Heart Failure Resilience Intervention for Caregivers

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JOHNS HOPKINS UNIVERSITY SCHOOL OF NURSING

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JHM IRB - eForm A – Protocol

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1. Abstract

Heart failure (HF) is a major source of suffering, premature mortality, and $108 billion annually in global health care costs to individuals, families and communities.[1] Caregivers of persons with HF save the United States healthcare system as much as 6.5 billion dollars each year.[2] While studies have demonstrated the positive effects of HF caregivers on *patient* depression, symptom management and quality of life (QOL), caregivers have an increased risk of their *own* worsening physical health including cardiovascular disease (CVD) risk, emotional health and caregiver burden.[3–6] Poor preventive health behaviors such as lack of exercise, stress management and poor sleep may help explain the increased CVD risk among caregivers, especially those with elevated caregiver burden.[7–9] However, little support is given to help unpaid family caregivers of persons with HF develop strategies to balance caring for the patient with caring for themselves, through preventive health behaviors or strategies to reduce caregiver burden.[7,10–12]

Therefore, we propose to develop and test a novel multi-component intervention tailored to caregiver goals, HEart failure Resilience Intervention for Caregivers (HEROIC), to improve preventive health behaviors, reduce caregiver burden and improve QOL among HF caregivers.[13] The HEROIC intervention will include individualized, nurse-led sessions focused on a) a whole-person assessment, preventive health behaviors, personal goals, and purpose in life, b) discussion of caregiving in the context of the caregiver's identified 'purpose' which supports meaning-making and provides rationale for goal-setting[14], c) co-development of a plan to address caregiver goals to improve preventive health behaviors and/or reduce caregiver burden, and d) 'walking meetings' to model the importance of physical activity while discussing incremental action plans to help caregivers achieve goals. Because the caregiver prioritizes what matters to them, this approach will address the intersections of race, gender and financial strain by design.

The first phase of the study will be an open label pilot (N=5) followed by a single masked, two-group, randomized trial (N=44) to test the feasibility and gauge an initial effect size of the intervention. Participants will interact with study staff by phone or in-person for data collection and intervention visits, dependent on COVID-19 policies and the participants' preference. Participants will be randomized to either the immediate intervention group or the waitlist control group. In the waitlist control group, participants will receive usual care for the first 12 weeks (which is limited to printed materials provided in the clinic) and then begin the intervention. The intervention will consist of 5 individualized, nurse-led, home-based sessions, with telephone check-ins and text reminders, according to participant preference. 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 12 weeks and 24 weeks by a research assistant (RA) masked to treatment condition. The primary outcome will be improvement in goal attainment of health behaviors, caregiver burden and QOL between baseline and 12 weeks. We will also examine the acceptability of the intervention using intervention compliance and participant satisfaction data.

2. Objectives

Aim 1: Test intervention components through an open label pilot (N=5) of the intervention, followed by in-depth interviews. We will assess the salient features of the novel intervention components using mixed methods including examination of all quantitative measures and qualitative interviews to explore acceptability, participant/interventionist interactions, home environment factors, goal achievement and perceived value of intervention. Intervention components will be adapted for the trial participants (who will be randomized) based on results of Aim 1.

Aim 2: Conduct a single-masked, waitlist control pilot trial of the HEROIC intervention (N=44). We hypothesize that caregivers who receive the intervention will have improvement in primary outcomes (goal attainment of health behaviors, caregiver burden and QOL) and potential mechanisms (self-efficacy and heart rate variability, a biomarker of resilience) between baseline to 12 weeks (immediate intervention group) and 12-24 weeks (waitlist).

Aim 3: Assess the salient features of the intervention components and delivery using mixed methods to explore acceptability, participant/interventionist interactions, home environment factors, goal achievement and perceived value of the intervention.

