, provided additional medical information and strategies for coping with illness, had more time to talk with healthcare team, explored questions more deeply/reflect on answers, the conversation-like setting and support group' environment ("Not alone") and the learning from other patients' questions/ experiences as well as opportunity to share own experiences. Among the concerns expressed, one patient expressed that others were judging him and inhibited his openness going forward and another patient expressed: "*Group providers and patients don't know me as well and not a safe environment to voice personal issues as they can be misconstrued*"; "*your personal doctor isn't there*". These are important lessons learned to control group dynamics and avoid stigmatization, earn the trust and have guidelines for participation to protect privacy. Some patients needed clarification on whether SMA is meant to replace visits to doctors (possible misunderstanding among new SMA patients about

the role their SMA provider plays). In our current model, the patients are advised that all treatment plans are communicated back to their primary providers via CPRS (provider decision support).

Overall, the above data support the feasibility of SMAs in HF, experience of the team in RCTs and multi-site studies. However, the ***effectiveness*** of HF-SMA in improving patient outcomes is still unknown despite strong theoretical underpinnings, and further investigation is warranted.

C. STUDY DESIGN OR APPROACH

1. Overview This will be an open-label multi-center randomized-controlled trial of parallel design, to study the ***effectiveness*** of HF SMA in improving the health status (Aim 1), hospitalization or mortality (Aim 2) of patients discharged from a HF hospitalization. In addition, we will study intermediate outcomes such as process measures of HF-self-care and a biological measure of clinical status (BNP levels) (Aim 3). Finally, we will conduct fidelity assessments and a pre-implementation evaluation through interviews with patients (and caregivers if available and willing) to determine satisfaction and possibilities of refinement of the HF SMA, and physician stakeholders to assess for potential barriers of implementation.[71] We will enroll patients within 12 weeks of discharge from a HF admission and/or IV diuretic therapy, who will be randomized to receive either HF-SMA versus usual care. The conduct of the clinical trial will follow the suggested best practices in the conduct of randomized trials as published in the British Medical Journal.[72] The study duration will be 180 days from the time of randomization. Both quantitative and qualitative methods will be utilized to assess the outcomes of this intervention. The HF-SMA will consist of four sessions of 2-hour duration that occur every other week for 8 weeks or based on the clinics' appointment availability.

2. Population

Inclusion criteria: 1) All subjects >18 years old, 2) within 12 weeks of discharge from a hospitalization with a principal diagnosis of HF (ICD-9 codes in Appendix Table) and/or IV diuretic therapy, 3) able to participate in a group setting and 4) able to sign informed consent, will be eligible for enrollment. *The study team will work with subjects with transportation problems to help resolve travel issues if needed using VA channels (e.g., identifying support persons to help, Veteran vans, Community-Based Outreach Clinics with shuttle transport to the main hospital, etc.) since in most cases, VA provides support for transportation for Veterans to attend clinic.*

Exclusion criteria: We will exclude patients who are:

1) Unable to attend the group sessions due to either psychiatric instability (acutely suicidal, psychotic) or organic brain injury (e.g. severe dementia, encephalopathy) that precludes self-reporting on health status.

2) Discharged to hospice or nursing home facilities for long term care, or patients with a code status of comfort-measures-only since the setting and goals of disease management will be very different compared to the general HF patients after discharge, who are the target of our intervention.

3) Recipients of heart transplant or ventricular assist devices, patients receiving intravenous inotropic infusions for heart support, women who are pregnant, and patients with end-stage liver disease or renal disease on dialysis since these conditions would preclude them from standard HF care. All women of childbearing age will have a pregnancy test before study enrollment.

We will not exclude patients who are currently enrolled in HF education classes, support group or HF clinics, as these co-interventions are often present in optimal "usual care" and patients are often referred to SMA from these settings. In addition, it would be important to know the ***effectiveness*** of the SMA intervention, if any, in presence of potential co-interventions. We will account for co-interventions using stratified randomization, so equal proportion of patients participating in above-mentioned programs would be allocated to each study arm. It is possible that patients are referred in the middle of the study, for which we will track them carefully and accounted for them in the analysis plan.

3. Registry of excluded patients: For patients who were approached but do not wish to participate in the study, we will still ask them for a written consent to follow on their medical outcomes through medical chart review and authorization for release of medical information for 180-days after registry enrollment. In this way, we will compare the outcome of these patients against those randomized, to assess for systematic differences between the enrolled and the excluded population.

4. Recruitment: Patients will be recruited from 2 sites, Providence VAMC and Phoenix VAMC (please see track record of the investigator team in recruitment and conduction of multi-center trials from preliminary studies section and bio-sketch). First, study investigators (Drs. Wu and Dev) will present the study to primary care physicians, hospitalists and cardiologists during staff meetings and conferences in each of the respective

hospitals. We will then ask the IRB for a waiver of informed consent to screen for potential participants by chart review of patients with HF hospitalizations within the previous 12 weeks.

