Official title: Activate For Life: mHealth Intervention To Address Pain And Fatigue In Low-income Older Adults Aging In Place

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PROTOCOL TITLE:

ACTIVATE FOR LIFE: A NURSE DELIVERED HYBRID TELEHEALTH/mHealth AGING IN PLACE INTERVENTION TO ADDRESS PAIN AND FATIGUE IN LOW-INCOME OLDER ADULTS

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1.0 Objectives / Specific Aims

Overview: Chronic pain and fatigue are among the most pervasive and expensive health complaints in the United States, with 53% of adults aged 65 and older (about 18.7 million) reporting pain at any one time (Patel et al., 2013), and 31% of those over 51 reporting fatigue.[1] **Adults, and older adults in particular with pain and fatigue, have reduced ability to successfully *Age in Place*, as these symptoms can impact activities of daily living, increase fall** risk[2-6] and **diminish mental health and subsequent motivation to remain physically active**. Unfortunately, integrated programs to address pain and fatigue, and thereby increase likelihood of aging in place, such as those that target muscle tone, mobility, strength and mental health are not common, and those that exist may be beyond the reach financially and logistically to poor older adults who might most benefit from them.

This project proposes to evaluate feasibility of ***Activate for Life***, an integrated home-telehealth delivered intervention that combines ***Otago +Yoga + Behavioral Activation*** to address both physical and mental health factors to increase likelihood of successful Aging in Place. The Otago Exercise Program (OEP) focuses on strength and balance training[7], and is endorsed by the CDC[8] as an effective fall prevention intervention[8,9]; Yoga (including *asana*/poses and *pranayama*/breathing;) emphasizes balance and stretching, and can be practiced even by individuals with significant physical disabilities, and Behavioral Activation (BA) addresses withdrawal and social isolation to enhance mental health and is an evidence based intervention for depression validated with older adults, including validation of its effectiveness by our team, when delivered via home based telehealth[10-12].

PREMISE*:* This project conceptualizes factors that negatively influence aging in place, namely pain, fatigue and mental health problems within the socio-ecological model to explain the multiple dynamic and complex influences that impact their presentation. For example, pain and fatigue in older adults may reduce their mobility, which reduces muscle tone and increases risk of falls. Reduced mobility also contributes to social isolation, thereby increasing depression and further reducing motivation to engage in exercise. These factors constitute a negative feedback loop, amplified in many older adults by limited income and resources, that perpetuate deterioration in both physical and mental spheres, leading to reduced ability to Age in Place. Therefore, the potential benefit of a comprehensive, integrated treatment, delivered directly into older adults' homes via telehealth technology, to address both physical and emotional health dimensions, as well as limited access to transportation, is high.

Preliminary pilot data on telehealth-delivered Otago Exercise Program revealed high rates of participation and satisfaction, and most important, significant improvement in physical stability and movement. However, high levels of anxiety and depression were observed, indicating a potential need to complement Otago with mindfulness and action-based strategies to reduce negative mental health symptoms while addressing pain and fatigue symptoms. We subsequently added Yoga and telehealth delivered Behavioral Activation to the program in one series of participants and would like to fully explore the effectiveness of this integrated intervention.

Thus, the **Overall Aim** of the present proposal is to evaluate the feasibility of an integrated mind-body intervention, *Activate for Life,* to improve overall physical activity and mental health and reduce pain and fatigue, resulting in increased likelihood of Aging in Place. Both subjective self-report (i.e., NIH PROMIS measures of pain, fatigue, depression and anxiety) and objective accelerometer data will be collected, along with standardized measures of balance, strength, and stability. In addition, the measures will be complemented with biomarker-based measures of stress, including cortisol based and 1,5-AG assays before, during, and after treatment that are correlated with stress, and fatigue symptoms.

Thus, the Specific Aims of the project are to:

AIM 1. Integrate evidence-based components of "*Activate for Life*" a telehealth delivered, nurse-led behavioral health program for low income older adults targeting pain and fatigue through balance training (Otago), strengthening and mindfulness (Yoga), and affective state (Behavioral Activation).

We hypothesize that the evidence-based Otago and Yoga components of this intervention will integrate with the 'infrastructure' format of the Behavioral Activation mental health treatment insofar as a 60-minute session, 6-10 session intervention will be developed.

Aim 2. Test the feasibility of Activate for Life in terms of its individual components by comparing Otago vs. Otago+Yoga vs. Otago+Yoga+Behavioral Activation in a pilot RCT design with 10 participants in each of the 3 conditions in terms of recruitment, intervention 'dosage' (frequency/density), adherence, treatment satisfaction, attrition, rates of missing data, and other feasibility metrics, including qualitative feedback from participants for final intervention refinement.

We hypothesize that adherence will be adequate (65% scheduled activity compliance), satisfaction will be high (above 80%), attrition will be limited (below 25%), and followup data collected (below 20% missing data)

AIM 3. Determine an initial efficacy signal for the intervention that will inform future power estimates. *We hypothesize that the combined intervention will show significant within subject improvement over baseline on measures of pain, fatigue, and depression.*

Supplemental ARM 4 - AIM 4. Test the feasibility of a 12-week e/mHealth gentle yoga+yogic breathing (GYYB) intervention for alleviating symptoms of burden in aging Cargivers (CG) of persons (N=20) with dementia (PWD); measure initial changes in stress and QoL indicators in CG and PWD (post- vs. pre-intervention).

Impact. This pilot feasibility study will set the stage for a full scale RCT demonstrating the additive benefit (if present) of each additional component over the CDC approved balance intervention Otago. Self-management of pain and fatigue through strength and balance training in low-income older adults can improve quality of life, decrease health care costs, and increase the ability of the person with these symptoms to age in place.

2.0 Background

***Aging in Place* is by far, the preferred option for older adults from both the perspectives of older adults themselves, and the healthcare community.** The population of older adults in the United States is growing rapidly and will double in size by 2060[13]. Older adults numbered 46.2 million in 2014, which represents about 14.5% of the total U.S. population[13]. By 2060 the projected number of older adults will be about 98 million[13]. However, this population is financially ill equipped to address care needs that often accompany aging, hence, maintaining health to 'age in place' is key. For example, in 2013 4.2 million (9.5%) older adults were below the poverty level[13]. This was an increase from 9.1% in 2012[13]. Another 5.6% or 2.5 million older adults were classified as "near poor" or having income between the poverty level and 25% above this level in the United States[13]. Not only is there a lack of resources to pay for qualified caregivers, and a lack of qualified caregivers themselves, there is also a lack of facilities to accommodate the elderly who may not be able to care for themselves in their home environment even if they could afford it[14]. This underscores the importance of interventions to facilitate aging in place, especially for the low-income elderly. Moreover, 90% of adults 65 and older prefer to age in place[15]. One of the main reasons for this is cost. The National Aging in Place Council reported that care per person annually can cost on average $86,000 in a

nursing home, $60,000 for someone in assisted living and $23,000 for someone aging in place at home[16]. In addition, older adults view aging in place as being synonymous with increased quality of life. In fact, older adults fear losing independence (26%) and moving to a nursing home (13%) much more than they fear death (3%)[17].

Pain and fatigue are significant barriers to aging in place. A retrospective study conducted in the United States based on the National Health and Aging Trends Study found the incidence of chronic pain in adults aged 65 and older to be 52.9% (about 18.7 million)[18]. Similarly, fatigue affects 31% of adults 51 years of age and older[1]. Older adults with pain and fatigue are less likely to successfully age in place, as these symptoms can impact activities of daily living, reduce exercise, and increase fall risk[2-6,19]. Programs to address pain and fatigue, such as those that target increasing mobility, are not always within the reach of these older adults, both literally, due to geographic isolation and rurality, and figuratively, due to cost. Indeed, low income older adults who suffer from pain and fatigue face a multitude of barriers that prevent them from participating in traditional physical activity or behavioral self-management programs. These include access to transportation, financial resources, ability to participate due to preexisting mobility problems, the need for assistive devices, being chair bound and or bed bound. Medicare does not cover programs to enhance aging in place through physical conditioning and self-management interventions, except in the small minority of instances where the Medicare eligible recipient is in need of Physical Therapy (PT) and determined to be: 1) homebound, 2) to qualify due to specific criteria, or 3) is under the order of their physician. In addition, PT for qualifying Medicare patients is episodic, or time and visit limited, and not ongoing[20]. As such, PT, and PT under Medicare is not a viable option to address pain and fatigue in older adults.

The need for *Comprehensive* behavioral health pain and fatigue management programs. Physical activity can improve strength and endurance, overall health, and quality of life among older adults with chronic conditions, which in turn may reduce hospitalizations and nursing home stays[21]. The impact of physical activity on joints may reduce a person's pain by improving flexibility, density and quality of connective tissues, and potentially on bony mass[22]. There is no evidence of increased pain with physical activities such as exercise, although this belief may be a barrier for older adults with pain in starting an exercise routine[2].