3. Background

There are five significant gaps in the science of HF caregiving. First, most caregiving interventions focus on conditions like dementia, which have a predictable trajectory; HF is characterized by unpredictable exacerbations.[15–17] Second, HF caregiver studies have included predominantly white, middle income caregivers.[18–22] Third, current HF caregiver interventions often place additional responsibility on the caregiver and have a deficit-focus instead of a strengths-based approach.[19,23,24] Fourth, there is a dearth of interventions that decrease emotional distress and improve preventive health behaviors of HF caregivers.[12,18,19,25] Fifth, trialed interventions have had limited impact.[18,19] In addition, the National Academies have called for research to meet the needs and values of diverse family caregivers and to improve caregiver health.[6,26,27] **Therefore, the purpose of this study is to improve preventive health behaviors, caregiver burden and QOL in caregivers of patients with HF through a resilience-building intervention delivered in the home (HEROIC).**

The proposed study is significant because we will test an intervention to improve health behaviors, caregiver burden and QOL among caregivers who are at risk for negative health outcomes and who receive little attention in our current healthcare system. Further, this study will test the HEROIC intervention in an ethnically diverse, predominantly low-income population with a large number of non-spousal caregivers.

We have completed 2 mixed methods studies with advanced HF caregivers. The first, with caregivers of advanced HF patients living with a left ventricular assist device and the second, was phase 1 of our P30 pilot study and enrolled recently hospitalized advanced HF patients and their caregivers. We have learned that caregivers are adapting their homes and lifestyles to accommodate HF monitoring, work and worry and that caregivers often lose track of their own needs in the midst of crisis caregiving for advanced HF patients. We have also developed the Caregiver-Support intervention, which has been approved by the IRB and is ongoing, which includes 2 of the intervention components that will also be tested in the proposed HEROIC study – the whole person assessment and purpose in life activities. However, the P30 intervention is focused on instrumental and social support. Thus, this pilot will build from the previous work and add an important focus on preventive health behaviors.

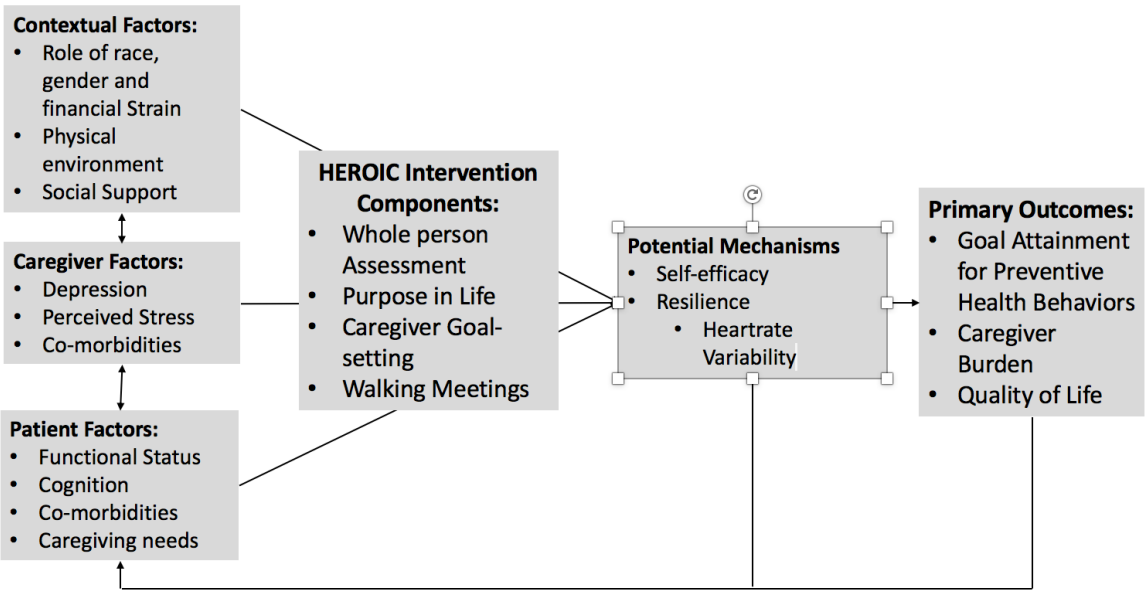
Investigators

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

Conceptual Framework

Figure 1: Conceptual Framework for Heart Failure Resilience Intervention for Caregivers (HEROIC)