For recruitment from the inpatient setting, we will partner with hospital's discharge planning staff to obtain a list of potential or soon to be discharged patients. Once eligibility is confirmed through medical record review, we will contact the potential participant's inpatient providers to ask for their permission to approach these patients. Once permission obtained, we will approach the patient while in the hospital with an information sheet and ask to contact them for the study after discharge. For recruitment in outpatient settings, once eligibility is confirmed, we will contact the potential participant's personal physicians to obtain permission to contact the patient. Once permission and endorsement is obtained, we will send a joint recruitment letter from the patient's personal provider along with the investigators that will include a return envelope with a response card to contact them for the study. In order to enhance participation and after permission from the IRB, we will send information material to discharge planning staff and place signage in each of the cardiac testing laboratories, rehab facilities, and cardiologist and primary care physicians' offices. Once contacted and agreeable, the patient will come for an initial study visit with the research assistant and informed consent will take place. Our preliminary data showed that in 2013, there were ~130 patients discharged with HF at Providence VAMC and ~250 patients at Phoenix VAMC; of which, we plan to annually recruit 50 and 75 patients in each site, respectively, over 36 months for a total of 375 patients.

5. Randomization and retention: Once enrolled, patients will be randomly assigned on a 1:1 ratio to intervention or placebo arms using a stratified block randomization method with block sizes of 4 in each site to ensure balance of the stratified variables. Stratification will be based on the study site and the presence or not of: a) co-intervention (enrollment to HF clinic, support group or education), b) ≤2 hospitalizations in the last 6 months, and c) left ventricular ejection fraction <40%. Randomization will be done by the call-in method to a central computer administered by the study coordinator at Providence VAMC, the coordinating site. To ensure subject safety and continuous engagement in study procedures, patients will be called by phone by study staff on a monthly basis following randomization to answer any questions that may arise, ask for participation in HF programs and doctor's visits, ER visits, document adverse events and maintain study engagement. Patients in the control arm will be invited to participate in HF-SMAs at the end of the study, to honor patient's preferences.

Our preliminary data showed that our recruitment in prior SMA research has been successful, ~50-60% of those screened and eligible agreed to enroll in SMAs; and then about 90% of those enrolled finished the study. Reasons for drop out are: geographic mobility, change in work schedule, incarceration, and homelessness. Yet, we have been able to maintain a good retention rate, through a combination of excellent relationships with participants, and a perceived value of the study to clients.

6. HF-SMA: The HF-SMA team includes a dietician, a health psychologist, a nurse, and a nurse practitioner and/or a clinical pharmacist; one of which will lead the group discussions. *Caregivers if available and willing, are allowed and encouraged to attend SMAs but NOT required, similar to how family members are allowed and encouraged to attend usual care clinic visits, but NOT required. Inadvertent loss of privacy is a concern in SMAs and we will clearly state that risk in the draft informed consent form (Appendix). At the beginning of each session the facilitator will provide SMA group guidelines for participation for the participants, caregivers and providers during the group interaction. Participants will be advised regarding appropriateness in sharing, as well as the expectations of privacy and confidentiality for patients and caregivers. Specifically, patients will not be asked to reveal any sensitive information about themselves and will be advised that the providers will not reveal any of the participants personal information during the group sessions. The SMA providers in both sites are very experienced and have been trained to respect privacy and avoid eliciting sensitive information.* The session will start with an assessment of the patients and their needs followed by pre-assigned disease self-management education, followed by patient-initiated disease discussion, and conclude with break-out sessions of individualized behavioral intervention, medication reconciliation and case management by the multi-disciplinary team. The HF-SMA group will consist of 4-6 patients (and caregivers if present), of 2h duration broken down into:

1) **Patient intake** (10 min): they will complete a salt intake survey (appendix), blood pressure, heart rate, weight, leg /sacral edema, heart and lung sounds (nurse, pharmacist, and/or nurse practitioner).

They will also undergo medication reconciliation (10-15 minutes each patient): Clinical pharmacist or nurse practitioner reviews patients' medications against hospital discharge instructions and performs brief medication therapy management evaluation. In order to perform a thorough assessment of medications and adherence, we will ask the patient to bring all the medications in all HF-SMA visits (prescribed and non-

prescribed). This list of medications will be corroborated with electronic medical records and local pharmacy (if non-VA medication) during the education sessions, so no time is spent in waiting. The same will be done if patients informed that a change had occurred since discharge from the hospital, so that the current list can be corroborated against the medication list from physician's offices records.

2) "**Meet and Greet"** and **patient need assessment** (5 minutes, all team members). Patients are introduced to the team and to each other and are asked about self-care topics they would like to discuss.