A large meta-analysis of self-management programs for pain reported by Taylor et al.[23] substantiated the need not only for a physical activity component for pain self-management programs, but also the addition of a supportive component that is delivered by health care providers. From this meta-analysis, Taylor et al.[23] also concluded that there was evidence that self-efficacy and depression at baseline can predict outcome and that pain catastrophizing and physical activity can mediate outcome from self-management[23], indicating that a mental health component may also be needed.

Three Evidence Based Programs that address aforementioned need and may, once integrated, enhance Aging In Place: Otago (Balance), Yoga (Strengthening and Mindfulness), and Behavioral Activation (Motivation and Affect).

Otago and Balance: Otago is a muscle strengthening and balance retraining program that can be delivered to the participant in their home. Otago was implemented and test in four randomized control trials of 1016 men and women aged 65-97 years of age. Findings from the trial showed that The Otago Exercise Program can reduce falls and fall related injuries, the program was most effective for adults 80 years and older, men and women benefited equally, and participants' strength and balance improved markedly as assessed by the Chair Stand and the Four-Stage Balance tests. The Otago exercise program is endorsed by the Centers for Disease Control as an effective fall intervention program for men and women[19], decreasing falls in older adults by 35%. [20-23]

Gentle Yoga and Yogic Breathing (GYYB) and Pain: In chronic pain, there is high contribution of the static load, due to habitual deep muscle tension that adversely affect microcirculation within muscles and the underlying viscera[24]. Yoga reduces the electromyographic activity in the musculoskeletal system and promotes relaxation (Balambekar, 1969)[25]. Awareness and progressive relaxation attained by Yoga practice could eliminate a substantial proportion of pain and the person feels more in control, which itself promotes pain reduction[24]. Yoga influences the endocrine system by increasing local blood flow by gravity, muscle contraction and pressure release resulting in reduced abdominal pain[26] Muscle stretching could potentially lead to the release of endogenous opioids[27] thus could reduce the need for exogenous opioids. While pain modifies frequency, depth and pattern of respiration confining it to strained, shallow, and thoracic breathing, the practice of Pranayama with long exhalation cycles relaxes the musculoskeletal system, increases the tonicity of parasympathetic response, and reduces overall stress, which together could reduce pain[28-29]. Diaphragmatic breathing is probably the single most valuable thing that a patient in chronic pain can learn on the road to recuperation[24]. Yoga practices, more commonly the ones involved in postures, has been used to test its usefulness in improving the quality of life in the aging population. In a pilot RCT in a community dwellers (mean age 68), the participants performed twice a week group yoga with an instructor for 12 weeks. The results showed the feasibility, and an improvement in balance and movement-related benefits[30]. Dr. Balasubramanian (co-I) has developed a combination of gentle yoga and yogic breathing (GYYB) program for people with limited mobility (GYYB handout, Balasubramanian). The GYYB program has been pilot tested among patients with scleroderma, and in a community dwelling elderly population and have shown feasibility, acceptance and a strong interest to continue the practice because of the perceived improvement (unpublished data).

Yoga and Biomarkers: The Balasubramanian lab (Co-I) has shown that acute practice of 20 minutes yogic breathing exercises stimulate salivary expression of nerve growth factor, immune response markers, and a reduction in inflammatory cytokines[31-33]. In a recent study 90 minutes of Yoga practice among the elderly (mean age 60) has been shown to stimulate salivary immune function (increased salivary IgA and testosterone), and decreased stress hormones (cortisol)[34]. Several recent studies have suggested saliva as a potential biomarker source in various physiological conditions[35,36]. Due to the non-invasive collection method involved, and the availability of procedures to quantify stress, mood and pain related biomolecules saliva could be preferred over blood sampling among the elderly. Cortisol is a glucocorticoid hormone expressed in the saliva and is commonly used as an indicator of stress due to the activation of hypothalamus - pituitary - adrenal cortex (HPA) axis, and aging is associated with an increased levels of salivary cortisol (https://www.ncbi.nlm.nih.gov/pubmed/27377692). Yoga practice reduces the salivary cortisol level among older adults. 1,5-anhydroglucitol (1,5-AG) is a biomarker for hyperglycemia (https://www.ncbi.nlm.nih.gov/pubmed/25249070) and is found to be reduced in aging (https://www.ncbi.nlm.nih.gov/pubmed/7835210; https://www.ncbi.nlm.nih.gov/pubmed/27036001) . Both clinical and preclinical studies suggest that exercises could increase the levels of 1,5-AG (https://www.ncbi.nlm.nih.gov/pubmed/15094482; https://www.ncbi.nlm.nih.gov/pubmed/28210043). This will be the first study that fully examines the impact of yoga practice on the levels of 1,5-AG.

Behavioral activation (BA) and Depression. Behavioral Activation is a manualized treatment for depression (Lejuez, Hopko, & Hopko, 2001) that has gained support for its efficacy[11,] Lejuez, Hopko, LePage, Hopko, & McNeil, 2001; Hopko et al., 2002). The primary goal of this intervention is to increase patients' engagement in social and healthy activities (e.g., interacting with supportive family and friends, community bingo, yoga, Otago) that are likely to produce reinforcement in the natural environment. Learning theory[47] forms the theoretical model supporting Behavioral Activation, which is hypothesized to reduce depression symptoms via increased frequency and density of reinforcing and personal values-consistent activities. This shift in balance of activities and reinforcement density

facilitates increased positive mood and cognitions (see[47, 48]), and is achieved by first identifying, then operationally defining, and ultimately formally scheduling the aforementioned reinforcing or functionally useful behaviors. One of the strengths of BA, relative to other cognitive behavioral and activation-based interventions, is that it is designed to incorporate components of complementary treatments. Specifically, BA is heavily reliant on identifying and scheduling healthy behaviors, and on identify and resolving barriers to implementation of these scheduled behaviors. These healthy activities are often specifically derived from complementary interventions. As such, it may be conceptualized as an 'framework' intervention, upon which other intervention components, such as Otego and Yoga, can be hung.

Gap in knowledge related to using telehealth delivered programs to improve pain/fatigue and facilitate self-management in older adults. There is little literature regarding the use of mHealth (e.g., tablet based applications) and eHealth (e.g., televideo via tablet) as a platform for nurse-managed (and eventual self-managed) pain in older adults.[22] A recent integrative review of the literature noted that a large proportion of older adults own a computer, tablet, and/or smartphone and regularly access the Internet.[22] This review points out that while there is little evidence of using digital technology for pain management in older adults, using an interprofessional approach along with high quality interventions, strong technical support and training, and connectedness with clinicians and increased self-awareness through personal diaries may provide a strong platform for its use in clinical practice.[22] Incidentally, none of the studies in this review addressed low-income older adults.

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Preliminary studies. Preliminary pilot data on telehealth-delivered Otago Exercise Program revealed high rates of participation and satisfaction, and most important, significant improvement in physical stability and movement. However, high levels of anxiety and depression were observed, indicating a potential need to complement Otago with mindfulness and action-based strategies to reduce negative mental health symptoms while addressing pain and fatigue symptoms. We subsequently added Yoga and telehealth delivered Behavioral Activation to the program in one series of participants and intend to fully explore the effectiveness of this integrated intervention.

INNOVATION: Otago only does balance and strengthening, y+O does balance and strengthening, and pain control, adding ba addresses motivation and depression so Activate for Life adds motivation

An interprofessional (IP) team of nursing, physical therapy and behavioral health clinical researchers will be collaborating to develop "Activate for Life" to address pain and fatigue by increasing physical activity and self- efficacy in low-income elderly. This project is innovative in the following ways:

- Integrates mHealth and eHealth

- Uses eHealth (televideo) to deliver interventions directly into participant's homes, dramatically enhancing convenience and overcoming barriers related to rurality
- Uses real time (EMA) activity monitoring and feedback with easily understood data presentation graphics to inform both patient and provider on progress through an application (app) on the tablet
- Uses ECA to assess parameter violations and trigger televideo visit for motivation/problem solving session with nurse

3.0 Intervention to be studied

ARMS 1, 2, and 3. Design Overview. Design Overview and Project Timeline:

This 12-week feasibility trial will use a 3x3 repeated measures (treatment x time) between groups randomized trial design to compare Otago (OG) vs. Otago + Yoga (GYYB) vs. Otago + GYYB + Behavioral Activation (ie., the complete *Activate for Life* intervention) in low-income older adults with chronic pain and/or fatigue at baseline, post-treatment and 3- month follow-up. Participants will be randomly assigned to one of the three conditions. Daily self-monitoring of program component adherence, PROMIS self-report measures of pain, fatigue, anxiety, depression, and social support. Physical activity measures will include actigrography, steps per day, 2-minute timed walk test, sit-to-stand test, and Mini-Best. Participants will be 30 adults (10 per group) age 60 and above with a PROMIS pain interference score of eight or above and/or a PROMIS pain behavior score of 15 or above (cut points based on a T-score that rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10 for each of these instruments).