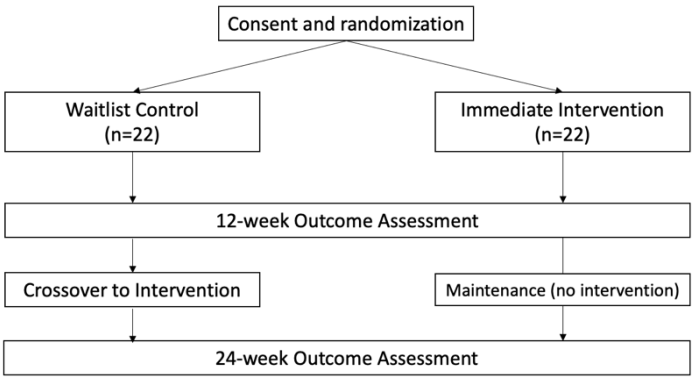


This study is grounded in a strong theoretical basis using principles of Bandura's Theory of Self-Efficacy and the Society to Cells Resilience Model.[28,29] Our theoretically-driven proposal posits that contextual, caregiver and patient factors influence caregiver self-efficacy, and resilience,.[28,29] Resilience, or positive adaptation when facing stressors, can be increased through person-centered interventions through incremental action plans to achieve goals, which can also increase self-efficacy.[5,30,31] Such interventions improve biomarkers of stress resilience such as heart rate variability which is related to CVD risk and self-reported outcomes such as caregiver burden and QOL.[32–34] In addition, articulating 'purpose in life' promotes resilience, placing the stressor in the context of larger values.[14,35–37] Based on these tenets, the conceptual framework ties together the many proposed levels of measurement such as context, self-efficacy, resilience, health behaviors, caregiver burden and QOL by intervening simultaneously on them to improve overall resilience (figure 1). **This flips the paradigm of caregiver intervention from a burden and difficulty focus to a strength-building and resilience focus.**

4. Study Procedures

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 HEROIC intervention to improve QOL. The immediate intervention group (n=22) will receive the intervention during weeks 0-12. The waitlist control group (n=22) will be provided written materials with community resources for caregivers during the first 12 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

Figure 2. Group assignment and outcome measurement



opportunity to receive the intervention at a later date.[38,39] This is especially appropriate given that very few services are currently offered to HF caregivers. To account for estimated 20% attrition we will recruit 49 participants.

Using the NIH Stage Model for Behavioral Intervention development, this proposal is congruent with a Stage 1A and 1B level of development.[40] Development of the intervention will be made more person-centered and acceptable through the use of human-centered design, involving end users in development and testing of the intervention. We will use mixed methods to evaluate the open label phase and the pilot RCT. The proposed development aim and mixed methods allow for triangulation of multiple forms of data to inform development, feasibility and acceptability (Table 1).

Recruitment:
Recruitment of caregivers of patients with HF treated in the Johns Hopkins Health System.

Target population: The recruitment sites provide early post-hospitalization guideline-directed HF follow-up care. The clinics serve primarily low-income older adults. Inclusion: Caregivers of patients served by these settings will be included if a) the patient was hospitalized within 6 months b) they agree to work on goals that address health behaviors and/or decrease burden c) caregivers live with the patient or visit them to provide care more than 3 times per week d) the caregiver is 50 years or older. Exclusions: Caregivers who themselves have a terminal diagnosis or are cognitively impaired (as determined by 6-item screener) will be excluded as goal setting and response to the intervention may vary in these groups. Caregivers who consented to IRB00203584 and participated in at least one intervention visit.

Method 1: Once we are notified of potentially interested participants through clinic referral, we will screen the caregiver for eligibility by a RedCap survey, phone, zoom, or in person in clinic.
Method 2: We will distribute a recruitment flyer in the waiting rooms of the recruitment sites. Once we are notified of potentially interested participants through self-referral though the recruitment flyer, we will screen the caregiver for eligibility by a RedCap survey, phone, zoom, or in person in clinic.

If the caregiver is eligible and interested in participating, then e-consent will be obtained (by phone, HIPAA compliant Zoom or DoxyMe video call) regardless of recruitment method. We will schedule the caregiver's baseline data collection visit within 10 days of e-consent.