3) **Group Education** (15-30 minutes): theme-based discussion based on curriculum published by the HF Society of America[73] into 4 sessions:

a) Taking control of HF and Self-care: we will discuss the causes and types of HF, early detection of HF symptoms and how to monitor for signs of worsening (i.e. leg swelling, shortness of breath), when to call provider, daily weights, and VA resources to help them in disease monitoring such as telehealth.

b) How to follow a low-sodium diet: discussion of low and high sodium foods, read food labels, eating out, cooking tips, supermarket tips/tour, cooking demo and meal planning.

c) HF Medicines: HF medication types and how they work, adherence, pill boxes, side effects and when to report them, medications or foods to avoid, among other topics.

d) Managing Feelings about HF and advanced care planning: coping with negative emotions such as depression symptoms, family and caregiver support, recognizing anxiety and depression, when to seek medical help, advance care planning discussion with their physician and when to consider turning off defibrillators (this topic was suggested by a caregiver)

4) **Patient-initiated guided discussion** about HF self-care barriers (15-30 min)

5) **Individual break-out session** (45-60 min): patients rotate with providers depending on their needs for Individualized Self-Management and Support (15-20 minutes each patient): needs-based problem solving, e.g. clinical pharmacist or nurse practitioner if medication discrepancies are found or dose up titrations are needed. They can also meet with the nutritionist, psychologist, and/or nurse. Our experience suggests that the patient meets health care professionals of an average of 2 disciplines during the break-out sessions.

6) **Documentation**: chart documentation of the visit interventions will be performed by SMA team members. Communication of the treatment plan with the primary care provider and/or the cardiologist will be through electronic alerts in medical records and/or letter to non-VHA providers. Phone calls and/or encrypted emails will be used when clinically indicated.

7. Usual Care in HF: All patients will receive standard of care in HF as dictated by their cardiology physicians and primary care providers. It is highly encouraged that all patients see their physicians/health care providers within 14 days after their HF discharge. Physician follow-up after that may vary depending on the patient and physician, for which we will capture carefully through chart review and patient interview to compare attention given to patients in both arms of the study. In institutions such as Providence VAMC or Phoenix VAMC, patients are often referred to HF clinics (traditional one-to-one visits) with nurse practitioner for closer monitoring, which will be carefully tracked for analysis. This usual care arm will allow us to study the additive effects of HF-SMA and not in replacement of another intervention. In addition, there can be unexpected effects of active comparators in patient's outcomes as stated previously with interventions that have worsened rehospitalization risk.[45,46] Therefore, a neutral standard of comparison such as usual care would be important. It will also allow the measurement of variation in effect size across different sites since usual care may vary.

8. Study Visits, Data Collection and Study Outcomes: There will be 3 research visits: 1) baseline for enrollment consent and data collection, and 2) at 90 days (+ or - 30 days) and 3) at 180 days (+ or - 30 days) after randomization for outcome collection, in addition to monthly phone calls in between study visits. All surveys will be self-administered unless the patient prefers otherwise. Only experienced interviewers will conduct the interviews, proficiency must be demonstrated to site PI. Training for the qualitative aspects of the study will be provided by the Cleveland site. All patient self-reported measures and interviews will be performed during the three research study visits. To accommodate patients, per request, study visits may be conducted over the phone or in a private location of their choosing with two study members present. Also to further accommodate patients, per request, de-identified surveys using only a study ID number may be mailed out along with a postage paid, self addressed return envelope. Patients will be instructed not to include their name on any of the returned surveys. Research assistants must demonstrate proficiency in data collection techniques to the site PI's.

Aim 1: Primary outcome is change in KCCQ and secondary is change in EQ5D.

Kansas City Cardiomyopathy Questionnaire (KCCQ)[15,17](Appendix): is a 23 item instrument validated in stable and decompensated HF patients with preserved or reduced ejection fraction.[15] The questionnaire takes 4-6 minutes to complete, and reflects disease-specific health status over the prior two weeks. The domains of KCCQ are physical limitation, symptoms, self-efficacy, social limitation, and quality of life. The domains of the KCCQ have a high internal consistency with a Cronbach's alpha of 0.95 for the Overall Summary Score and ≥0.62 for all individual scales. The KCCQ has a significantly higher responsiveness to changes in health status than the Minnesota Living with Heart Failure Questionnaire and the SF-36.[15] The overall summary score is 0-100 where higher score is better. The minimal clinically important change in survey score is 5 points, with a 10- and 20-point change reflecting moderate and large clinical changes, respectively.[74] In the Eplerenone Post-AMI Heart Failure Efficacy and Survival Trial (EPHESUS), each 5-point decline in KCCQ Overall Summary Score on serial assessments was associated with a hazard ratio of 1.11 (95% CI, 1.05-1.17) for subsequent cardiovascular death or hospitalization.[75] Preliminary data from Phoenix VA found a median Summary Score of 52.4±27.8 (n =32) in HF-SMA participants indicating fair/poor health status.

Overall health status (EQ5D) (Appendix): The EQ-5D is a well-known generic measure of health status. It has 5 questions that address five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with five levels ranging from 'no problems' to 'extreme problems' each.[76] Each health state (up to 3125) has a corresponding value reflecting references of the general population in various countries. Thus, the EQ5D can be summarized into an index value (utility) from 1 (full health) to 0 (dead) that can be used to calculate quality-adjusted-life-years in cost-utility analyses.[77] The instrument takes only a few minutes to complete and is undemanding for self-completion. The EQ5D also contains a self-rated 20cm visual analogue scale (EQ VAS) ranging from 'best health you can imagine' to 'worse health you can imagine.' The EQ5D has moderate-strong convergent validity in relation to other measures of health-related quality of life as well as discriminative validity to detect clinical changes. However, it is less responsive to HF-related clinical changes than KCCQ.[74] HF Studies reported strong correlation with disease severity in EQ-5D scores ranging from mean values of 0.78 ± 0.18 in mild disease to 0.51 ± 0.21 for severe disease.[78]

Aim 2: Event outcomes (hospitalization or death) will be captured immediately after randomization. All events will be captured by monthly phone calls and chart reviews, as well as interview to study patients or caregivers during study visits. Copy of medical records for the reported hospitalizations, emergency room visits, or deaths will be obtained to confirm the event.

