Caregiver Support in the Context of Multiple Chronic Conditions
(NCT04090749)
Updated 3/29/23

Protocol

1. Abstract

Family caregivers who care for older adults living with multiple chronic conditions, including heart failure (HF), provide substantial cost savings to the US healthcare system.[1] While caregiving can be meaningful and rewarding, extensive research also demonstrates high rates of chronic disease, fatigue and physiologic measures such as stress hormones among caregivers.[2] Family caregivers are often left juggling their loved one's healthcare as well as their own. Unmet needs have been identified including increased stress, financial strain and social isolation, but interventions to address these needs in HF caregivers have had mixed results.[3] Due to the limited impact of many caregiver interventions, experts have called for a greater understanding of the dynamic and contextual factors of family caregiving including resources, needs and social support with an increased focus on individualization of interventions for high-risk caregivers to improve outcomes.[3–6] Following a mixed methods study to better understand these contextual factors and to address this gap between the evidence and uptake of proven strategies by caregivers, we have developed a resilience-promoting intervention to improve quality of life for family caregivers of individuals with multiple chronic conditions, including HF, Caregiver-Support.[7–9] This home-based intervention is guided by effective strategies implemented by our co-investigator, Dr. Sarah Szanton, to support older adults in goal setting to promote healthy aging. Using these strategies, Caregiver-Support will help caregivers articulate statements of purpose in life, set goals to address fatigue and caregiver burden, provide instrumental support through a benefits check-up and promote identification and increased connection with the caregiver's social network.

The first phase of the study will be an open label pilot (N=5) followed by a single-masked, two-group, randomized trial (N=40) to test the feasibility and gauge an initial effect size of the intervention. Participants will be visited by study staff in their homes for data collection and intervention visits. Participants will be randomized to receive either the immediate intervention group or the waitlist control group. In the waitlist control group, participants will receive usual care for the first 16 weeks (which is limited to printed materials provided in the clinic) and then begin the intervention. The intervention will consist of 5 in-home sessions with a nurse interventionist. Each participant will receive each intervention component but interventionists will systematically tailor content to the participants' goals based on protocols. All participants will be reassessed at 16 weeks and 32 weeks by a research assistant (RA) masked to treatment condition. The primary outcome will be improvement in quality of life between baseline and 16 weeks. Other endpoints include group differences in fatigue, caregiver burden, self-reported and physiological measures of resilience up through 32 weeks after the intervention. We will also examine the acceptability of the intervention using intervention compliance and participant satisfaction data.

2. Objectives

Aim 1: Test the feasibility and gauge an initial effect size of the intervention to improve QOL (primary outcome), fatigue and caregiver burden (secondary outcomes) among family caregivers from baseline to 16 weeks.

Aim 2: Test whether fatigue and caregiver burden are associated with a physiological measure of resilience, inflammatory cytokines (Il-6 and IL-10) detected in sweat patches and a self-reported measure of resilience, controlling for covariates.

Aim 3: Evaluate changes in heart rate variability (HRV), an indicator of physiologic stress, pre- and post-intervention.

Aim 4: Describe care recipient 6-month palliative care utilization, all-cause hospitalization, and mortality, comparing intervention and control.

3. Background

Heart failure (HF) is a syndrome of multiple chronic symptoms and commonly co-occurs with 10 other chronic conditions.[10] Nearly 30% of patients who have been hospitalized for HF will be readmitted within 30-60 days and 53% of patients hospitalized for HF will die within 5 years.[11,12] As older adults manage worsening HF, caregiving responsibilities often increase, a phenomenon that has a greater impact among vulnerable populations.[4,13–15] Throughout the provision of care, family caregivers must address a wide range of patient needs: assistance with everyday activities, help with a range of healthcare activities, transitions between settings of care, medication management and wound care. **However, because family caregivers are not routinely assessed in health care delivery, little is known about the context of their contributions to health care activities or the caregiving-related effects they experience.**[16]

Previous studies of family caregivers of patients with HF have identified worsening quality of life (QOL) over the course of the patient's illness.[13,17,18] For patients, being able to stay in the home as HF worsens, provides a sense of security, freedom and improved symptom awareness. However, many caregivers report increased distress while supporting the patient in the home, feeling alone and fully responsible for care.[19] Fatigue and burden have been found to be significantly associated with decreased QOL, demonstrating the need to improve caregiver outcomes.[13] Additionally, caregivers of patients with high symptoms perceive they spend more time on difficult tasks, have worse affective symptoms, and have poorer physical health-related QOL than those caring for patients with low symptoms.[18] Thus, there is great need to provide interventions that improve QOL and decrease fatigue and caregiver burden of family caregivers of patients with HF, particularly in the home when patient symptoms are high.

Stress response and autonomic nervous system dysregulation have been noted among caregivers.[20,21] Several cellular and systemic changes accompany the stress response network including: cytokines, namely Interleukin 6 and 10 (IL-6 and IL-10) and tumor necrosis factor alpha receptor 1 (TNFαR1), brain derived neurotropic factor (BDNF) and heart rate variability (HRV). Heart-rate variability detects variation in the length of time between heart beats and is considered an indirect view of autonomic nervous system function. Autonomic nervous system dysregulation is important in chronic diseases such as depression, diabetes, cardiovascular disease, stroke and certain neurological disorders.[22] Symptoms like sleep, fatigue, and pain are also correlated with autonomic nervous system activity.[23,24]

The proposed study will implement a program using evidence-based strategies. This study builds on our success in previous randomized control studies that support community dwelling, low-income, older adults with functional limitations age in place by addressing individually tailored goals to improve resilience.[8,25] We will also contribute to caregiving science by evaluating implementation and maintenance of goals by participants. We will measure response to the intervention by examining both self-reported measures and physiological measures such as IL-6, IL-10 and HRV. The proposed study will address the National Academies of Sciences, Engineering, and Medicine recent call to promote the well-being of family caregivers for older adults with a focus on ensuring respect for families' diverse contexts, beliefs, and preferences.