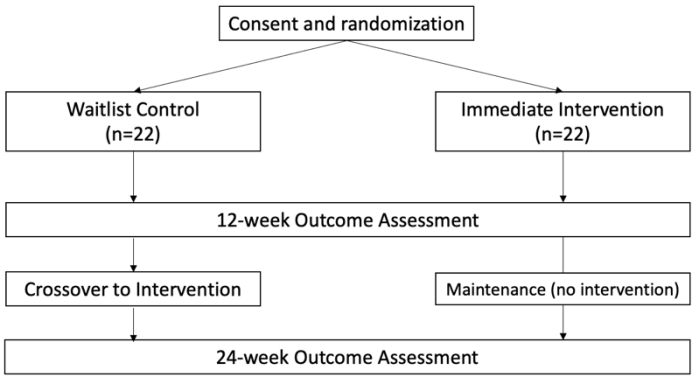
Open Label Phase:
The first five participants will be enrolled into an open label pilot study, in which they will automatically receive the HEROIC intervention. The participants will be interviewed after program completion to get feedback on the data collection instruments, intervention content including the number of visits and user-friendliness of intervention components (e.g., purpose in life activity), and satisfaction with the overall program process. These interviews will be conducted over phone, zoom, or in-person. This feedback will be used to modify the HEROIC intervention for the waitlist control trial that will begin enrollment following the open label phase.

Randomization:
Caregivers will be randomized using REDCap to receive either: (1) intervention or (2) waitlist. Random assignment will be stratified by spousal vs non-spousal caregivers due to evidence of increased caregiver

burden among non-spousal caregivers.[6] Within 48 hours of the baseline data collection visit, we will randomize using REDCap randomization and communicate the assignment to participants by letter.
Waitlisted Control Group: The waitlisted group will receive usual care for caregivers for the first 12 weeks, which is normally limited to inclusion in some clinical assessment, teaching during patient visits and informational handouts. Waitlisted participants will receive monthly study postcards to encourage retention. After 12 weeks, they will begin the intervention. The 24-week assessment will measure improvement following the intervention for waitlisted participants.
Immediate Intervention Group: 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. After 12 weeks, immediate intervention group participants will do a post-intervention assessment. The 24-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.

Intervention Delivery Characteristics:
The intervention will consist of an assessment-driven, tailored package of interventions delivered by a nurse interventionist. We propose an intervention incorporating 5 individualized, nurse-led, home-based or virtual (phone, HIPAA compliant Zoom or DoxyMe video call) sessions, with telephone check-ins and text reminders, according to participant preference. We have based the timing of study visits on previous experiences of the mentorship team and similar studies with this population, however we will use the open-label pilot interview feedback to provide feedback for further refinement of timing visits.[41–43] The intervention will be guided by the theory and evidence-based practices that have been successful in previous work (Table 1).[31,41] Every participant will receive each component of the intervention but interventionists will tailor content to each participant's goals.

Figure 2. Group assignment and outcome measurement



Nurse interventionists will be trained and equipped with education materials vetted by national organizations leading preventive health research such as the American Heart Association (Healthy for Good[44]) and National Institute of Aging (Go4Life[45]) for each broad category of preventive health behaviors (nutrition, physical activity, stress management, sleep and healthcare utilization).

As part of the intervention, the nurse and caregiver will prioritize the health category that they would most like to address and then set goals. Allowing the caregiver maximum control over this goal setting, without placing additional burden on the caregiver is one aspect of increasing self-efficacy and person-centeredness. Because the intervention will allow participants to pick their own health goals, we will measure goal attainment related to health behaviors, rather than a standardized survey of predetermined preventive health behaviors.

Table 1: Intervention Components and evidence basis for component selection

Intervention Component	Evidence Basis for Component
1) Whole-person assessment including physical, psychosocial, preventive health behaviors and challenges in caregiving	- Caregiver physical and psychosocial assessment is suggested by HF guidelines, but not commonly used in practice[17,46–48] - Involving the caregiver in assessment and encouraging them to set their own goals is person-centered, builds rapport and increases participation.[41,49,50]