Aim 3: change from baseline in patient's HF Self-Care activities will be measured by HF Self-care Index *and change in baseline BNP levels will be assessed through routine blood draw.*

HF Self-Care - The HF Self-care Index (v.6)(Appendix): is a 22-item self-administered instrument composed of 3 scales: self-care maintenance, management, and confidence. It addresses diet, exercise, medication use, when to call the health provider, keeping doctor's appointments, weight monitoring, and recognition of change in health status or symptoms. Each scale is scored separately and has a range of 0-100. A score of ≥70 on each scale is considered adequate self-care, though benefit occurs at even lower levels. A score change of half standard deviation (≈8 points) is considered a clinically relevant change.[79,80] Pilot data from Phoenix VA showed low self-care scores in HF patients (64.9±19.9) at baseline.

Plasma BNP levels: is a hormone released mainly by the heart in response to excessive stretching of heart muscle cells in cases such as HF.[81] It is a test that is already being collected routinely in the clinical setting for HF patients. A cut-off of >100 pg/mL in patients with new-onset dyspnea is suggestive of acute HF. It can also be used in outpatients after HF discharge to monitor for clinical deterioration and is highly predictive of death or rehospitalization,[42,43] with a hazard ratio per unit increase of ln BNP of 1.84 (95% CI: 1.42 to 2.39). BNP provides clinicians with an objective and simple measure of the loading conditions of the heart.[43]

Aim 4: Pre-implementation assessment.

1) Patients: We will conduct interviews of 20-25 patients in each study site who have undergone HF-SMA (with their caregivers if willing). Interviews will attend to patient (and caregiver) satisfaction and feedback on refinements for continuous quality improvement and determine, in what ways, the HF-SMA helped or did not help them feel better and/or avoid hospitalizations. We will strive for a maximum variation sampling of patients based on sociodemographic characteristics (age, women and minorities), number of co-existing conditions, social support and engagement during the sessions to achieve maximal thematic heterogeneity.

2) Stakeholders – Providers and administrators: We will interview ~10 physician stakeholders at each site, which will include primary care providers or cardiologists and one physician administrator (e.g. Chief of Cardiology, Medicine or Primary Care). We will purposefully select physicians who oversee HF patients who

participated in HF-SMA, and were interviewed, as part of the Aim 4 of the study. These will be informant interviews[71] intended to provide insights on provider's perceived benefits of HF-SMA (any added value or detriment), and potential barriers for referrals. We will inquire specifically what type of patients, providers would refer to HF-SMA and what barriers may exist for them to incorporate this intervention into their referral practice.

3) Formative Evaluation: Will consist of fidelity assessment based on direct observation of HF-SMA. Dr. David C Aron and his research staff will perform fidelity assessments for Providence VAMC, and through video-teleconferencing unit for Phoenix VAMC, in addition to two in-person site visits for direct observation as guided by the Fidelity sheet in Appendix. As an accompaniment to the fidelity assessment worksheet, we will also jot down explanatory field notes which will flesh out and provide depth to the assessment score. In line with field research best practices,[71] raw records will be typed up within 36 hours to accompany the numerical scores, and this data—along with the interview data—will provide a rich and multi-sourced qualitative depth to the study. Dr. David C Aron and his research staff will provide training on how to collect and record field notes. We will observe one HF-SMA session per site each month for 24 months to ensure fidelity.

Other data collection tools:

Aside from demographics (age, gender, housing situation, social support, marital status, service connection, employment, education), we will also collect data about depression symptoms and patient's perception of care coordination for subgroup analysis and risk adjustment.

Depression symptoms – The Patient Health Questionnaire-8 (PHQ-8, appendix) is a 8-item well validated self-administered instrument that is a reliable measure of depression severity and depression symptom burden and is responsive to treatment outcomes over time.[82] Scores can range from 0 to 24, with a higher score indicating a greater burden of depressive symptoms.[83] PHQ-8 scores of 5, 10, and 20 represented mild, moderate, and severe depression, respectively. Internal reliability estimates range from 0.86 to 0.89 using Cronbach's alpha. Two day test-retest reliability is estimated to be 0.84 with nearly identical mean total scores. The advantages of the PHQ-8 include the following: 1) It is self-administered; 2) It contains only 8 questions that help identify patients with clinically meaningful symptoms of depression; 3) Can be reasonably administered in 5-10 minutes; and 4) Can be scored in 1-2 minutes. For safety guards in place regarding suicidal ideation, please refer to Human Subjects section.[82,83]

Perceived patient-centeredness and coordinated care (PACIC survey) (Appendix):[84] The PACIC is a well-validated 20-item questionnaire that has 5 subscales: Patient Activation, Delivery System Design/Decision Support, Goal Setting, Problem-solving/Contextual Counseling, Care Coordination; with the various scales, as well as the overall score, to be both internally consistent and moderately stable during test-retest. This tool assesses the health care system from the patient's perspective (patient centeredness). The questions are general enough that we can ask the patient to answer in the context of their heart disease care.