Alternative design: The progressive nature of this feasibility trial allows the proven evidence-based modalities of OEP and GYYB to be combined with behavioral activation to not only address physical activity but also the mental health aspects of chronic pain and fatigue. Therefore, this feasibility trial scaffolds the components to show that the modalities of OEP and GYYB are effective and their success is dependent on motivation. However, we are not testing these three interventions alone, or in every possible combination.

Supplemental ARM 4 - Design Overview:

For the supplement, the CON SSMC will leverage its expertise in technology-enhanced SM interventions and community-engaged research to establish the feasibility of an mHealth GYYB (physical activity + breathing) intervention on adherence, acceptability, and short-term health outcomes related to burden in CG of PWD. We will recruit 20 older CG who are caring for PWAD/ADRD receiving services in social and medical RCCs connected with an active R01 investigation, Mealtime Partnerships for People with Dementia at Respite Centers and at Home (R01 NR016466; PI: Kelechi). Two data collection points will occur at the beginning (Week 1, pre-intervention, or baseline, "V1") and end (Week 12, post-intervention; "V2") of the 12-week study. Preliminary changes in CG health indicators such as physical function, fatigue, depression, and social isolation as well as CG/PWD QoL will be examined to support a future RCT and build opportunities for faculty training in dyadic analyses. The relationship between salivary stress biomarkers (cortisol and 1,5-anhydroglucitol, or 1,5- AG) and self-reported reduction in stress symptoms will also be examined. Based on results from past SSMC studies, we posit that adherence will be adequate (≥80% scheduled activity compliance), satisfaction will be high (≥80%), attrition will be limited (≤25%), and follow-up data collection sufficient (≤20% missing data) to establish the validity of a future, full-scale RCT.

4.0 Study Enpoints (all ARMS)

Study end points include: Successful study completion, participant consent withdrawal, and PI termination due to failure to adhere to the protocol, loss of contact with the patient, and/or unexpected adverse events.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion criteria for ARMS 1, 2, and 3 are as follows:

- Males and females 60 years of age and older living in a Humanities Foundation apartment complex, HUD funded housing or living at 150% of poverty level
- PROMIS pain interference score of eight or above and/or a PROMIS pain behavior score of 15 or above
- Able to ambulate 150 feet with or without the use of an assistive device
- Able to follow simple instructions
- Able to read, speak, and write English,
- Able to operate tablet device and wearable activity tracker,
- Not currently enrolled in an exercise program.

Exclusion criteria for ARMS 1, 2, and 3 are:

- Inability or unwillingness of participant to give informed consent,
- Physical, cognitive, sensory or psychiatric disability that would limit participants from engaging in self-management program as noted by a Mini-Cog[26] score of 0-2.
- Unwillingness to wear a physical activity tracker during the course of the study.

Inclusion criteria for Supplemental ARM 4 are:

- CG must be able to speak and read English
- CG must be 45 years of age or older
- CG must be able to provide consent for themself
- CG must live with or on same property as the PWD
- CG be primarily responsible for care provision of the PWD in the home (i.e., is not paid for services; provides 4 hours or more of care/day; assists with ADLs)

Exclusion criteria for Supplemental ARM 4 are:

- CG for whom yoga techniques would be detrimental due to physical limitations,
- CG who are enrolled in other Yoga-related clinical trials, or who are currently engaged in regular Yoga activity once per week or more.

6.0 Number of Subjects

The number of ~~P~~participants enrolled under ARMS 1, 2, and 3 will be 30 adults age 60 and over. Thirty participants should allow for recruitment of 10 participants from at least 3 different Humanities sites to avoid cross-contamination of study groups. The number of participants enrolled under Supplemental ARM 4 will be 20 adults aged 45 and older. The total number of participants under this research project will be 50.

7.0 Setting

ARMS 1, 2, and 3. The Humanities Foundation is a non-profit affordable housing provider in South Carolina, Georgia, Virginia, and Louisiana. The Foundation, in place for over 20 years, has 1400 units of affordable housing for low-income populations including disabled, single mothers, and senior citizens. To qualify to live in these low-income facilities the residents must have income that is no more than 60% of the Area Median Income. The study sites will be the six Humanities Foundation older adult living complexes in the Charleston, SC area, other HUD funded housing, or low-income persons living at 150% of poverty level. The study would be conducted within the facilities community meeting room and in individual participants apartments. All research activities and study procedures

will be conducted by IRB approved MUSC study personnel. No employees and/or agents of Humanities Foundation will engaged in any research activities.

Supplemental ARM 4 Setting: All CG participants will be recruited from within the greater Charleston Tri-county area. All research activities and study procedures will be conducted by IRB approved MUSC study personnel. Research activities will take place at CON as well as at participant's homes.

8.0 Recruitment Methods

ARMS 1, 2, and 3

IRB approved flyers will be distributed to the residents at each of the Humanities Foundation apartment complexes as well as posted in general public community areas. Educational sessions, headed by the PI, will also be held at the complexes to allow potential participants to learn about the program and ask pertinent questions. Individuals who are interested in the program will be directed to contact the study PI or their designee via phone or at the information sessions. If interested participants meet the eligibility criteria and voluntarily consent to join the study they will be enrolled.

Additionally, we will recruit individuals who have had recent services through MUSC ED that have authorized research contact permission in MyChart through the MUSC electronic 'opt in' EPIC designation and have been identified by the Bioinformatics Center (BMIC) as over 60 years old, have had a recent fall and reside at one of the Humanities Foundation complexes. We will then contact potentially eligible patients by telephone to determine if they are interested in participating in the study and if so, schedule an informed consent meeting.

Supplemental ARM 4:

All CGs will be recruited through local affiliations with social and medical Respite Care Centers (RCC) and home health services for families of PWD established through our Mealtime Partnerships R01 study. We will devise and use IRB approved study recruitment flyers and letters that will be dessimated electronically and handed to RCC caregivers, as well as directly contact CGs by phone that have previously expressed and noted their agreement to be contacted regarding other research studies as documented on their consent form. In addition, we will conduct outreach activities and enage outside network RCC providers in the local community to inform them of the opportunity for their clients to participate in this study.

9.0 Consent Process (ALL ARMS)

In-person

Research activities will not be conducted without the patient's written informed consent. Informed consent will be conducted by the PI and/or their designee as noted on the IRB study delegation log, and will occur in the comfort and privacy of a private room at the facility or the participant's place of residence prior to any screening procedures being conducted and/or data collection. Potential participants will be given the informed consent document to read and review in advance, and/or may have it read to them by the researchers, if they prefer. After reviewing the consent document, the patient will be given the opportunity to ask any questions about the study that they may have, and will be requested to demonstrate what is expected from them should they agree to enroll in the study through a questioning of their understanding of study procedures and risks. Prior to consenting, all questions will be resolved to the patient's satisfaction. If a participant does not appear to understand the information contained within the Consent document or of what is expected of them as a study subject, then the study coordinator will review the consent document again with the participant. If after this second review, the subject does not demonstrate an understanding, they will not be enrolled in the study. Only participants, with no observed cognitive impairment, will be consented and enrolled into the study.

The consent form will meet the requirements of the Code of Federal Regulations and the MUSC Institutional Review Board; and, include the following elements:

- The purpose, nature, and objectives, potential risks and benefits of the intended study.
- The length of study and the likely follow-up required.
- The name and a contact of the investigator(s) responsible for the protocol.
- The right of the participant to accept or refuse study interactions and to withdraw from participation at any time.

All consented subjects will be given a copy of their executed and countersigned Consent form. The researchers will maintain a means of contact with all enrolled study participants in the eventuality that reconsenting of currently enrolled participants is needed and/or the disclosure of new study information is warranted to previously enrolled participants.

E-Consent
In light of institutional guidelines pertaining to COVID-19 and the conduct of human subject research, study participants may also be consented using MUSC IRB approved REDCap e-consent process.

In the case of obtaining e-consent, potential participants will have been introduced to the opportunity to participate in the study. All potentially interested participants will be referred to the MUSC research team either directly with the participant's verbal permission or self-referred through contact information on the study recruitment flyers. Upon making contact with the referred individual, the researchers will identify themselves, indicate how they received the individual's personal contact information, provide the reason for the call and an overview of the study and study procedures. If the individual expresses an interest in learning more about the study and/or becoming a participant, the researchers will ask the individual for a working email address where the e-consent will be sent and set-up a follow-up telephone call for the e-consent process. These individuals will be allowed as much time as needed to read and review the e-consent document in the privacy of their own home or at a place of their choosing. During the e-consent call, the researcher will review the e-consent document in its entirety and be available to further answer any questions that they may have prior to the individual adding their respective signature to the form and submitting the e-consent. Upon submitting the e-consent, a REDCap trigger will immediately notify the researcher, who will then provide their countersignature to the document. All e-consents will be maintained in the REDCap study e-consent database for regulatory purposes and compliance monitoring.
All participants will be electronically sent a copy of the fully executed e-consent form to their email address. Hard copies will be mailed to participants upon request.