2) Develop a statement of purpose in life, discussing caregiving in the context of the caregiver's purpose.	- Purpose in life was associated with lower mortality and CVD[51], stroke[52], MI[53], better preventive health behaviors[54], lower allostatic load[55] - Purpose in life can be improved through intervention[56–58] and is linked to down-regulation of pro-inflammatory genes[59]
3) Goal setting though co-development of incremental action plans to address personal goals to improve preventive health behaviors and reduce caregiver burden. Caregivers will design and work on incremental action steps related to goals, through tailored strategies aligned with statement of purpose in life.	- 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.[41,49] - Studies incorporating this technique have resulted in improved QOL, self-efficacy related to falls, depression and decreased disability.[41,50,60] - Goal attainment achieved in 73% of functionally impaired older adults- independent of age, race, gender – higher pain group less likely to achieve goals.[50]
4) 'Walking meetings' to model the importance of physical activity while discussing progress on incremental action plans to help caregivers achieve goals	- Modeling an activity promotes self-efficacy through enactive mastery and vicarious experience[28,61] - Higher social support increases activity levels and motivates caregivers[13,62–64] - Tailored interventions to participants needs increase physical activity.[13,64]
5) Instrumental support through exploring local resources to access benefits related to medications, healthcare, income assistance, etc.	- Instrumental support may enhance emotionally supportive interventions[65–67] - 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.
6) Social support through connecting caregivers to existing family and community to engage in relationships for support in caregiving.	- Perceived social support can be enhanced through interventions[65] - 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[68]

Intervention Protocol:

The RN will meet with the caregiver in-home or virtually (phone, HIPAA compliant Zoom or DoxyMe video call) 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 health goals and make plans to achieve those goals. The study will provide the HEROIC 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 2 such as Go4Life and AARP materials), and provides education and resources to address future needs.

Following the session, the RN will find additional resources, tailored to each caregiver. In the final session**,** the RN will review the participants' strategies and help 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. See Section "Data Collection: Physical Readiness Assessment" for details. 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	Heartrate Variability Measurement Survey
Randomization	Mail randomization results
Virtual Visit Week 1	Whole Person Assessment Set goals and discuss priorities Walking meeting (if virtual: suggest participant take a walk during call)
Virtual Visit Week 3	Purpose in Life activity Instrumental Support activity: Benefits Check Up Assess goal attainment and revisit strategies Walking meeting (if virtual: suggest participant take a walk during call)
Phone Check-in Week 4	Review/edit purpose statement Assess goal attainment and strategies to achieve goal Walking meeting (suggest participant take a walk during call)
Virtual Visit Week 6	Social Support Activity Assess goal attainment and strategies to achieve goal Follow-up re: instrumental support Walking meeting (if virtual: suggest participant take a walk during call)
Phone Check-in Week 8	Review/edit purpose statement Assess goal attainment and strategies to achieve goal Walking meeting (suggest participant take a walk during call)
Virtual Visit Week 10	Review of progress, goals and purpose/closure activity Discuss how caregiver will involve social support in next goals Walking meeting (if virtual: suggest participant take a walk during call)
Phone Check-in Week 12	Review/edit purpose statement Assess goal attainment and strategies to achieve goal Walking meeting (suggest participant take a walk during call)
Data Collection Visit Week 12	Heartrate Variability Measurement Survey
Data Collection Visit	Heartrate Variability Measurement

Week 24	Survey

* Waitlist control group will begin intervention at week 12.

Death of the Patient: If the patient/care recipient of the enrolled caregiver/study participant dies during the study, we will send a sympathy card. In that communication, we will ask the caregiver if they would like to participate a modified version of the intervention for bereavement: 1-3 visits (scheduled every other week) with a nurse for bereavement support within two months of the death of the care recipient. Additional instrumental support resources will be suggested such as grief support groups, referral to Roberta's House and bereavement resources for tasks to complete after someone you love dies. If the caregiver chooses to discontinue their participation, we will discontinue study contact and data collection. Data from caregivers whose care recipient dies will be excluded from analysis of primary and secondary outcomes.

Research Variables and Measurement

We chose measures (Table 2) based on previous RCT experience of mentors 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; 4) Common Data Elements to connect this work with the broader literature 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, 12 and 24 weeks. Patient characteristics will be obtained from chart review.