Medical co-morbidities and cardiac history: based on the Charlson Co-morbidity index, this data will be collected through chart abstraction by our research assistants at baseline and confirm it with patient and caregiver. The Charlson Co-morbidity index is a weighted index that takes into account the number and the seriousness of comorbid disease.[85] The index is well validated for its ability to predict risk of death from co-morbidities at 1-year and 10-year follow-up periods. We will also obtain cardiac testing data including echocardiography, cardiac catheterization, and stress test data through review of medical records. Non-VA sources will be contacted if indicated to track non-VA care (Table 1 of data collection below)

Table 1. Timeline of Data Collection	Baseline	90 days	180 days	Data Source
Charlson Comorbidity Index	X			Patient, family and chart
Caregivers / Demographics	X			Patient, family and chart
Echocardiography, cardiac testings	X			Patient and chart
KCCQ, EQ-5D	X	X	X	Patient
HF Self-care Index, PACIC, PHQ-8, *BNP*	X	X	X	Patient
Patient (± caregiver) satisfaction	Ongoing			Interview
Provider perception	Ongoing			Interview
Hospital admission or death	Ongoing			Patient, family and chart
HF clinics / programs	Ongoing			Patient, family and chart
Outpatient physician and ER visits	Ongoing			Patient, family and chart

9. Quantitative Analytic Plan:

Aim 1: To compare between the intervention versus usual care arms in the change from baseline in KCCQ (Primary outcome) and EQ5D (secondary outcome) at 90 and 180 days. The analysis will be performed from an intention to treat principle. First, descriptive statistics (mean, standard deviation, median, inter-quartile range, and frequency distribution) will be calculated to summarize, at baseline, patients' demographic and comorbidities including previous hospitalizations, cardiac history (heart function and coronary disease), medical and health service utilization information (including medication possession ratio, HF self-care index, *BNP levels,* enrollment into HF clinics / programs, visits with primary care and cardiologists), and the primary outcome of interest (KCCQ, overall score) according to randomized arms. Log-transformation of variables and outcomes of interest will be performed to approximate normality when appropriate. Linear mixed-effects (LME) model[86] will be utilized for the analysis of this aim, where the response variable is KCCQ, fixed effects include treatment group, time (0 = baseline, 1 = at 90 days, 2 = 180 days), treatment group by time interaction, and other important demographic variables identified in the descriptive analysis, and random effects include site-specific random intercept, subject-specific random intercept (nested within site) and subject-specific random slope of time. This modeling approach has been shown to provide an unbiased and efficient estimate of the longitudinal treatment effect in a variety of situations, such as in the presence of missing data, imbalance of the primary outcome at baseline, and covariance heterogeneity between treatment groups.[87,88] In this way, we could compare the intervention effects at 90 days and whether residual effects exist at 180 days. The random site effect is used to model the clustering effect of patients in the same study site and random subject effects are used to model the variability in the subject-specific trajectory and the correlation of repeated measures within subject. Residual analysis will be conducted to examine the appropriateness of the functional forms of each fixed effect, and Information criteria (AIC, BIC) will be used to choose the correlation structure.

Secondary: Same modeling technique will be used to study EQ5D as the outcome instead of KCCQ.

Aim 2: To compare between the intervention versus usual care arms in hospitalization or death at 90 and 180 days after the randomization. For this analysis Cox proportional hazards model[89] will be utilized where the event is a composite outcome that represents either hospitalization or death. Any patient who does not experience the event by 180 days will be denoted as censored. The main exposure is treatment group and other covariates include patient demographic and comorbidity information as described above. We will examine the differences in outcome at both 90 and 180 days. The appropriateness of the proportional hazards assumption will be examined and any violation of the assumption will be addressed. The appropriateness of the functional forms of each covariate will be assessed through residual analysis.

Aim 3: To compare between the intervention versus usual care arms in the change from baseline in patient's (a) HF Self Care index *and (b) BNP levels*, we will use the same linear mixed-effects modeling approach as described in Aim 1.

Subgroup and Sensitivity Analyses: In order to understand potential heterogeneity of treatment effects, stratified analyses will be conducted by our randomization stratifiers such as co-interventions or not, ejection fraction (≥40% & <40%), and hospitalizations in the previous 6 months (>2 & ≤2). Given that baseline KCCQ scores,[15] HF self-care behavior,[90,91] comorbidity burden,[85,92] depression symptoms[93] and caregiver support[94,95] could potentially change the outcome of HF, we will conduct test for multiplicative interaction between the condition of interest (e.g. depression with PHQ-8≥10 vs.<10) and the study arm allocation (intervention vs. usual care arm) on the patient outcomes of interest described in Aims 1and 2. *If any these interaction terms are significant at an alpha level of 0.05 or less,* subgroup analyses will be conducted (e.g. number of comorbidities below and above the median, baseline KCCQ scores above and below the median, and by presence or absence of significant depression symptoms or caregiver support) depending on the feasibility by sample size. Sensitivity analyses will be performed by study site to determine the impact of setting in our study findings and potential variation of findings.