10.0 Study Design / Methods

ARMS 1, 2, and 3: Once a participant has consented and been enrolled they will be randomized by computer (stratified by gender) to one of three treatment groups and the PI and/or their designee will set up a home visit appointment to meet with the participant to obtain baseline data (Table 1). Part of the baseline screening includes the PROMIS Emotional Distress-Depression Short Form 8a. If a participant scores in the severe depression category (raw score 33 and above) a referral will be placed to a mental health professional. Additionally, participants that score in the moderate depression category (raw score 23 to 32) further screening for suicidal ideation will take place. If the participant would admit to suicidal ideation at any time during the study, an emergent mental health consult will be placed through the Charleston/Dorchester Mental Health Center Assessment/Mobile Crisis.

The participant will then be trained on the use of the tablet including the application that will record and transmit their self-entered pain and fatigue symptom scores, the vital sign measuring equipment as well as the video platform for the nurse and self-management program to which they are randomly assigned. The vital sign recording equipment have all been FDA approved and gone through multiple rounds of formal verification. These are also Medical University of South Carolina (MUSC) and South Carolina (SC) Telehealth recommended devices as MUSC is arm of SC Telehealth Alliance. The tablet will be an iPad air 2, which has the communication protocol to connect to all these devices and send encrypted data securely back to servers. In addition, the participants will be given and receive training on a Garmin Vivofit wearable activity tracker that is able to record, steps taken per day, heart rate, distance walked, stairs climbed, and sleep. Garmin Vivofit wearable fitness trackers meet high reliability and validity requirements for parameters such as step counts (Simunek et al., 2016). The training will be conducted via a prerecorded video shown to participants on their tablet at the initial meeting that also explains the program rationale, use of the tablet, activity tracker, and video and app platforms. This video will allow participants access to training at all times in case of issues or questions surrounding the equipment. The PI will contact the participant via their tablet on a weekly basis via the HIPAA compliant telehealth platform Vidyo. Vidyo, a real-time software video communication tool, is HIPAA Compliant with all of the media, signaling, and user login being encrypted to ensure patient privacy and compliance (Vidyo, 2014).[28] Each tablet will contain the app "Activate for Life". This app will allow the participant to transmit, via Bluetooth technology their blood pressure and pulse. The app also allows the participant to rate their pain and fatigue scores on a 1-10 scale, document their daily activity and their use of pain medication, and has the ability for the pariticipants to record a voice diary of their daily progress or thoughts. Each participant will receive a blood pressure cuff and will take their blood pressure prior to participating in their PA for the day. The blood pressure and pulse information from the blood pressure monitor will be transferred via Bluetooth to the Activate For Life app on the participants iPad. Once the app has received the data, it will automatically upload the information to the server at MUSC and will be available to be reviewed by the research team. The app will also allow for the participants to input their pain and fatigue scores which will be utilized to monitor pain scores on a daily basis. The vital signs and pain scores will allow for individualizing of the physical activity program to increase or decrease activity based on worsening, improving, or stability of participant's pain as measured by the pain score or through prolonged elevations in blood pressure or pulse. Weekly telehealth visits will allow for delivery of each conditions intervention components, review of pain and/or fatigue, VS, and sleep data. These data will be assessed by the PI and discussed during the weekly telehealth visits with the participants. The burden of self-monitoring and data entry will be captured during feasibility assessments. Saliva samples will be collected from all groups at the beginning and end of the sessions on week 1 and 12 to measure salivary biomarkers including cortisol, and 1,5-AG. Feasibility

Table 1: Prescription of Exercises

Strengthening	Balance Retraining
The Otago exercise program focuses on major lower limb muscles ▪ Knee flexors, knee extensors, and hip abductors, which are important for function and mobility ▪ Ankle dorsiflexor and plantar flexor muscles, which are important for maintaining balance. Determine the starting level of each exercise by the amount of ankle weight the patient can lift to perform eight to ten good quality repetitions before fatigue. This must be assessed for each muscle group on each leg. Recommend that patients aged 80 and older start with two to four pound weights. Starting with light weights at the outset will minimize both muscle soreness and compliance problems. Ensure throughout prescription that: ▪ The patient uses adjustable ankle weights. ▪ There is minimal substitution of other muscle groups. ▪ The participant uses the correct breathing technique (inhale before a lift, exhale during, and inhale while lowering the lift). ▪ The participant does the exercises slowly (two to three seconds to lift the weight, four to five seconds to lower the weight) through the functional range of active joint movement. ▪ The participant takes a one to two minute rest between sets.	▪ Observe the participant during the holding portion of each balance exercise. Make sure they can recover their balance using lower body strategies (as opposed to grabbing with their arms) before prescribing the exercise without support. ▪ Not everyone will start at the first level or be prescribed all of the balance exercises. Unstable patients may initially need a wider base of support. ▪ Ensure the patient's eyes stay looking ahead ▪ It is okay to make lower limb balance adjustments, such as taking a recovery step, while doing the exercise and is confident in doing so.

Otago. Once a participant has been enrolled and oriented to their tablet, a certified physical therapist (PT) will contact the participant to set up an in-person appointment for initial assessment. During the initial assessment, the nurse PI will conduct the physical assessment screening tests as noted in Table 2. The nurse will then discuss the Otago exercise program with the participant and provide a printed binder of the Otago exercise as well as demonstration on how to appropriately conduct each exercise. The Otago exercise program consists of the following: 1) A series of

warm-up exercises, 2) Select exercises from the 17 Otago exercises which challenge the participant's strength and balance for up to 30 minutes, three times a week, 3) A walking program for up to 30 minutes, three times a week. Each Otago will be tailored for each participant's ability level. See exercise prescription in Table 1.

3C3.B. Otago + GYYB + (GYYB): The GYYB program will be administered to the participants by a qualified and certified Yoga instructor in a group setting once a week for 12 weeks. The GYYB is a one-hour program containing gentle physical Yoga postures that participants could practice sitting on a chair for 30 minutes. These exercises are designed based on improving the overall flexibility, bodily control and mindfulness in movements. Following the gentle yoga postures, the participants will perform Yogic breathing exercises for 30 minutes. These exercises are known to promote relaxation, mood, pain and anxiety scores that are highly relevant to the target population and are reported to stimulate measurable biomarker changes in the saliva. During the in-person session the Yoga instructor will explain the GYYB program to participants in the Otago+GYYB group each exercise and their perceived benefits. The participants will have a chance to practice the exercises in the presence of the instructor and clarify any question that they might have about the exercises. The instructor will make sure that the participants can perform the exercises independently. The participants will be provided with a video and a handout for the study exercises that they will follow for 1 hour every day (any time at their preference). Any deviations in the practice will be noted by the participants in a diary indicating the length of the practice with date on it. Saliva samples will be collected at the beginning and end of the sessions on week 1 and 12 to measure salivary biomarkers including cortisol, and 1,5-AG. The OEP and self-management as detailed above will also take place in this group.

3C3.C. Otago plus GYYB + Behavior Activation (*Activate for Life).*
This condition will incorporate OEP and GYYB as above and will also include behavioral activation to address motivation and affect. Behavioral Activation incorporates daily planners and worksheets to identify and rate reinforcing behaviors and is often used in conjunction with other interventions because components of these interventions are easily incorporated into the daily planner based activities. Each participant outlines general values and specific behaviors that 'demonstrate' each value, compiling a list of the latter. This list is then used to generate 10 to 20 highly defined values-based, reinforcing activities. Next, this list is combined with the activities outlines in Otago and GYYB and this master list is used to schedule these values-based activities for the next two days. One of the strengths of the BA protocol, relative to other cognitive behavioral and activation-based interventions, is that it is designed for implementation over a brief period. Additionally, sessions of the often require as few as 15-30 minutes of contact time due to the straightforward, simple structure of these sessions. Patients begin with a weekly self-monitoring exercise, charting behaviors and mood every hour, that serves as a baseline assessment of daily activities, and orients the patient to the quality and quantity of his or her activities on a daily basis. Also, baseline assessment assists in generating ideas about activities to target during treatment.

Session 1: Begins with rationales for Behavioral Activation. The core points made are that what one does often plays a role in how one feels. Clients then proceed to identify 5 classes of values (e.g., family, work, spirituality) with specific behaviors that 'show' the patient's value, thus the treatment is tailored for each individual. For example, the value 'time with family' might be shown by 'throwing the baseball with son for 20 minutes'. Lists of specific behaviors are derived for each value and written on the daily planner. Participants are then given a daily planning calendar and behaviors that are reinforcing and relatively easily accomplished are planned each day, for two days in advance with the objective of planning at least 2 hours of reinforcing activities and scheduled homework from Otago and GYYB each day. Session 2: Begins with a review of homework and verbal reinforcement of completed planners, completed reinforcing behaviors, completed Otago and GYYB homework,

restatement of the rationale (ie., that what one does affects how one feels and doing positive things will help one to feel positively), and problem solving. Behaviors that were consistently planned but not completed are removed and alternative behaviors suggested. The next 2 days' activities are planned. This session usually involves a significant amount of problem solving, and identification of avoidance, with planning in place to counter this avoidance. Sessions 3-4: These sessions begin with a review of homework, followed by asking the patient to state, in their own words, their interpretation of the rationale for Behavioral Activation. Obstacles to completing behaviors are discussed and additional exposure-based and reinforcing behaviors are generated. The next 2 day's activities are planned. Session 5: Includes discussion of the rationale and treatment gains obtained thus far. Discussion is also centered on the need to continue planning activities and using a daily planner for at least 6 months. Relapse prevention strategies are reviewed. Additional sessions are conducted every other week until week 12 (Otago and GYYB completion).