Table 4: Constructs, Instruments and Reliability

Theoretical Construct	Instruments and variables	Cronbach's alpha
	Contextual Factors	
Financial Strain	1)How well does the amount of money you have take care of your needs? 2)In general, how do your finances usually work out at the end of the month?	-
Social Support	ENRICHED Social Support Instrument[69]	0.88
	Caregiver Characteristics	
Demographics	Age, Race, Gender	-
Depression	Patient Health Questionnaire (PHQ-8)[70]	0.86
Perceived Stress	Perceived Stress Scale[71]	0.82
Co-morbidities	Charlson Comorbidity Index[72,73]	0.81
	Patient Characteristics	
Functional Status	New York Heart Association Class (chart review)	-
Cognition	Mini-mental status exam (chart review)	-
Co-morbidities	Charlson Comorbidity Index (chart review)[72,73]	0.81
Independence of Care Recipient	Katz independence in activities of daily living[74] (caregiver report) Lawton instrumental activities of daily living[75] (caregiver report)	0.84 0.85
	Potential Mechanisms	
Self-efficacy	Coping self-efficacy[76]	0.91
Resilience	Heart rate variability	-
	Caregiver Outcomes	
Goal Attainment: Preventive Health Behaviors	Goal Attainment Scaling[77]	0.91
Caregiver Burden	Oberst Caregiver Burden Scale[78] 2 domains: time caregiving and task difficulty	0.90
	Modified Caregiver Strain Index[79,80]	0.86
Quality of Life	NeuroQOL	0.85
	RAND 36-Item Short Form Survey	
Health care utilization	1) "Since our last contact, were you seen at an emergency room or a medical facility (e.g., Urgent care) for outpatient treatment?" 2) "Since our last contact, were you hospitalized, or did you stay in a hospital observation unit for any reason?"*	-
Fatigue	PROMIS Fatigue – Short Form	
Family Function	Family Assessment Device - Global/General Functioning Scale	

***adapted from the Atherosclerosis Risk in Communities (ARIC) study annual follow-up questionnaire for healthcare utilization**

Data collection and management:

Data Collection:

1) Questionnaires - Baseline, 12 and 24-week data will be collected by research assistants masked to treatment assignment. All data will be entered into RedCap.[81]

2) Semi-structured interviews l – Interviews will be completed following intervention completion after the open label phase and also after the trial phase (phone, HIPAA compliant Zoom or DoxyMe video call). An interview guide, using open-ended questions, will be used. Interviews with caregivers will be audio-recorded (no video will be recorded) and transcribed using a transcription service, Production Transcripts, Inc. In addition, study team members will take field notes and meet regularly to summarize key points.
3) Heart rate variability (HRV) - An electrocardiogram approximately 5 minutes in length will be captured using the commercially available KardiaMobile ECG device (AliveCor, San Francisco, CA, USA).
4) Cost – Study staff will track time spent scheduling, traveling and during data collection visits which will be summarized with feasibility data.

Trained research assistants will send electronic surveys to the participant's email using REDCap or verbally elicit questionnaire data from participants in-person or in virtual meetings. If research assistants elicit questionnaire data verbally from participants, they will directly enter the participant's responses into the REDCap data entry and management system. Virtual meetings include either telephone conversations or video calls via HIPAA compliant Zoom DoxyMe. DoxyMe is a HIPAA compliant virtual meeting software used for telehealth purposes.

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 data collection 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.

Physical Readiness Assessment

During the course of this intervention, the participant will be developing personal goals with the guidance of the nurse interventionist. When a physical activity goal is identified, the nurse interventionist will administer the Physical Activity Readiness Assessment tool. If participant answers "No" to all questions, they are cleared for physical activity and will set a moderate activity goal with the nurse interventionist. If the results of the Physical Activity Readiness Assessment tool do not clear the participant for physical activity, the nurse interventionist will contact the study nurse practitioner - Melissa Hladek, PhD, CRNP, FNP-BC - to determine the safety of the participant's physical activity goal. In addition, if results of the Physical Activity Readiness Assessment tool and/or guidance from the study nurse practitioner suggest seeking further advice from a medical professional, a goal to schedule a primary care visit will be made in lieu of a physical activity goal to discuss a medically-supervised exercise plan.

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.

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 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, 12 and 24-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) 50 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 1.5 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.

4) Caregivers who consented to IRB00203584 and participated in at least one intervention visit. These participants have received components of the intervention.

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.