Mediating Factor Analyses: In order to understand the mechanisms by which HF-SMA improves health status and hospitalization or death, we will explore potential mechanisms from the process measures such as HF-self-care index and perceived care coordination (PACIC survey). In order to prove mediation, four conditions must be met: (1) correlation between the change in treatment variable (HF-SMA or not) with the change in mediator (change in process measure, e.g. HF self-care index); (2) variation in the mediator must be correlated with variation in the outcomes (e.g. KCCQ); (3) controlling for the mediator substantially reduces or eliminates the relationship between the treatment and outcomes; and (4) the treatment variable must temporally precede the mediator, which is inherent in our study because enrolled patients will be treatment naive.[96] We will

compare multivariate regression model specifications that serially exclude and include the potential mediators and the treatment variable.

Exploratory Analysis on Study Generalizability and External Validity: We will compare the baseline characteristics and study outcomes of enrolled patients with those in the Registry of Excluded patients to assess for potential differences in characteristics and outcomes. If there are significant differences in baseline characteristics, an "as treated" analysis will be performed to compare on the study outcomes while adjusting for differences in baseline characteristics between excluded patients and patients who received HF-SMA using the same approaches we described for Aims 1 and 2. Although we understand that the excluded patients may be fundamentally distinct from the study population, these analyses will help to make inferences on the potential effects of the intervention on untreated patients and explore the generalizability of our findings.

Missing Data Issues: Since these are primary data collected as part of a clinical trial, we do not anticipate significant missing data. We will also record and report all reasons for dropout and missing data, and account for all patients in our reports as well as study publications. Overall, if the number of observations with missing values is small (<5%), we will conduct analyses by removing the variables with missing values. If the number of observations with missing values is many, we will compare characteristics between dropouts and those who had completed all the study visits. If it is determined that missing data is random, we will resort to methods that impute values, SAS Proc MI and MIANALYZE readily impute maximum likelihood estimates from incomplete data.[97,98] If significant differences are found in the attrition rates across study arms, both 'intention to treat' and 'as treated' analyses will be performed to determine the extent to which the missing data may be biasing the results. For the 'intention to treat' analysis, we will generate actual random raw data values suitable for filling in gaps in an existing database. Typically, five to ten databases are created in this fashion. We will then analyze these data matrices using an appropriate statistical method, treating these databases as if they were based on complete case data. The results for these analyses are then combined into a single summary finding.

Sample Size and Power Considerations: The overall study sample will be 375 (225 patients from Phoenix VAMC and 150 patients from Providence VAMC). Statistical power for the aims 1 and 2 is estimated given these are the most relevant and the most restrictive in terms of power estimations. Under a conservative dropout rate of 15% for 180 days of follow-up for the main outcomes (Aims 1 and 2), we estimate the power with an effective sample size of 316 (15% less than the total sample) and a 2-sided significance level of 0.05 using nQUERY Advisor 7.0®. For aim 1, we assess the power to detect a clinically significant change in KCCQ of 5 points, assuming a baseline score of 63 (our preliminary studies), with a common standard deviation of 15 for the study arms, using a 2-sample t-test. For aim 2, we assess the power to detect a relevant decrease in rehospitalization or death risk of 25-30% at 180 days using a Cox Proportional Hazards model. Based on our preliminary data of 20,000 Veterans with ejection fraction <40% hospitalized with HF, their rehospitalization rates at 6 months is ~40%.[70] Assuming similar event rates for rehospitalization or death, as shown in Table 2, we have good power to detect the proposed outcomes at very conservative estimates of effective sample size (n=158 in each arm, which is 85% of the total proposed recruitment target). Repeated measures at 90 and 180 days are also likely to add to the statistical power in Aim 1 to detect differences at the subgroup levels.

Table 2. Power / Effect Size Calculations at 180 days Intervention vs. Usual Care

Aim 1: Difference in KCCQ		Aim 2. Risk of Rehospitalization or death	
Difference in mean KCCQ	Power	Hazard Ratio	Power
4.5	.76	0.74	0.75
5	.84	0.73	0.80
5.5	.90	0.71	0.85
6	.95	0.69	0.90

10. Qualitative Analysis: All interviews will be audio recorded and fully transcribed. We will use qualitative data analysis software, *NVivo (*QSR International, Melbourne, Australia)[99] to organize, code and retrieve qualitative data, summarize linkages across themes and maintain analytic notes of the coders. Transcripts and field notes from observations of the intervention (not video recorded for privacy reasons) to monitor fidelity will be entered in the database and line- by-line open and thematic coding will be conducted to identify key themes/factors. Qualitative data analysis will be conducted through an iterative process in which members of the research team engage in both data collection and analyses throughout the study. This allows for researchers to refine