Investigators

Our research team has worked together on studies in various combinations for years and represents nationally and internationally known investigators with expertise in the proposed methods. The PI is a

junior investigator (Dr. Abshire) with extensive clinical and research experience with heart failure patients and caregivers. As a junior investigator, she will be mentored by Drs. Szanton and Davidson. Dr. Sarah Szanton has fielded multiple community trials that involve nurse-led home visits and goal setting.[7, 8] Dean Patricia Davidson is a global leader in HF and has an established program of research improving cardiovascular care and caregiving.

Innovation

The proposed study is innovative in several critical ways: 1) Supporting caregivers of patients with HF to discuss their purpose in life, set their own individualized goals, while providing instrumental and social support is both a person- and family-centered approach to improve QOL; 2) it addresses both intrinsic, individual factors and extrinsic factors through the instrumental support and social network strategies which has not been reported previously; 3) it allows participants the opportunity to tailor their goals to their own needs, rather than the heart failure management needs of the patient.

Conceptual Framework

This study will be guided by the Society to Cells Resilience Framework (Figure 1), first-authored by Dr. Sarah Szanton (co-Investigator for this pilot). The Society to Cells Resilience Framework posits that intervening on more than one socio-ecologic domain (in this case, physiologic, individual, and family) leads to more lasting effects on individual resilience compared to intervening on one domain. Second, that resilience can be fostered at critical times in the life course, such as when there are increased caregiving responsibilities that can both create meaning and strain. Based on these tenets, the resilience framework ties together the many proposed levels of measurement such as fatigue, caregiver burden and quality of life by intervening simultaneously on them to improve overall resilience.

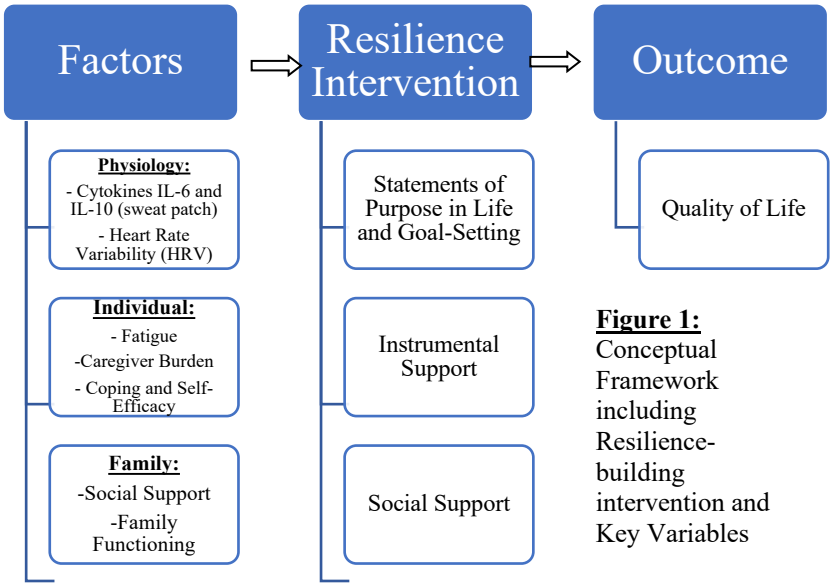
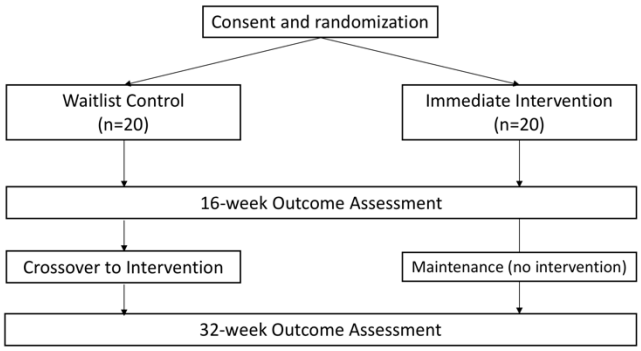


Figure 1: Conceptual Framework including Resilience-building intervention and Key Variables

4. Study Procedures

Figure 2: Flowchart of Study Design



Overview of Study Design (Figure 2): We propose an open label pilot (n=5) with a subsequent single-blind, two group randomized pilot trial to test the feasibility and gauge an initial effect size of the Caregiver-Support intervention to improve QOL. The immediate intervention group (n=20) will receive the intervention during weeks 0-16. The waitlist control group (n=20) will be provided written materials with community resources for caregivers during the first 16 weeks, then they will begin the intervention. Waitlist control groups are used to first provide an untreated comparison and second to allow wait-listed participants an opportunity to receive the intervention at a later date.[26,27] This is especially appropriate given that very few services are currently offered to HF caregivers. To account for estimated 20% attrition we will recruit 53 participants.

Johns Hopkins Clinic Recruitment:
Method 1: We will enroll caregivers of patients with HF treated in the Johns Hopkins Health System. Once we find potentially interested participants through clinic referral, we will screen the caregiver for eligibility then contact them by phone, zoom, or in person in clinic to explain study procedures. If eligible by screening and interested in participating, we will schedule the caregiver's baseline interview within 10 days of initial contact. During the baseline interview the research assistant will re-explain the study, obtain written consent (if interview is in-person), or e-consent (if the interview is by phone or DoxyMe or Zoom video call).