Table 2: Measurements/Instruments/Interventions and Time Points

Major tasks and domains; monitor/ evaluate	***Measures/instruments/questions and Cronbach's alpha ( )***	***Data sources and time points***
Screening	Ability to ambulate 150 feet with or without assistive device; Short version of Test for Functional Health Literacy in Adults (0.97)[37] Tablet Computer Familiarity Questionnaire (0.92)[38] Mini-Cog[26]	Participant interview and observation; Baseline
Demographics	Personal health, medical, health history—co-morbidities, medications, use of pain medications, race/ethnicity	Participant interview; Baseline
Weekly nursing self-management	Review weekly diary entries, pain scores, yoga and /or Otago progress, fatigue, and sleep.	Weekly
Reach: Sample Recruitment	Progress monitoring of sample representativeness; types of recruitment activities and rates; % eligible, consented, oriented	Tracking forms; weekly quality checks by PI; weekly team meetings
Effectiveness:		
Functional impacts	Numerical rating scale NRS (0.99)[39]	Baseline; Daily; Study end
Pain	PROMIS Pain Interference Short Form 6b (0.98)[40]	Baseline; Study end
	PROMIS Pain Behavior Short Form 7a (0.98)[40]	Baseline; Study end
	PROMIS Fatigue Short Form 6a (0.91)[41]	Baseline; Daily; Study end
Fatigue		
Lower extremity strength	30 Second Chair Stand Test (not determined)[42]	Baseline; Study end
Balance and Function	Mini Balance Evaluation Systems Test (MiniBEST) (0.91)[43]	Baseline; Study end
Walking capacity	Two Minute Walk Test (0.82)[44]	Baseline; Study end
Self-report measures	PROMIS Physical Function (0.95)[45]	Baseline; Study end
Function	PROMIS Depression Short Form 8a (0.95)[46]	Baseline; Study end
Depression	Revised UCLA Loneliness Scale (0.94)[47]	Baseline; Study end
Social support	Pain Self-Efficacy Scale (0.93)[48]	Baseline; Study end
Self-efficacy		
Adoption		
Adherence	Participation in weekly self-management telehealth visits; frequency of participation in Otago and/or Yoga as recorded in participant diary and data from activity tracker; frequency of use of self-management techniques as recorded in participant diary; # of patients who successfully complete self-management program; # of and reasons for dropouts	Tracking forms; weekly review of participant diary; weekly assessment of feedback; end of study participant interviews and satisfaction questionnaires
Acceptability		

Endorsement	Usability of tablet technology and activity tracker; # and types of problems encountered; participant satisfaction with self-management program and technology	Assess at weekly team meetings; acceptability checklist and tracking forms; end of study participant interviews and satisfaction questionnaires
Implementation		
Technology Site set up Consistency of intervention	# of problems encountered with tablet, activity tracker, vital sign equipment; # and types of problems encountered with study setup; was fidelity to training protocol maintained; was orientation completed as planned; was standardized checklist used to instruct participants; assessment of participant for suggestions; # of changes made to intervention based on suggestions	Tracking forms; weekly team meetings; end of study participant interviews and satisfaction questionnaires
Maintenance		
Projection of future adoption	# patients who would continue intervention; potential for future applications	End of study participant interviews and satisfaction questionnaires

End of Study Interviews: At the end of Visit 2, participants under ARMS 1, 2, and 3 are scheduled an end of study phone exit-interview with Dr. Davis at University NC Charlotte (UNCC). This interview will be recorded and temporarily stored on a digital voice recorder while the participant is on speaker phone. Prior to the beginning of the recording, Dr. Davis will inform the participant that the recording is about to commence and at the end of the interview he will notify them that the recording has ceased. In this manner, no PHI will be collected. Prior to performing qualitative analysis, Dr. Davis will immediately upload the recording to the patient's electronic case record in the REDCap database on MUSC secure servers and the delete the recording from the portable storage device.

Supplemental ARM 4 Study Design:
Participants enrolled under this study arm will solely receive the gentle yoga and yoga breathing 12-week (GYYB) component exercise program which will be loaded on to a tablet that will given to the participant while enrolled in the study. There are only two study visits (baseline and week 12) with no 3 month follow-up, at which timepoints saliva samples will be collected.

CG measures to be collected under the Supplemental ARM at the two timepoints include:

- Demographics. Age, race/ethnicity, sex, marital status, socioeconomic status, education, living arrangement, medications, # co-morbid conditions (health status) will be recorded.
- PROMIS v1.0/1.1 Short Forms (intraclass correlation coefficient)
- Health status: Global Health Scale (0.81)
- Functional health: Physical Function (0.95)
- Fatigue: Fatigue 6a (0.91)
- Sleep disturbance: Sleep Disturbance 6a
- Depression: Depression 8a (0.95) and CES-D (0.90)
- Anxiety: Anxiety 6a (0.94)
- Loneliness: UCLA Loneliness Scale (0.96)
- Social support: Medical Outcomes Study Social Support Survey Instrument (MOS-SS) (0.97)
- Burden: Zarit Burden Scale (0.89)
- Relationship quality (CG): Mutuality Scale (0.94)
- QoL (CG): Euroqol-5D (0.83)
- QoL (PWD): Quality of Life-Alzheimer's Disease (0.82)
- Function (PWD): Functional Assessment Staging Tool (0.87)
- Activities of Daily Living Questionnaire (dementia) (0.86)
- International Physical Activity Questionnaire for the Elderly (IPAQ-Short Form)

- End of study satisfaction survey (researcher developed)

The participant sample will be characterized using univariate descriptive statistics and frequency distributions for all variables as appropriate. We will also explore differences in demographic and other variables such as age (45-74, ≥75 years), sex, health status, functional activity, and QoL across the 2 time points.

Participant Compensation: Participants under ARMS 1, 2, and 3 will receive $20 for screening, and $20 at the initial enrollment visit for completion of the initial enrollment assessment and baseline surveys (total of $40 if eligible and enrolled). Additionally, participants will receive another $40 at suiccessful completion of the post-treatment (week 12) and 3 month followup visits. Total compensation for successful study completion is $120.00. All payments will be made to the participant in the form of a gift card.

Participants under the Supplemental ARM 4 will be provided a total amount of $80 in study compensation $40 for enrollment and completion of the baseline visit, and $40 at successful completion of study at visit 2. Payment will be made in the form of a check that will be mailed to the participant's home address. Will will collect social security numbers for MUSC IRS tax reporting purposes.

11.0 Specimen Collection and Banking

Saliva Sample Collection (all ARMS): One 3mL saliva samples will be collected from participants at each of the three study visits. At the first two visits (baseline and week 12) the samples will be collected before and after the 30 minutes GYYB session. Saliva will be naturally allowed to accumulate in the oral cavity and the participant will discharge it into the specimen tube (5 mL capacity) with lid. Due to COVID-19 precautions, participants will be given the option to either 1) drop off their saliva samples at MUSC CON, or 2) to arrange to have their saliva sample picked up from their place of residence or at a location that is convenient to both themselves and the researchers. Immediately after collection the saliva samples will labelled with the participant's study ID number and the collection dates, and then placed on ice for immediate transporation to MUSC in a biohazard cooler. The samples will subsequently be stored at -80 degree C until analysis by Dr. Balasubramanian at his lab. For analysis, the samples will be slowly thawed, centrifugation at 14000 RPM at 4 degree C.

Salivary Biomarker Measurement (all ARMS): Owing to their possible involvement in pain and/or fatigue, the following biomarkers will be assessed in saliva: cortisol and 1,5-AG. Dr. Balasubramanian (Co-I) will perform the analysis of salivary biomarker expression in the saliva samples similar to their laboratory's recent reports (https://www.ncbi.nlm.nih.gov/pubmed/27538513; https://www.ncbi.nlm.nih.gov/pubmed/25873979; https://www.ncbi.nlm.nih.gov/pubmed/25101659). Dr. Balasubramanian has over 20 years of experience in ELISA and other biochemical techniques for biomarker measurement (Balasubramanian, & Kuppuswamy, 2003; Balasubramanian et al., 2006; Balasubramanian, Mani, Kasiganesan, Baicu, & Kuppuswamy, 2010; Balasubramanian et al., 2012; Moschella et al., 2013; Prabhasankar, Ragupathi, Sundaravavidel, Annapoorani, & Damodaran, 1993).