interview questions as needed to address the goals and foci of the study, to create accurate thematic analysis that are reflective of the emerging data, and to cease data collection when theoretical saturation has been achieved.[71] It is anticipated that 20+ interviews for patients and their caregivers (it is anticipated that at least 10 caregivers per 20 patients will participate), 10+ for providers and one physician administrator (e.g. Chiefs of Medicine) at each site will be sufficient to identify common themes relevant to intervention refinement, as well as to identify unanticipated themes and issues (i.e. to obtain saturation of the data).[100] The participation of the patient's caregivers is voluntary and only if permitted by the study subjects (draft consent form for the interview subgroup attached in appendix). Data will be examined by multiple coders for themes on the perceived effectiveness of SMAs. Experienced coders at the Cleveland VA site will participate in a training session on the specifics of this study as well as an approach to coding that will maximize the usefulness of patients' feedback to program improvement. The coders will meet on a monthly basis via conference call to create a qualitative codebook, compare results to assure comparability of perspectives, and to discuss and resolve competing interpretations. On a bi-monthly basis, we will invite patients and caregiver consultants (2 from each site) from both sites to participate in the interpretation of the interviews. We will specifically elicit participant ("insider") interpretation of the themes and transcripts from patients and caregivers by utilizing tools from Beebe's Rapid Assessment Process. This team-based approach ensures data analysis and findings are representative of participant perspectives and experiences by "checking back with the local participants" and seeking their level of agreement with emergent themes presented by the researchers. Upon consultation with participant informants, the study team will identify themes/factors that are evident in the 2 study sites and determine how these differ or not across sites, thus providing insight into how our intervention changed the patient, caregiver and other stakeholder's perceptions, attitudes and satisfaction. In anticipation for this study, we already asked 1 patient and 1 caregiver at each site to participate as consultants (see letters of support).

11. Limitations and potential shortfalls: First, it is possible that secular trends such as an increase in the availability for co-interventions threaten our experimental design and cause underestimation of our treatment effects. We are using stratified randomization to balance current co-interventions and will track this carefully during the enrollment period. Adjusted analyses for imbalanced in exposure to co-interventions during follow-up will be performed when necessary and stratified analyses by co-interventions will also be explored as detailed in our analysis plan. In addition, it is likely that the effects of secular trends should be randomly distributed in a randomized controlled study, such that co-interventions should not have a differential effect. Second, our study duration is only 6 months. Based on our previous data on diabetes, the effect of SMAs on patient's outcomes are the highest while the patient is enrolled in the program and gradually declines after the stop of sessions unless booster sessions are planned. Given limitation of resources, we would like to test the short and mid-term ***effectiveness*** of the intervention first, prior to studying maintenance programs. Third, there is always a risk of not achieving the targets for patient recruitment. Fortunately, the project team is very experienced, and has had excellent track records in patient recruitment and retention in previous studies of similar characteristics. The use of 2 study sites will provide us with additional protection to achieve recruitment goals. Fourth, variation in effect size: It is possible that we found that the intervention may be ***effective*** in one site but not another, or in certain patient subgroups but the overall effect may not be large. This problem can arise due to distinct standards of usual care provided to patients and different settings of care. However, understanding these differences through this study will be important to know which settings and patients to target to derive the most benefits.

D. RESEARCH TEAM AND ENVIRONMENT

Please refer to investigator biosketch for details in qualifications and letters of support from consultants. The study team led by Dr. Wu has a long history of collaboration as well as of expertise in conducting SMAs. Drs. Wu, Taveira and Cohen have conducted 4 RCTs in SMAs including a 3-site multicenter trial (please see preliminary data section). This team will partner with Dr. Dev's team at Phoenix VAMC. Dr. Dev has been collaborating with Dr. Wu for 2 years and has been conducting HF SMAs for a year (preliminary data under Phoenix VAMC). Both sites have a robust research infrastructure, with Providence VAMC being home for the HSRD Center of Innovation in Long Term Care Services and Support for Vulnerable Veterans. The Cleveland site will support Dr. Wu in the training and analysis of the qualitative data. For the quantitative portion of the study, the statistician Lan Jiang has known and worked with Dr. Wu since Lan Jiang's previous Brown University employment and has maintained their research collaborations. This team is greatly enhanced by Dr. Grady (Northwestern) and Dr. Kim (Loma Linda VAMC). Both Drs. Grady and Kim have a background in cardiovascular nursing and care organization. Dr. Grady is a well-funded researcher (NIH, AHA) with expertise

in patient-centered outcomes. Dr. Kim has strong experience in disease management from the private sector and plan to initiate HF-SMA in Loma Linda VAMC if this trial yielded positive results. In addition, we have engagement from 2 patient and 2 caregiver consultants from each site who will serve as consultants to help us interpret the qualitative data (see qualitative analysis above).