Analysis Plan:

Qualitative Analysis (Aims 1 and 3) - A qualitative descriptive analysis approach will be applied to data analysis of semi-structured interviews.[82,83] The codebook will be adjusted as needed. Similar codes will then be grouped into categories/themes that express the latent idea of grouped codes which will be used to refine the intervention protocol.

Aim 1 – In addition to qualitative analysis, descriptive analysis will be used to examine all quantitative data. Joint displays will be used to provide a structure to discuss the integrated quantitative and qualitative analysis and assist the study team in making changes to intervention components and overall protocol to improve feasibility and acceptability.[84]

Aim 2 -

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 12 and to 24 weeks for QOL (primary outcome). 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.[85] 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 12 and to 24 weeks for self-efficacy and HRV (secondary outcomes) using a similar approach (as described for primary outcome).

In addition, the correlation between the change in the mechanisms and change in primary outcomes will be examined. We will also examine cost of the intervention.

Mixed Methods Analysis - Qualitative analysis and joint displays will be used to compare those with improvement in quantitative outcomes after the intervention to those who did not have improvement to elucidate unmeasured or unpowered change as reported by participants. This mixed methods analytic approach to intervention evaluation maximizes what we will learn from the pilot by increasing understanding of context, responsiveness to ethnically and culturally diverse populations and how implementation influences outcomes.[86] **Thus, the development and testing of the HEROIC intervention will address preventive health behaviors of HF caregivers, using rigorous methods to**

promote inclusivity and tailor the intervention to caregiver needs to decrease caregiver burden and improve quality of life.

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

Sample Size:

Aim 1) For our open-label pilot we will include 5 caregivers to test intervention components, feasibility, acceptability, delivery and communication.

Aim 2) As a pilot study, the analyses will not have adequate power to detect significant differences. Therefore, initial effect sizes, rather than statistical significance, will be examined for evidence of the effectiveness of the intervention. With a target sample size of 44, 22 in the waitlist control and 22 in the intervention, we will be able to gauge an initial estimate of the effect size associated with the intervention as compared to usual care for caregivers. 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.[87] This is especially appropriate given that very few services are currently offered to HF caregivers. We will also conduct debriefing interviews with all participants following the trial. To account for an estimated 20% attrition, we will recruit a total of 49 to the trial with the goal of 44 participants completing the study.

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. There is a low risk of physical injury for participants that set goals related to physical activity. For participants that want to set a goal related to physical activity, the interventionist will assess current physical activities, weekly duration and intensity and the safety of physical activity with Physical Activity Readiness assessment. If participant answers “No” to all questions, they are cleared for physical activity and will set a moderate activity goal with the nurse interventionist. If the results of the Physical Activity Readiness Assessment tool do not clear the participant for physical activity, the nurse interventionist will contact the study nurse practitioner - Melissa Hladek, PhD, CRNP, FNP-BC - to determine the safety of the participant’s physical activity goal. In addition, if results of the Physical Activity Readiness Assessment tool and/or guidance from the study

nurse practitioner suggest seeking further advice from a medical professional, a goal to schedule a primary care visit will be made in lieu of a physical activity goal to discuss a medically-supervised exercise plan.

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 Saylor 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, Production Transcripts, Inc. 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 a virtual video call software, either HIPAA compliant Zoom or DoxyMe. 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/).

Data Safety and Monitoring: Investigators will use the REDCap data entry system. Deidentified data sets will be exported from REDCap for analysis. The study data will be 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. However, any paper copies of consents or other study data will be stored in locked file cabinets.

The PI 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 PI will be to a) provide monthly 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) support 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 PI 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 PI will receive reports of the number of study participants who discontinue from the treatment group and/or the study and reasons for discontinuation.

Adverse Event (AE) Reporting: The principal investigator is notified of any serious AE within 48 hours of initial notification to the project team. 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 the study team may be in people's homes or able to see their homes by virtual video, 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. 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) • Major infestation	Research staff member notifies RC within 24 hours. RC (or designate) completes Alert form.

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, Production Transcripts, Inc. 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 a virtual video call software, either HIPAA compliant Zoom or DoxyMe. 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/).

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 12 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 $50 Amazon claim code at the start of the intervention, 12 weeks and 24 weeks following completion of surveys. Participants without a wifi-capable device will also be given a wifi-capapble tablet (approximate value $75) 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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