Specimen access and disposal (all ARMS): A chain of custody log will be maintained for the collection, handling and disposition of all participant biological specimens. Dr. Balasubramanian will only have access to unidentifiable biological data, which will be stored on MUSC secure servers. No genetic analysis or specimen banking will be conducted. Data will not be sent outside of the MUSC enterprise, and all specimens will be destroyed six months after study completion. As specified in the

Informed Consent document, participant's may withdraw their consent to participant in the study at any time. Revocation of consent either verbally or in writing will immediately withdraw the consent of the participant's specimen analysis for any collected and unanalyzed saliva samples to date. The PI will work directly with Dr. Balasubramanian to notify him of consent withdrawals and to unblind group allocations for analysis purposes.

12.0 Data Management

Sample Size Determination. This feasibility study will recruit 30 participants under ARMS 1, 2, and 3. Thirty participants should allow for recruitment of 10 participants from at least 3 different Humanities sites to avoid cross-contamination of study groups. 20 participants will be recruited under the Supplemental ARM AIM 4 to allow for outcome size effect determinations.

Data analysis plan. Measures of feasibility including recruitment and reach, fidelity and adherence, formal satisfaction, and drop-out proportions will be evaluated. Then 95% confidence intervals for proportions will be used to estimate dichotomous outcomes (e.g., the proportion of subjects who: agree to participate out of the number that are approached, the proportion who complete the intervention, the proportion who report satisfaction with the intervention, and the proportion who exit the study prematurely [drop out]). Further, the participants' reasons for drop out, and problems/issues encountered with the intervention will be described via frequency distributions. For continuous measures (e.g. satisfaction scores), frequency distributions and the median and mean responses (with 95% confidence intervals) will be obtained. Formative and summative qualitative interviews will be recorded with the residents and students, transcribed, analyzed with discourse analysis[36] and interpreted to evaluate the program design and effectiveness and to make necessary changes based on feedback. Univariate descriptive statistics and frequency distributions will be calculated as appropriate for all variables. Demographic variables obtained at baseline will be described via measures of central tendency (mean, median), variability and frequency distributions as appropriate. Additionally, characteristics for those who were eligible for study versus those who were not eligible and for those who adhered to the study protocol (study completers) versus those who did not adhere (non-adherers and drop-outs) will be compared to better describe the population for this study.

Data sharing with the NINR/NIH: As a condition of this National Institutes of Nursing Research (NINR) award, de-identified patient data will be shared by the researchers with the NINR and stored electronically on an NIH password protected secure server (https://cdrns.nih.gov/). The purpose of sharing this information is to build a NINR repository of data using Common Data Elements (CDE) for future research purposes among the general scientific community and for public health benefit. Patients will be allocated a random identifier through the NIH supported GUID Tool. The GUID Tool (https://cdrns.nih.gov/node/39) is a customized software application that generates a Global Unique Identifier for each study participant. The GUID is a subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII). The GUID is made up of random alpha-numeric characters and is NOT generated from PII/PHI. As such, it has been approved by the NIH Office of General Counsel. GUID Generation complies with HIPPA regulations for the protection of PII/PHI. Patients are made aware of this data sharing agreement with the NINR/NIH in the study's Informed Consent document. Further protections are afforded to participants through an NIH Certificate of Confidentiality conferred upon the study.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

There is a well-developed and NIH/NINR prepared Data and Safety Monitoring Plan (DSMP) that involves the use of a Safety Monitoring Committee (SMC) which shall meet semi-annually post initial participant study enrollment. The Committee is comprised of key individuals that include: an

independent safety monitor (ISM), a biostatistician (BS), and the Program Manager (PM). Post initial study enrollment, the SMC will convene semi-annually and all reports will be forwarded to the IRB and Sponsor in accordance with institutional policies and sponsor requirements.

DATA AND SAFTEY MONITORING PLAN (ARMS 1,2, and 3)
SECTION A. Monitoring Entity.
Considering the study rationale, population, procedures, and the risk:benefit profile as outlined, the overall risk level for participation in this study is classified as: Minimum Risk. As such, this study will utiize a Safety Monitoring Committee (SMC) with an Independent Safety Monitor (ISM). Post initial study enrollment, the SMC will convene semi-annually.

Principal Investigator, (PI). Although not part of the SMC, as PI, **Dr. Kelechi** will overall be responsible for the immediate protection of all human participant study participants enrolled in the study.

1) Safety Monitoring Committee (SMC)
The study's SMC will be comprised of the following individuals, who will perform data safety management and monitoring of the study:

- **Dr. Charlene Pope, PhD, MPH, BSN, RN, FAAN (ISM)**
- **Martina Mueller, PhD (BS)**
- **Mohan Madisetti, MSc. (PM)**

2) Individual Roles and Responsibilities
Independent Safety Monitor, (ISM). **Dr. Pope** is a Research Associate Professor in the College of Medicine (COM), Medical University of South Carolina with secondary appointments I the MUSC Department of Internal Medicine and College of Nursing. She is also Chief Nurse for Research aht the Ralph H. Johnson VA Med Center, Charleston, SC. She is trained as a health service researcher and a sociolinguist who studies variations in communication, in how patients and health providers speak with one another, and in an array of circumstances as a mixed methods and qualitative methodologist. Dr. Pope has collaborated with multidisciplinary health and social science teams in studies of health service and community-based disparities and participated in rural outreach. Dr. Pope will act as the study's Independent Safety Monitor (ISM). Dr. Pope has no real or apparent conflict of interest that would affect her performance in this role on the study. Dr. Pope will correspond semi-annually with the SMC to review de-identified cumulative AE study data to assess any impact on the safety of participants or on the ethics of the study. As the ISM, she will be responsible for reviewing all cumulative reported SAE related to study treatment and data safety monitoring reports generated by the BS to provide study recommendations to the PI, MUSC's IRB and NINR. Dr. Pope will be immediately notified of the occurrence of any SAE by the PI or PM and will be provided with the necessary study information to provide an informed recommendation in real-time regarding the protocol and human participant safety.

Martina Mueller PhD, Biostatiscian (BS). **Dr. Mueller** is a Professor in the College of Nursing with a joint appointment in the Department of Biostatistics, Bioinformatics and Epidemiology (DBBE) at MUSC. Dr. Mueller has served and is currently serving as a member of several NIH/NINR R01/R21 DSMB Committees and SMCs. Dr. Mueller will be responsible for conducting semi-annual interim analyses, generating semi-annual AE safety reports from the electronic study research database and disseminating de-identified information to the ISM and other members of the SMC. The interim data analyses will only include safety related results; analyses in regards to study outcome will not be performed. The interim AE reports will provide typology, frequency data and outcomes of all reported and documented AE in the electronic study database. With no patient contact, Dr. Mueller has no apparent conflict of interests to serve in this capacity.

Mohan Madisetti MSc, Program Manager (PM). **Mr. Madisetti** is the P20 Progam Manager at the College of Nursing and a member of MUSC Institute of Human Values with Fellowship certification in Research Ethics. Mr. Madisetti has served and is currently serving as a member of several NIH/NINR R01/R21 and FDA Industry Sponsored Clinical Trials DSMCs and DSMB. With no patient contact, Mr. Madisetti will be responsible for the classification of all reported adverse events (AE) and for ensuring that all serious adverse events (SAE) are forwarded to the PI and ISM in real time and in compliance with MUSC IRB policies and procedures. In addition, and in conjunction with the PI, Mr. Madisetti will be responsible for amending the protocol in accordance with the ISM recommendations, submitting reportable SAEs and protocol deviations to MUSC IRB, and, submitting annual Progress Reports to the NIH/NINR through MUSC's OSRP. He will also be responsible for maintaining the regulatory binder, ensuring data management validation and verification of the electronic study research database, conducting monthly internal quality control audits on all participant records, notifying the PI of any deficiencies, and the forwarding of reportable SAE to the NIH/NINR Program Official through MUSC's OSRP within 72hrs of IRB review and acknowledgement

SECTION B. Procedures for Safety, Risk and Confidentiality

1) Monitoring Study Safety

From the initial screening of participant by inclusion and exclusion criteria to the informed consent process to the provision of participant study instruction to staff training in Good Clinical Practices (GCP) and regulations pertaining to the Conduct of Human Participant Research to study contact with participants to internal monthly quality control audits and protocol fidelity monitoring to the real-time review of AE by the ISM to the oversight of MUSC's IRB, procedures for monitoring study safety are consistently afforded throughout study. Specific procedures include:

- Participants will be screened for inclusion and exclusion per the protocol; the PI shall verify 100% of participants' eligibility prior to study enrollment through review of inclusion and exclusion criteria with potential participants.
- Participants will be fully informed as to all know risks and the possibility of risk from study participation in the informed consent process. **These risks are minimal.**
- Participants will be instructed to notify the researchers of any/all suspected or experienced adverse events whether they believe them to be related or not to the intervention.
- All reported participant AEs will be tracked through to resolution.
- All investigators and researchers will maintain active CITI Human Subject Research and Good Clinical Practice training.
- The PM will conduct a monthly internal quality control audit of all participant records to ensure compliance with MUSC IRB regulations; the PI and Program Coordinator (PC) will work together to correct any errors.
- The PI and/or designee will observe and evaluate ten (10%) percent of eligibility screening visits, informed consents and study instructions performed by IRB approved study personnel and provide feedback and/or retraining of study personnel if fidelity to both applicable federal regulations and the protocol is not observed.
- The BS willl generate semi-annual AE reports for the PI and SMC to review.
- The ISM will have access to real-time study data and will be able to provide immediate recommendations to the PI.
- Investigator performance and compliance will be provided for through MUSC IRB and ORI study oversight.