Method 2: We will distribute a recruitment flyer in adult medical/surgical clinics in the Johns Hopkins Health System. Caregivers that respond to the recruitment flyer will be screened for eligibility. If they are eligible, we will contact them by phone to explain study procedures. If interested in participating, we will schedule the caregiver's baseline interview within 10 days of initial contact. During the baseline interview the research assistant will re-explain the study, obtain written consent (if interview is in-person), or e-consent (if the interview is by phone or DoxyMe or Zoom video call).

Method 3: Caregivers of patients with heart failure will be identified through recruitment screening of Dr. Martha Abshire Saylor's study "Palliative Care Needs of Community-Dwelling Patients with Heart Failure and Physical Frailty" (IRB00262188). Patients will be sent a recruitment flyer for their caregiver. Caregivers that respond to the recruitment flyer will be screened for eligibility. If they are eligible, we will contact them by phone to explain study procedures. If interested in participating, we will schedule the caregiver's baseline interview within 10 days of initial contact. During the baseline interview the research assistant will re-explain the study, obtain written consent (if interview is in-person), or e-consent (if the interview is by phone or DoxyMe or Zoom video call).

Johns Hopkins Bayview Clinic Recruitment:
We will distribute a recruitment flyer in the heart failure clinic at the Johns Hopkins Bayview Medical Center. Caregivers that respond to the recruitment flyer will be screened for eligibility. If they are eligible, we will contact them by phone to explain study procedures. If interested in participating, we will schedule the caregiver's baseline interview within 10 days of initial contact. During the baseline interview the research assistant will re-explain the study, obtain written consent (if interview is in-person), or e-consent (if the interview is by phone or DoxyMe or Zoom video call).

Heart Failure Center at Ascension St. Agnes Hospital Recruitment:
We will distribute a recruitment flyer in the heart failure clinic at St. Agnes. Once we find potentially interested participants through self-referral though the recruitment flyer, we will screen the caregiver for eligibility then contact them by phone, zoom, or in person in clinic to explain study procedures. If eligible by screening and interested in participating, we will schedule the caregiver's baseline interview within 10 days of initial contact. During the baseline interview the research assistant will re-explain the study, obtain written consent (if interview is in-person), or e-consent (if the interview is by phone or DoxyMe or Zoom video call).

Open Label Phase:
The first five participants will be enrolled into an open label pilot study, in which they will automatically receive the Caregiver-Support intervention. The participants will be interviewed after program completion to get feedback on the data collection instruments, intervention content including the number of visits and user-friendliness of intervention components (e.g. purpose in life activity), and satisfaction with the overall program process. This feedback will be used to modify the Caregiver-Support intervention for the waitlist control trial that will begin enrollment following the open label phase.
Randomization: Within 48 hours of the baseline interview, we will randomize using redcap randomization and communicate the assignment to participants by letter. At that same time, we will inform the nurse interventionist of the new participant. The intervention nurse will contact the participant within one week to schedule the first appointment. The waitlisted group will receive usual care for caregivers for the first 16 weeks, which is normally limited to inclusion in some clinical assessment and teaching during patient visits. Waitlisted participants will receive monthly study postcards to encourage retention. After 16 weeks, they will begin the intervention. The 32- week assessment will measure whether immediate intervention participants continue the strategies on their own and whether they continue to improve on the self-report scales and will measure improvement following the intervention for waitlisted participants.

Intervention Delivery Characteristics:
The intervention delivery characteristics will consist of an assessment-driven, tailored package of interventions delivered by a nurse interventionist. The intervention will be guided by the theory and evidence-based practices that have been successful in our previous work drawing upon clinical approaches such as patient-centered care and motivational interviewing.[23,38] Every participant receives each component of the intervention (assessment, goal setting, interactive problem-solving, training) but interventionists clinically tailor content to each participant's goals. Nurse interventionists will be trained and equipped with education materials vetted by national organizations leading caregiving research such as the National Alliance for Caregiving, National Council on the Aging (NCOA) and the, American Association for Retired Persons (AARP). We propose an intervention incorporating 5 individualized, nurse-led, home-based or virtual sessions, with telephone check-ins and text reminders, according to participant preference. Baseline, 16 and 32-week data will be collected by interviewers masked to treatment assignment and without interventionist contact. Each design component, related evidence supporting component selection and intervention delivery is described below.

Table 1 Intervention Components and Evidence Basis for Component Selection

Intervention Component	Evidence Basis for Component	Intervention Delivery
1) Whole-person physical and psychosocial assessment including personal goals	- Caregiver physical and psychosocial assessment is suggested by HF guidelines, but not commonly used in practice[28–31] - Involving the caregiver in assessment and encouraging them to	A trained nurse will assess the caregiver using a holistic physical and psychosocial assessment used in previous studies. The nurse will focus on caregiving tasks and factors contributing to a sense of burden.