E. DISSEMINATION AND IMPLEMENTATION PLAN

The dissemination will be performed via direct and indirect (meetings and publications) methods.
1) Presentation of our findings at National meetings: at the last year of the grant at National VA (if available) and non-VA scientific meetings: American Heart Association and/or the Heart Failure Society of America.
2) Publication in peer-reviewed journals: The manuscripts will follow the format set forth by the "Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomized controlled trials (RCTs) published in medical journals". Authorship requirements in each manuscript will be followed as outlined by the recommendations of the International Committee of Medical Journal Editors. We will provide guidance and scientific support to our patient and caregiver consultants to meet the publication criteria if so they wish for the qualitative papers. Our trial will be registered in ClinicalTrials.gov. We anticipate the writing of articles during the LAST year of the grant, which will include:

a) "***Effectiveness*** of a multi-disciplinary HF group intervention program to improve patient centered outcomes" will analyze the ***effectiveness*** of the group intervention and its comparison with usual care.

b) "Group Intervention in HF Collaborative Care: Pre-Implementation Assessment" will describe the qualitative results and will serve as the guide for the implementation to other VHA or non-VHA hospitals.

c) "Mediating factor analyses of the HF SMA", analyzes the factors that mediate the change in KCCQ and reduction of hospitalization or death, if any, in HF SMA intervention.

3) Direct Dissemination: Although SMAs have been advocated by the VHA, the applicability and ***effectiveness*** of this intervention in HF is unknown. For effective dissemination, our results will be presented at multiple levels of hospital leadership for immediate implementation if found ***effective***:

a) Hospital Level: The results of the study will be presented to the Hospital Director, the Chief of Staff, Chief of Medicine, Chief of Primary Care, Clinical Pharmacy, Nutrition, and Nursing of the respective study sites at the last year of the study. This will be done by Drs. Wu (for Providence) and Dev (for Phoenix).

b) National Level: Nationwide dissemination and implementation of the HF SMA will be facilitated by the HF-SMA manual which will be drafted in the last year of the grant and submitted to CHF QUERI for website upload. If proven ***effective***, the nationwide implementation of HF SMA will be performed through design of an implementation trial through either the VA Cooperative Studies Program or the VA Service Directed Research mechanisms. We have already engaged national stakeholders (CHF QUERI – Dr. Heidenreich, VHA National PACT Coordinator – Dr. Kirsh and National VA Coordinator for Cardiology – Dr. Rumsfeld) as consultants in the grant to help us disseminate the results. Dissemination to the private sector will be facilitated by Dr. Grady. If ***effective***, they will also facilitate and support the design of a cost-effectiveness study for broad implementation within the VA. Through these additional funding mechanisms, study investigators will be able to provide training to conduct the group sessions across different sites. The study investigators will also be able to visit hospitals to aid on the set-up of HF-SMA on solicitation.

Based on our previous experience with implementation of SMAs, it is possible that clinical inertia and lack of provider interest exist as barriers to nationwide HF-SMA implementation. In anticipation, we have included physicians in our stakeholder interviews to understand their opinion and perception of HF- SMAs. If the results of this study are positive, we will be able to overcome potential clinical inertia with the support of the same clinicians that helped us shape and refine the SMAs as well as organizational leaders.

F. PROJECT MANAGEMENT PLAN

The project will last 4 years. It will be divided in 3 parts: randomized controlled trial, data analysis, and dissemination of results. Although all investigators are involved in all the aspects of the study, specific committees are formed to take advantage of each person's expertise. Dr. Wu is the Providence PI and the overall PI, ultimately responsible for the coordination and execution of the entire research program. Dr. Dev is the Phoenix PI and the study co-PI. Both Drs. Wu and Dev will be in charge of the study execution and ensure completion of the randomized trial. Lan Jiang is the study's statistical analyst, and will ensure completion of the quantitative data analysis. The qualitative portion of the study is ongoing and will be overseen by the Cleveland site. Dr. David C Aron and his research staff from the Louis Stokes Cleveland VA Medical Center will conduct interviews, analyze qualitative data and conduct fidelity assessments of the Heart Failure –Shared Medical Appointments (HF-SMA) for both the Providence and Phoenix sites. All qualitative researchers will have

monthly conference calls (in addition to the study conference calls) to discuss about coding and ongoing analysis of the qualitative data. Dr. Tracey Taveira is an SMA expert and will oversee the conduction of HF SMAs in both Providence and Phoenix (through Vtel). Dr. Lisa Cohen is an expert in HF SMA and will be responsible to lead the HF-SMA efforts in Providence as she is currently doing. Upon completion of the trial, Drs. Wu and Dev will work with our study consultants, Drs. Rumsfeld, Kirsh, Grady, Kim and CHF QUERI leader (Heidenreich) to disseminate the results and plan the implementation efforts if proven ***effective***. Monthly investigator meetings (separate from the qualitative analysis sessions), in form of conference calls (VANTs line) of one hour duration, will take place to discuss the progress of the entire project and future objectives to be achieved. Face-to-face meetings of key study staff will take place yearly, both in Providence and Phoenix VAMC, in an alternate fashion. At the end of the study, we will track healthcare utilization and costs of our participants in all sites for an economic analysis. The Gantt chart outlines the key study tasks and activities (below).

	STUDY TIMETABLE															
	Year 1				**Year 2**				**Year 3**				**Year 4**			
	Months of Study															
Function	0-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48
Study announcement to providers and patients																
Recruitment																
Randomized controlled trial																
Qualitative data coding and analysis																
Quantitative data cleaning and analysis																
Publication of study manuals and results																
Local dissemination and presentation																
Preparation of National Dissemination through CSP or SDP																

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