2) Minimizing Research-Associated Risk

Diligent study safety monitoring will be conducted by all member of the research team and the SMC throughout the conduct of this study in compliance with the following required elements of MUSC IRB's continuing review process:

1. Tracking and follow-up of participant accrual (inc. withdrawn consents) will minimize risk by identifying, disclosing, and mitigating any potentially unknown risk(s) of harm to study participants. **The risks associated with this intervention are not considered greater than those that patients would otherwise be exposed to when receiving normal standard of care.**
2. Timely and appropriate reporting of informed consent process deficiencies, protocol deviations, privacy breaches, conflicts of interest, and/or changes in personnel.
3. Ongoing soliciting, monitoring and appropriate reporting of adverse event activities.
4. Timely and appropriate IRB submission of safety-related documents such as audit reports, sponsor progress reports, ISM reports, and other materials or communications that might impact the safe conduct of this study.
5. Active cooperation with the IRB, ACO, sponsor, and other applicable entities in the event of a random or for-cause internal or external audit.

Institution-Wide Assurances

This protocol will be conducted fully in keeping with the signed MUSC IRB Principal Investigator Statement of Assurance and Department Chair's Statement of Assurance, when submitted to the IRB as a required component of the MUSC IRB Human Research Review Application.

3) Protecting Confidentiality of Participant data

Certificate of Confidentiality. This study will be conducted in accordance with recently enacted policy regarding the automatic granting of Certificates of Confidentiality to NIH/NINR federally funded research. Participants will be made aware of their rights and the limitations of the release of Protected Health Information through the Informed Consent document.

Participant Screening and Enrollment. All data from participants screened for the study will be entered directly into an electronic study database. Designated research staff will collect, gather, and enter required data (written informed consent, HIPAA Authorization, and demographics) onto study data forms. Screened patients who do not meet study eligibility will have specific screening data entered into the study database. The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include reason for exclusion. All dates will be shifted and other Personal Health Information (PHI) will be removed from the study database upon study completion. All data obtained from this study will be used for research purposes only and will comply with Federal HIPAA regulations. Master Screening and Enrollment Logs will used by the PM to prepare reports on accrual and attrition for the PI and SMC.

Case Report Forms (CRF). All proposed study specific case report forms (source documents) for data collection will be designed by the PI, and, when possible, transferred into electronic Case Report Forms (eCRFs) for use in the study's REDCap database. These study specific eCRFs source documents (study logs for correspondence, compensation and other forms such as pre-eligibility screens) will be coded by the participant's unique study ID# for all data collected including study instruments will be maintained in the participant research record. Completed instruments that require signature on a paper CRF will be scanned and uploaded into the study database to all for remote electronic safety monitoring as well as maintained on file in accordance with MUSC policies and applicable Federal Regulations for the Conduct of Human Participant Research.

Binders. The PC will prepare and maintain a participant-specific CRF binder for each participant containing all non-eCRFs records. A regulatory file will be maintainedby the PM to include the IRB-approved Protocol, original Informed Consent documents, HIPAA forms and other required study-related regulatory documents. All paper research records and CRFs will be maintained in a locked file cabinet, stored in a room for research files that is accessible only via a password protected entry system that features security cameras, within the College of Nursing. Access to the research records, study database and PHI's will be restricted to study personnel as approved by the PI and MUSC IRB. As with all studies conducted at MUSC, this study is also eligible for a random audit by MUSC Office of Compliance.

Data Processing. This study will use Research Electronic Data Capture (REDCap) for data capture and management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The study-specific REDCap electronic database will be designed and developed by the PI, CI, or PC. The provision of REDCap is made available through the South Carolina Clinical & Translational Research (SCTR) Institute at MUSC with NIH Grant awards UL1RR029882 and UL1TR000062.

Data Security. Ensuring data security, compliance with 45 CFR 46 and maintaining the integrity of PHI is a top priority. MUSC has Standard Operating Procedures (SOP) to ensure a high level of data security while coordinating electronic and paper data management activities for clinical research trials. The REDCap study database will be hosted in the Biomedical Informatics secure data center at MUSC, a secure environment for data systems and servers on campus, and includes firewall, redundancy, failover capability, backups and extensive security checks. The secure data center has strict access control; only authorized core personnel may access the facility un-escorted. Only authorized users are allowed to connect to the network, and the security of the network is actively monitored. Power and environmental controls have several layers of backups, from interruptible power supplies to alternate and redundant feeds to the local utility company. The REDCap system administrator contributes to the maintenance of institutional disaster recovery and business continuity plans. Load balancers and a highly fault tolerant SAN infrastructure contribute to high availability.

The REDCap system itself has several additional layers of protection including password protection. Access to the data and its security is managed institutionally by sponsored login IDs through a Shibboleth login with an MUSC issued NetID and features a user account management filter that controls who can access the data and to what degree. All personnel must pass an employment background check before being issued an ID. Password complexity, history and expiration standards are implemented at the institutional level. Access to individual REDCap projects and their data is managed by the owner of the project. All transactions are securely delivered to the application using Secure Sockets Layer (SSL – SHA-1 with RSA Encryption; 2048-bits). It is then transmitted internally (behind the firewall) to the database server. All transactions are logged at the server layer (httpd logging), application layers (REDCap logs activity to a database table), and the database layer, using both query and binary logging. This feature provides audit trails for all changes, queries, data exports and reports. MUSC Information security policies are available at: https://mainweb-v.musc.edu/security/policy/

Data Entry. Only MUSC IRB approved study personnel that are authorized to have access to the REDCap study database will be granted password access. Study personnel using computers that are connected to the Internet will directly enter data into the remotely housed database. As such, no

electronic study data will be stored on hard drives and/or any portable electronic devices. Additionally, all personnel with access to the database will have current University of Miami CITI training in the Conduct of Human Subject Protections, and HIPAA and Information Security trainings that are completed annually. Each participant will be assigned a unique study identifier, all PHIs will be masked, and data exports will be limited to the PI or the PC for generating reports and the conduct of statistical data analysis.

Data Monitoring. Ongoing quality control procedures will be implemented for data collection, storage and processing. The PM will conduct routine monthly monitoring of the study database and generate a report for review at study team meetings. Standing agenda items for these meetings will include participant recruitment and retention, AE's, protocol deviations, data integrity and overall study conduct. The PI and PC will work to resolve and validate discrepant data. Discrepancies that warrant clarification will be sent to appropriate parties for review and resolution. All data entry and changes made in the study database by authorized study personnel will be automatically logged by REDCap, and provide a transparent visible audit trail for reviewers.

SECTION C.
Procedures for Identifying, Reviewing and Reporting Adverse Events

1) Identifying. Potential minimum risks identified for participants are outlined in the Protection of Human Participants and will also be outlined in the IRB-approved informed consent document. Additional unknown risks may occur and, if so, will be identified through diligent monitoring by the PI or PC throughout the conduct of this study. During the informed consent process, participants will be advised of the potential risks of participation as identified in the IRB-approved informed consent document and reminded throughout the study that the researchers should be promptly informed about any concerns regarding potential side effects, adverse events, or clinical deterioration. Participants will also be instructed to notify the PI, PC, and/or designee of any suspected adverse events immediately if possible. The PI or PC will maintain an electronic record of all reported adverse events and notify the ISM of all reportable events as they occur. The ISM will have real-time access to the study database to review and monitor all reported SAE that were reported as related to the intervention. Additionally, the BS will generate and provide de-identified cumulative administrative human participant semi-annual safety reports for the ISM and SMC to review.

2) Reviewing. Adverse events will be initially be assessed and graded by PM and then reviewed by the members of the SMC according to the following MUSC's IRB Adverse Event Reporting Policy http://academicdepartments.musc.edu/research/ori/irb/HRPP/HRPP Guide Section 4.7

- **Expected/Anticipated**—Identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
- **Unexpected/Unanticipated**—Not identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
- **More Prevalent**—Occurs more frequently than anticipated or at a higher prevalence than expected.
- **Serious**—Results in death, is life threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity, cancer, overdose, or causes a congenital anomaly/birth defect.