	set their own goals is person-centered, builds rapport and increases participation.[25,32,33]	The nurse will share observations with the caregiver to inform goal-setting.
2) Discussing caregiving in the context of the caregiver's identified 'purpose.' A nurse will lead the caregiver through activities designed to help identify or refine a statement of purpose in life.	- Purpose in life was associated with lower mortality and CVD[34], stroke[35], MI[36], better preventive health behaviors[37], lower allostatic load[38] - Purpose in life can be improved through intervention[39–41] and is linked to down-regulation of pro-inflammatory genes[42]	A trained nurse will lead the caregiver through activities designed to help the caregiver identify and write a statement of purpose in life. For this purpose, a deck of question cards have been developed. The caregiver will choose one or more cards from each of 4 themes: purpose, experience caregiving, caring for yourself and emotions. Comments made will be used to create a summary purpose statement.
3) Co-development of incremental action plans that address personal goals to improve quality of life and reduce fatigue and caregiver burden. A list of goals will be constructed and prioritized. Caregivers will design and work on incremental action steps related to goals, through tailored strategies developed through collaboration with the nurse.	- Incremental action plans based on individually tailored goals, allowing the participant to prioritize their own goals and strategies, increases self-efficacy and encourages participants to use their new skills with other problems.[25,32] - Studies incorporating this technique have resulted in improved QOL, self-efficacy related to falls, depression and decreased disability.[8,25,33] - Goal attainment achieved in 73% of functionally impaired older adults-independent of age, race, gender – higher pain group less likely to achieve goals.[33]	A list of goals related to addressing fatigue, caregiver burden and perceived threats to QOL will be constructed and prioritized. During the nurse-led sessions, caregivers will work on action steps related to goals in order of priority through tailored strategies developed through collaboration with the nurse.
Instrumental Support refers to the tangible help that others may provide (e.g., help with financial needs, provision of transportation or support with medication management).	- Instrumental support may enhance emotionally supportive interventions[43–45] - Addressing needs to support instrumental activities of daily living may improve retention from participants - Interventions that provide instrumental support while equipping community members are more sustainable and impactful than providing the support without considering social support/network.	BenefitsCheckUp is a free, confidential service provided by the National Council on the Aging (NCOA) for people 55 and over and their caregivers. The nurse interventionist will help the caregiver explore the modules which include topics such as medications, healthcare, income assistance etc. Common unaccessed benefits caregivers may be eligible for include: Medicaid, Food bank access, home energy assistance and tax credits. In addition, the nurse will provide support for caregiving challenges such as medication management or communication with providers of multiple chronic conditions.

Social Support	- Perceived social support can be enhanced through interventions[43] - Helping the caregiver identify ways they are already supported may support a sense of perceived support - Setting goals to engage the existing social network may increase self-efficacy for future needs and engagement[46]	A trained nurse will lead the caregiver through activities to help caregivers connect to their existing family and community to engage these relationships for support in caregiving. The nurse and caregiver will work through these activities during an in-home visit.

Intervention Protocol:

The RN will meet with the caregiver in-home or virtually to perform the whole person assessment in which the nurse will focus on caregiving tasks and factors contributing to a sense of burden. In this assessment, the RN and the caregiver identify and prioritize goals, and make plans to achieve those goals. The study will provide the Caregiver-Support Handbook, including evidence-based educational materials, contact information, and a calendar of sessions that the participant keeps for reference. In each session, the RN assesses goal attainment, reinforces strategy use, reviews problem-solving, refines strategies (examples in Table 3 such as Go4Life and AARP materials), and provides education and resources to address future needs. If sessions are held virtually via phone or DoxyMe video call or Zoom video call, no physical activity goals will be pursued as part of this intervention due to the inability to safely assess the participants physical activity readiness.

Following the session, the RN will find additional resources, tailored to each caregiver. In the final session**,** the RN reviews the participants' strategies and helps to generalize them to other possible challenges or goals. Sessions will be spaced to encourage practicing new strategies independently after developing them together with the nurse. Although this intervention structure has been successful in work by the mentorship team, we will adjust the timing and frequency of study interactions based on feedback in the open label phase. Bi-monthly meetings of the RNs with the Research Coordinator and the PI will ensure smooth communication, address challenges, supervision, and adherence to intervention fidelity.

Table 2: Exemplar caregiver goals and intervention approaches

Example Goals	Intervention Approaches
Physical activity: Increase physical activity by 10% or 1 day per week	1) RN will assess current physical activities, weekly duration and intensity. 2) RN will assess safety of physical activity with Physical Activity Readiness assessment with final evaluation by nurse practitioner 3) RN implements NIA Go4Life physical activities, with emphasis on variety, strength training and cardio in a safe environment. 3) RN will assess interest in group activities or engaging social support to increase accountability and help participant get connected.
Stress management: Decrease exposure to stressors, increase use of coping strategies	1) RN will assess stressors with focus on caregiving-related stress 2) RN will work with caregiver to draft a list of caregiving concerns to be addressed at the next visit with the patient's cardiologist 3) Participant will identify coping strategies such as positive self-talk, ways to defuse stressful situations and prevent stress through restorative activities focused on purpose in life.
Rest: Improve nighttime sleep quality	1) RN to assess for duration, quality and sleep hygiene 2) RN will help caregiver identify modifications to sleep environment and bedtime routine 3) RN will assess for daytime fatigue and sleepiness.

Table 3: Study Visit Timeline for Immediate Intervention Group*

Format and timing of visits	Key activities
Baseline Data Collection	Sweatpatch application Heartrate Variability Measurement Survey
Sweatpatch Pickup	72 hours post-application, remove sweatpatch and deliver for storage and analysis
Randomization	Mail randomization results
Home Visit Week 1	Assessment Set goals and discuss priorities Remove sweatpatch and deliver for storage and analysis (if not already performed)
Home Visit Week 3	Purpose in Life activity Instrumental Support activity: Benefits Check Up Assess goal attainment and revisit strategies
Phone Check-in Week 4	Review/edit purpose statement Assess goal attainment and strategies to achieve goal
Home Visit Week 6	Social Support Activity Assess goal attainment and strategies to achieve goal Follow-up re: instrumental support
Phone Check-in Week 8	Review/edit purpose statement Assess goal attainment and strategies to achieve goal
Home Visit Week 10	Assess goal attainment and strategies to achieve goal Follow-up re: instrumental and social support
Phone Check-in Week 12	Review/edit purpose statement Assess goal attainment and strategies to achieve goal
Home Visit Week 14	Review of progress, goals and purpose Discuss how caregiver will involve social support in next goals
Data Collection Visit Week 16	Sweatpatch application Heartrate Variability Measurement Survey
Sweatpatch Pickup	72 hours post application
Data Collection Visit Week 32	Sweatpatch application Heartrate Variability Measurement Survey
Sweatpatch Pickup	72 hours post application

* Waitlist control group will begin intervention at week 16.

Research Variables and Measurement

We chose measures (Table 1) based on previous RCT experience as well as those that met the following criteria: 1) possess known reliability and validity with ethnically diverse samples; 2) are sensitive to change from an intervention; 3) have clinical relevance to QOL; 4) Common Data Elements to connect this work with the broader literature, other pilots and other P30 Center work and 5) represent objective as well as subjective indicators of the domains we seek to impact. Finally, we sought to achieve a balance between psychometric quality and practical considerations such as respondent burden. All instruments with the exception of demographics will be measured at baseline and 16 weeks post-intervention.

Table 4: Constructs, Instruments and Reliability

Theoretical Construct	Instruments and variables	Number of Items	Cronbach's alpha
Caregiver demographics and characteristics	Demographics Characteristics: Caregiving physical and supportive tasks description, employment Physical Activity Readiness Assessment	23	-
Fatigue	PROMIS-Fatigue Short form	7	0.9[47]
Caregiver Burden	Oberst Caregiver Burden Scale 2 domains: time caregiving and task difficulty	15	0.90[48]
	Modified Caregiver Strain Index	13	0.86[49]
Social Support	ENRICHD Social Support	7	0.89[50]
	Family Functioning – Family Assessment Device Questionnaire: Global Family Functioning Scale (only)	12	0.9[51]
Resilience	Sweatpatch (IL6, IL10)	-	-
	Coping Self-Efficacy Scale	13	0.91[52]
	Heart Rate Variability	-	-
	Brief Resilience Scale	8	0.91[53]
Quality of Life	36-Item Short Form Health Survey (SF-36) 2 scales: Affective well-being and Physical health	36	0.85[54]
Depression	PHQ-8	8	0.82[55]
Care Recipient Palliative Care Utilization	Palliative care referral or encounter in electronic medical record within 6 months after caregiver completion of intervention	-	-
Care Recipient Hospitalization	Hospitalization (admission) encounter in electronic medical record within 6 months after caregiver completion of the intervention	-	-
Care Recipient Mortality	Documented as deceased in electronic medical record within 6 months after caregiver completion of the intervention	-	-
Care Recipient Hospice Enrollment	Enrollment in hospice in the electronic medical record within 6 months after caregiver completion of the intervention	-	-

Data collection and management:

Questionnaire Data:

Trained research assistants will verbally elicit questionnaire data from participants in person or in virtual meetings. Virtual meetings include either telephone conversations or video calls via DoxyMe or Zoom. DoxyMe is a HIPAA compliant virtual meeting software used for telehealth purposes. We have created a HIPAA compliant Zoom account for video calls as well. Research assistants will directly enter data into the RedCap data entry and management system.

Due to COVID-19 research restrictions we will not collect sweat patch or HRV data until approved by the School of Nursing research restart committee.

Sweat patch:

Interleukin 6 & 10 will be collected via a non-occlusive adhesive patch which remains in place on the caregivers' skin for 72 hours. The sweat patch will be placed on the participant's skin at their baseline data collection visit. The participant will be instructed to leave the sweat patch in place for 72 hours. A study team member will then return to the participant's home to remove the sweat patch. The sweat patches will be prepared and delivered to the Johns Hopkins School of Nursing for temporary storage. Then the patches will be analyzed at the Johns Hopkins School of Nursing according to the Gill Lab Sweat Patch Extraction protocol and analyzed using a 3-step digital immunoassay, running all samples in duplicate. Due to COVID-19 research restrictions, sweat patches will not be utilized until the Johns Hopkins University IRB phase 2A to allow study team members to go to participants homes.

HRV:

An electrocardiogram approximately 5 minutes in length will be captured using the commercially available KardiaMobile ECG device (AliveCor, San Francisco, CA, USA). Participants will place their forefingers on the touch pad while seated and resting for the reading. Data will be captured using Kubios HRV software, a software tool for heart rate variability analysis (Kubios, Inc. Kuopio, Eastern Finland). The device will automatically save the rhythm strip on the iPod app and study personnel will download the rhythm strip after the home visit when it is performed. The file will be sent to the University of Oklahoma Heart Rate Variability Laboratory where it will be analyzed for measures of heart rate variability and counts of abnormal beats (if any). These files will have no identifying data other than time and date of measurement. If any suspected abnormality is seen on the analysis, the PI will be notified of any abnormalities that could impact health, and the subject would be notified and informed to contact their physician. Due to COVID-19 research restrictions, sweat patches will not be utilized until the Johns Hopkins University IRB phase 2A to allow study team members to go to participants homes.

Physical Readiness Assessment

During the course of this intervention, the participant will be developing personal goals with the guidance of the nurse interventionist. If a physical activity goal is identified, the nurse interventionist will administer the Physical Readiness Assessment tool. The results of the physical activity readiness assessment will be evaluated by the study nurse practitioner - Melissa Hladek, PhD, CRNP, FNP-BC - to determine the safety of the participant's physical activity goal. Due to COVID-19 research restrictions, the physical readiness assessment will not be performed, and physical activity goals will not be pursued for participants who have virtual data collection and intervention interactions.

Care Recipient Data:

Six months after the caregiver completes the intervention, trained research assistants will search the electronic medical record of the caregiver's care recipient related to palliative care utilization (referral), hospice enrollment, hospitalization (admission), and death. Research assistants will directly enter data into the RedCap data entry and management system.

Data Management:

Data from screening, intervention sessions, and final data collection will be entered onto forms that the data manager will check for completeness and appropriateness. The data manager will send reports of missing or inappropriate entries to the PI every week for clarification and resolution. As a phase 1 pilot study, a Data Safety and Monitoring Board is not required, however, as part of the P30 PROMOTE Center, a Data Safety and Monitoring Board has been established. Details are provided in the human subjects section.

Fidelity: The fidelity plan is based on the NIH Behavior Change consortium developed by national leaders. We will enhance fidelity through design elements (intervention is distinct and based on theory), training (using an intervention manual), delivery (reminder calls the night before intervention sessions, and measure fidelity through records of home sessions (by date and duration), checklists completed by study team

members and direct observations and discussions concerning intervention engagement to evaluate receipt, and enactment. Ten percent of sessions will be audio taped which will be reviewed by the research coordinator using a priori monitoring checklists developed for this pilot trial. All data collection and intervention interactions will be recorded. Evaluation will include periodic assessments of data quality, participant recruitment, accrual, and retention. Feedback will be provided to each interventionist who will provide case presentations in supervisory sessions. Bi-weekly meetings of the nurse interventionist with the Research Coordinator, the PI, and Dr. Szanton will assure on-going fidelity to the intervention.

Study duration and number of study visits required of research participants: Participation in the study will consist of initial study consent, baseline, 16 and 32-week data collection and 5 study interactions for the intervention. Based on participant preference, the nurse interventionist may also arrange phone calls between visits to assess progress towards goals.

Blinding, including justification for blinding:
Research staff performing outcome assessments will be masked to assignment. Prior to follow-up assessment, staff will use standardized language to instruct participants not to discuss their treatment allocation with staff.

Justification of why participants will not receive routine care or will have current therapy stopped: n/a

Justification for inclusion of a placebo or non-treatment group: Both groups will receive the intervention. We are using a waitlist design to have a comparison to usual care.

Definition of treatment failure or participant removal criteria: n/a

Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely: n/a

5. Inclusion/Exclusion Criteria

Screening:

1) Six-Item Screener; Callahan CM et al., 2003

To be eligible for inclusion caregivers must:

1) 18 years or older and
2) English speaking
3) Live with the heart failure patient or visit the patient at least 3 days per week to provide care or support.
4) Provide support to the patient for at least 1 Instrumental Activity of Daily Living
5) Care for a heart failure patient hospitalized in the last 6 months
6) Live within a 1 hour driving radius of the Johns Hopkins Hospital

Exclusion Criteria:

1) Caregivers with cognitive impairment using the six-item screener will be excluded. Severe Cognitive Impairment would make active participation in interviews and survey completion very difficult.
2) Non-english speakers will be excluded. Non-english speakers may have unknown needs that cannot be addressed with this intervention.

3) Caregivers with terminal diagnosis will be excluded as goal-setting at end of life may be different than without a terminal diagnosis.

6. Drugs/ Substances/ Devices

N/A

7. Study Statistics

Exploratory and descriptive analysis will be completed for all study variables. Variables will be examined for normality and examined with means and standard deviations or medians and interquartile ranges accordingly. Baseline characteristics comparing the two groups (waitlist vs. immediate intervention) will be assessed. Any differences between the groups will be adjusted for further analysis. The significance level will be set at 0.05. Sensitivity analyses will be conducted adjusting for variables on which the group differ and compared to the pattern of results in the main analyses.

a. Primary outcome variable.

Generalized estimating equations (GEE) will be used to examine the difference between intervention and waitlist groups in change from baseline to 16 and to 32 weeks for QOL (primary outcome), considering affective well-being and physical health separately and together as an aggregate measure of QOL. Time, group and the group by time interaction will be included in the model. We will also calculate Hedges' g for differences in change over time between the groups in change in primary outcomes. Hedges' g is recommended over Cohen's d' to correct of an upward bias in small sample sizes.[55] The effect size associated with the variables will be compared to established clinically significant improvement reported in the literature, rather than placing emphasis on statistical significance.

b. Secondary outcome variables.

Generalized estimating equations (GEE) will be used to examine the difference between intervention and waitlist groups in change from baseline to 16 and to 32 weeks for fatigue and caregiver burden (secondary outcomes) using a similar approach (as described for primary outcome). We will use a similar approach to analyze cytokines and HRV. Given previous research in adults with chronic disease, we assume that the cytokine data will require log transformation to approach normality.

We compare differences in care recipient palliative care utilization, hospice enrollment, hospital admission, and mortality 6 months after caregiver completion of the intervention between intervention and control groups. We will use chi-square test to determine differences in rates of these outcomes and t-tests to compare average time to event between groups.

c. Statistical plan including sample size justification and interim data analysis.

As a pilot study, the analyses will likely not have adequate power to detect significant differences. Therefore, effect sizes, rather than statistical significance will be examined for evidence of the effectiveness of the intervention. With a total sample size of 53 we will be able to estimate the effect size associated with the intervention. This effect size will be compared to the literature for similar interventions and used to estimate the needed sample size to a fully powered effectiveness trial. There will be no interim data analysis.

Understanding the factors that predict which intervention components are successfully implemented and for which participant subgroups will be critical for fine-tuning this multicomponent intervention for future proposals that will extend efficacy examinations and effect modification analyses. Acceptability of the intervention will be examined in multiple ways. We will examine percentages of people who stayed in each arm of the study and conduct numerous descriptive correlational analyses of the association between

the intervention compliance and other variables. These analyses will quantify intervention implementation by demographic and participant health variables. Analyses that utilize the post-randomization data (e.g. treatment compliance) [40-43] will be evaluated in supplementary analyses. We will distinguish non-compliance with intervention from attrition or loss to follow-up, i.e. missing data. We will also use the participant satisfaction data to examine acceptability of the intervention.

d. Early stopping rules.

As this is a low-risk behavioral intervention pilot, we have not defined any early stopping rules.

8. Risks

Minimal risks to study participants are expected. Some participants may experience some discomfort or fatigue in study interactions or in answering questions about their caregiving. Interviewers and interventionists will be trained to handle these minimal discomforts if they should occur, offering opportunities to rest throughout the interviews and intervention sessions.

Education in protection of human research participants: All investigators have completed the Johns Hopkins University School of Medicine Research Compliance course and have been certified to conduct human research. The course consists of the University of Minnesota Web modules on Informed Consent, the consent Process, and After Informed Consent, Johns Hopkins University School of Medicine module on local IRB requirements, and achievement of a passing score on the Johns Hopkins Knowledge Assessment module. According to the policies of the Johns Hopkins University, approval for this research will be obtained from the IRB office for research using human subjects prior to collecting data. Minorities and women are included in this study, and all data will be presented in group format. Participants will be assigned a code number on initial entry and all subsequent questionnaires will be identified only by code number. Information needed for follow-up contact (names and addresses) will be kept separately from all other data.

Procedures for protecting against and minimizing potential risks: The interviewer will notify the Principal Investigator (a nurse) of any concerns for distress related to the study and participants will receive a follow-up telephone call to assure that the mild distress has resolved. In situations where there is initial severe distress or when the distress has not been resolved, we will consult with our Co-Investigator, Melissa Hladek, PhD, FNP-BC. Furthermore, if any physical problems emerge during any of the study for either patients or caregivers, immediate medical attention will be sought for the participant. The research assistants will all be nurses and will be trained to call 911 if they have serious concerns of an emergent issue.

The risk of invasion of privacy will be addressed with participants during the informed consent process. All personnel involved in the study will be fully trained and certified in the protection of human subjects and HIPAA regulations. This certification will be kept current throughout the study. As part of the informed consent process, participants will be notified of their rights pertaining to protected health information. Participants will be informed that they can stop the questionnaire and rest at any time. All study participants will be provided referral information to existing health services as in typical or usual care. Thus, participants have the information to access any services that they may perceive as necessary independent of their study participation.

The risk of breaching study participant confidentiality will be minimized by identifying all participants by code numbers and securing all data collected in locked files in the PI's office and screening information to locked file cabinets with limited staff access. Pre-coded data collection instruments are prepared for use with study participants at each testing occasion. Identification numbers to assure subject confidentiality will be used. Only one master log of subject name, address and telephone number and study identification assignment will be maintained on site in the locked PI's office. This log, in both hard copy and electronic

file saved to an encrypted USB drive, will be stored in a locked filing cabinet separate from other identifying information. All completed data collection instruments are stored in locked filing cabinets. Audio recording of screens, interviews, and intervention will be identified by numbers only and stored on the Johns Hopkins Secure Analytic Framework Environment (SAFE) virtual desktop of Dr. Abshire who will provide fidelity oversight of the interventionists. Access to these computer files will be password protected, audio recordings will not contain respondent name or other personal identifying information. Recorded interviews and key stakeholder meetings will be transcribed by a transcription service.All recordings and transcripts will be password protected and stored on the Johns Hopkins SAFE virtual desktop. Each transcript will be redacted for identifiers prior to analysis. Audio recordings from intervention sessions will be used only for quality control and training purposes and then destroyed (deleted from computers) within one year of trial completion. We will use either DoxyMe or Zoom. DoxyMe is encrypted, collects no protected health information (PHI) and any data transmitted during the call is destroyed when the call ends. It is both HIPAA and HITECH compliant (https://doxy.me/en/about/). We have created a HIPAA compliant Zoom account through the Johns Hopkins School of Nursing IT department dedicated to this research study and it will only be used for study participant virtual visits and will only be available to the study team.

Data Safety and Monitoring: The PROMOTE Center will have a standing DSMB to review this pilot study. The Center will provide for collection and storage of data across pilot studies. These data will be de-identified and stored in databases on the Johns Hopkins Secure Analytic Framework Environment (SAFE) virtual desktop. Data will be restricted to those with permission to access it. Investigators will use the REDCAP data entry system. However, any paper copies of consents or other study data will be stored in locked file cabinets.

The DSMB will be responsible for reviewing the safety of study participants during the conduct of this study and provide recommendations to the research team on specific aspects of the research protocol as it pertains to safety, potential study alerts and adverse events. Specific responsibilities of the DSMB will be to: a) provide an independent periodic review of recruitment and enrollment progress; b) review adverse events (AEs) including serious events and offer recommendations regarding the trial based on such observed events; c) serve in a consultative capacity to the research team regarding study procedures to address ethical dilemmas (e.g., reporting of abuse), safety of subjects in the trial, and appropriateness of all study procedures. We will not conduct interim analyses for this pilot study.

Recruitment, Adverse Events (AE) and Alert Reports: Reports presented to the DSMB will include data on enrollment (study accrual by month; comparison of expected to actual enrollment; number of individuals screened, number eligible and number ineligible, number randomized by gender), AEs, and alerts. Also, the DSMB will receive reports of the number of study participants who discontinue from the treatment group and/or the study and reasons for discontinuation. We propose that reports be provided to the DSMB twice yearly. However, the DSMB will decide upon the schedule of reports at their first organizational meeting. Also, the DSMB may request reports as needed as well as the unmasking of the data should they deem this necessary. If unmasked efficacy data is required, the biostatistician for this study (Dr. Nancy Perrin) will serve as a liaison between the PI, database and the DSMB in order to assure that the PI and investigative team remains masked. For the first meeting of the DSMB, members will receive and review the following materials: a) Grant proposal, relevant appendices, reviewers' comments; b) Standard Quality control procedures (see Facilities/Resources); c) IRB approved consent forms; d) Baseline and follow-up batteries; e) Shell of data base for management of interview schedules and enrollment information; f) Subject tracking forms; g) Alerts and Adverse event procedures and forms; h) Intervention treatment documentation forms; i) Shell for reporting recruitment and enrollment; j) Data shells for reporting tracking information and baseline characteristics; k)
Decision rules for intervention termination (e.g., death, extended hospitalization, relocation);

Adverse Event (AE) Reporting: The DSMB is notified by the principal investigator of any serious AE within 48 hours of initial notification to the project team. All members of the DSMB will receive copies of all safety reports at the time of submission to the IRB of JHU. In addition, a listing of all AEs and their attribution (e.g., study related, intervention related, or unrelated to study or treatment) will be provided to the DSMB on a monthly basis. We do not anticipate any adverse reactions to the intervention. Based on our previous work and studies in this area by others, there is only a small risk that participants will become increasingly anxious as a consequence of the intervention and being involved in an active problem-solving, behavioral activation approach. However, interventionists will be well trained to manage this reaction or make an effective referral if necessary. Given that both data collection and interventions may occur in people's homes, there is the potential for a member of our research team to encounter a potential emergency situation that is not related to study participation (e.g., dehydration, environmental risk, medical emergency). We refer to such events as alerts and have well developed procedures for their management. All alerts are reported to the DSMB on a biannual basis. However, the reporting of alerts to the IRB of JHU is not required (see Chart below of potential alert events and plan for their management and reporting).

Plan for reporting unanticipated problems or study deviations: There are only minimal risks associated with the trial. It is anticipated that participants will experience more benefits than risks from their participation in the trial.

Table 5: Specific Alerts and Actions Taken

Alert	Action to be taken
Medical emergency: • Chest pains • Excessive bleeding • Fall and cannot get up • Difficulty breathing	If a JHU research staff person encounters this situation over the phone, the participant is put on hold and the research staff calls 911 immediately. If situation occurs within home, then staff person calls 911 immediately, and stays with participant until help arrives. Research coordinator (RC) and PI are informed within 24 hours of the event. RC then contacts individual as a follow up within two days. Research staff member completes alert form and gives to RC (or designate)
Evidence of abuse	Evidence of physical abuse is as follows: • Participant states to research staff that abuse occurs; • Research staff observes physical evidence (e.g. black eye, black and blue marks on arms/legs) Research staff member informs participant that a senior member of the research team will contact him/her later that day. Staff member informs RC immediately upon completion of interview or intervention session. RC (or designate) contacts participant to obtain further information. Participant is strongly encouraged to call his/her physician and/or Adult Protective Services (phone number will be provided). Based on the situation, the RC may notify Adult Protective Services. RC (or designate) completes Alert form. Note –The possibility of informing an agency about an abusive situation is stated in the informed consent.
Extreme Home Hazards • Exposed electrical • External door missing or cannot be locked • Ceiling, floors caved in • No temperature control (no air or heat; must be extreme)	Research staff member notifies RC within 24 hours. RC (or designate) completes Alert form.

• Major infestation	

PI – Principal investigator; RC = Research Coordinator

Legal risks such as the risks that would be associated with breach of confidentiality: The risk of breaching study participant confidentiality will be minimized by identifying all participants by code numbers and securing all data collected in locked files in the PI's office and screening information to locked file cabinets with limited staff access. Pre-coded data collection instruments are prepared for use with study participants at each testing occasion. Identification numbers to assure subject confidentiality will be used. Only one master log of subject name, address and telephone number and study identification assignment will be maintained on site in the locked PI's office. This log, in both hard copy and electronic file saved to an encrypted USB drive, will be stored in a locked filing cabinet separate from other identifying information. All completed data collection instruments are stored in locked filing cabinets. Audio recording of interviews and intervention sessions will be identified by numbers only and stored on the Johns Hopkins Secure Analytic Framework Environment (SAFE) virtual desktop. Access to these computer files will be password protected, audio recordings will not contain respondent name or other personal identifying information. Recorded interviews will be transcribed by a transcription service. All recordings and transcripts will be password protected and stored on the Johns Hopkins SAFE virtual desktop. Each transcript will be redacted for identifiers prior to analysis. Audio recordings from intervention sessions will be used only for quality control and training purposes and then destroyed (deleted from computers) within one year of trial completion. We will use either DoxyMe or Zoom for video calls. DoxyMe is encrypted, collects no protected health information (PHI) and any data transmitted during the call is destroyed when the call ends. It is both HIPAA and HITECH compliant (https://doxy.me/en/about/). We have created a HIPAA compliant Zoom account through the Johns Hopkins School of Nursing IT department dedicated to this research study and it will only be used for study participant virtual visits and will only be available to the study team.

Financial risks to the participants: There are no anticipated financial risks to the participants.

9. Benefits

Participants in the waitlist control group will not directly benefit during the waitlisted period of 16 weeks. Participants will receive study visits from a nurse when receiving the intervention.

10. Payment and Remuneration

The research participants in both the immediate intervention group and the waitlist group will each receive $20 at the start of the intervention, 16 weeks and 32 weeks following completion of surveys. Participants will also each receive an Amazon Fire 7 tablet in order to facilitate virtual intervention visits.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs to study participants.

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