The relationship of adverse events to study participation will be determined by the SMC according to the MUSC IRB Adverse Event Reporting Policy:

- **Unrelated**—There is not a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

- **Possibly Related**—The adverse event may have been caused by the drug, device, or intervention, however there is insufficient information to determine the likelihood of this possibility.
- **Related**—There is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

3) Reporting. All reportable AE, SAE and unanticipated problems experienced by participants will be reported to the NIH/NINR and MUSC IRB in compliance with their Adverse Event Reporting Policy requirements, using the IRB's password protected on-line secure server adverse event reporting system. Within 24 hours after a reportable AE, SAE or unanticipated problem has been reported by the participant, it will be graded by the PM, forwarded to the study's ISM for review, and then will be submitted by the PI to MUSC IRB. The Institutional Official(s) will review the event and discuss the report with the IRB Chair and the Director of the Office of Research Integrity. After IRB review and acknowledgement, the PI will further review, and the PI or PM will forward a copy of the reportable AE, SAE or unanticipated problem and IRB acknowledgement letter to the NIH/NINR Program Officer through MUSC's OSRP. The activities will be reported to the NIH/NINR within 72hrs. In addition, all cumulative reportable AE, SAE and unanticipated problems included in the ISM reports will be submitted to the NIH/NINR in the PI's Annual Progress Reports.

4) Examples of Potential Reportable Adverse Events: In accordance with MUSC IRB Adverse Event Reporting Policy, an AE is reportable is it meets all of the following criteria: 1) is unexpected 2) is related and/or possibly related, and 3) is serious and/or suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Additionally, per MUSC's policy all participant deaths, protocol deviations, complaints about the research, and breaches of confidentiality are reportable events. An example of an AE would be new onset chest pain and discomfort (symptom) that could potentially be associated with increased physical activity. The participant's parent reported he/she recently ran out of his/her medication. The steps to be taken include withdrawing the subject from the study and inviting him or her to restart the study after symptoms subside. An example of an SAE would be the death of a participant from acute chest syndrome or stroke, which although would be viewed as unexpected and unrelated to the intervention is nonetheless a reportable serious event. No further steps would be taken except to review, grade and report the event. An example of an unanticipated problem would be the participant trips and falls while participating in the exercise program. The steps in this case would be to report the event as per the IRB and NINR policy, and to discuss appropriate actions regarding whether the participant should remain in the study with the ISM and SMC. These events and problems will be reported in accordance with the IRB and NIH/NINR policy as noted in Section C.3.

SECTION D. Multi-site Monitoring and Compliance

This is not a multi-site study.

SECTION E. Assessment of External Factors

The PI will conduct a semi-annual assessment of external factors through a review of literature related to new developments in the areas of self-management and symptom management of chronic pain and/or fatigue, symptom reporting and other approaches that may have an impact on the safety of participants or on the ethics of the study.

SECTION F. Interim Analysis

This study aims to test the feasibility of a multi-component, technology-based intervention to promote self-management and symptom management of chronic pain and fatigue among low- income older adults. To our knowledge, there are no similar interventions specifically designed for this patient

population and purpose. As such, the PI and BS will generate semi-annual qualitative interim analysis reports on a) adverse events; and b) data obtained during phone call and returned end-of-study surveys to understand issues related to the uptake, usability, and adoption of this platform among this population. We will evaluate the screening and enrollment procedures, barriers to participation and retention, including, safety, adherence, acceptability, technology problems encountered if any, and user feedback from the participants and providers. This information gained from this structured process will be used to both guide the refinement of the current protocol and to inform the design of a larger efficacy trial. Interim analysis of outcome variables (pain, and fatigue) was not considered to avoid inexact inferences and increased chance of error due to few data points, as well as potential for bias if interim results were known to the investigators. Therefore, there are no planned stopping rules for this study.

SUPPLEMENTAL ARM 4: DATA SAFETY AND MONITORING PLAN (DSMP)

SECTION A. Monitoring Entity

Considering the study rationale, population, procedures, and the risk to benefit profile, the overall risk level for participation in this study is classified as: **Minimum Risk.** Accordingly, the study will employ the use of a Safety Monitoring Committee (SMC) that will meet semi-annually post enrollment of the first participant into the study. The SMC members are charged with reviewing safety, trial progress, ethics, and with providing recommendations to the PI and MUSC IRB with respect to study continuation modification, and termination.

1) Data Safety Monitoring Committee (SMC)

The study's SMC is comprised of the following individual members:

- Elaine Krug, PhD, RN, FAAN; Gerontological and Alzheimer's Disease Expert (G/ADE) and Chair (C);
- Martina Mueller, PhD; Biostatistician (BS); and,
- Mohan Madisetti, MSc; Project Director (PD)

2) Individual Roles and Responsibilities

Principal Investigator, (PI). As PI, Dr. Kelechi will overall be responsible for the immediate protection of all human participant study participants.

Gerontological Expert, **Dr. Krug** is a Geriatric Nurse Practitioner and Professor Emeritus at the College of Nursing, MUSC. Dr. Amella will serve as the Chair of the DSMC and will correspond semi-annually with the SMC to review de-identified cumulative AE study data to assess any impact on the safety of participants or on the ethics of the study. As Chair, Dr. Amella will be primarily responsible for the reviewing of all cumulative reported SAE that are related to study treatment, and the provision of SMC recommendations from data safety monitoring reports to the PI, MUSC's IRB and the NIH. Dr. Krug will be immediately notified of the occurrence of any reportable SAE by the PD and will be provided with the necessary information to provide an informed recommendation in real-time regarding the protocol and human subject safety.

Biostatistician, (BS). **Dr. Mueller** is a Professor at the College of Nursing at MUSC with a joint appointment in the Department of Public Health Sciences. Dr. Mueller will be responsible for conducting semi-annual interim data analyses, generating semi-annual AE safety reports from the REDCap study database and disseminating de-identified information to all members of the SMC. The interim data analyses will only include safety related results; analyses in regards to study outcome will not be performed. The interim AE safety reports will provide typology, frequency data and outcomes

of all reported and documented AEs in the electronic study database. As a member of the SMC, Dr. Mueller will also participate in semi-annual DSMC meetings.

Project Director, (PD). **Mr. Madisetti** is a Research Associate at the College of Nursing at MUSC. Mr. Madisetti will be responsible for the classification of all reported adverse events (AE) and for ensuring that all serious adverse events (SAE) are forwarded to the PI, C, and IRB, and in compliance with MUSC IRB and NIH's reporting requirements. In addition, and in conjunction with the PI, the Mr. Madisetti will be responsible for amending the protocol in accordance with the SMC's recommendations, submitting reportable SAEs to the IRB, and submitting annual SMC reports to the IRB and NIH. As part of the SMC, he will be responsible for: conducting internal quality control audits on all participant records and notifying the PI of any deficiencies; assisting in the generation of ad hoc participant data safety reports; and, forwarding reportable SAE to the NIH/NINR Program Official through MUSC's OSRP within 72hrs of IRB review and acknowledgement. Mr. Madisetti will also be responsible for following up on reported AEs to monitor outcomes and provide for the continuity of care for participants.

SECTION B. Procedures for Safety, Risk and Confidentiality

1) Monitoring Study Safety

From the initial screening of study participants by inclusion and exclusion criteria to the informed consent process to the provision of participant study instruction to staff training in Good Clinical Practices (GCP) and regulations pertaining to the Conduct of Human Participant Research to regularly scheduled study contact with participants to internal quality control audits and protocol fidelity monitoring to the real-time review of AEs, and to the oversight of MUSC's IRB - procedures for monitoring study safety are consistently afforded throughout study. Specific procedures include:

- All participants will be screened for inclusion and exclusion per the protocol
- All participants will be fully informed as to all known risks and the possibility of risk from study participation in the informed consent process. **These risks are minimal.**
- AEs and changes in medical status will be elicited at every participant visit and contact.
- All participants will be given a 24 hrs. AE reporting phone number and will instructed to notify the researchers of any/all suspected or experienced adverse events whether they believe them to be related to the intervention or not.
- The PD will track all reported participant AEs through to resolution. Please see Section C. 1 – 4.
- The BS shall generate semi-annual AE reports for the PI and SMC to review.
- The PD will conduct quarterly internal quality control audits of the study and all records to ensure compliance with MUSC IRB regulations and notify the PI of any deficiencies; the PD will work with the PI and Program Coordinator to correct any errors.
- The PI and/or designee will observe and evaluate ten (10%) percent of eligibility screening visits, informed consents and study instructions performed by IRB approved study personnel and provide feedback and/or retraining of study personnel if fidelity to both applicable federal regulations and the protocol is not observed.
- All investigators and researchers will maintain active CITI training.
- Investigator performance and compliance will be provided for through MUSC IRB and ORI study oversight.
- All reportable events, including protocol deviations will be forwarded to the NIH Program Official through MUSC's OSRP within 72hrs of IRB review and acknowledgement.

2) Minimizing Research-Associated Risk

Diligent study safety monitoring will be conducted by the PI and all members of the DSMC throughout the conduct of this study in compliance with the following required elements of MUSC IRB's continuing review process:

1. Tracking and follow-up of participant accrual including withdrawn consents will minimize risk by identifying, disclosing, and mitigating any potentially unknown risk(s) of harm to study participants. These risks are minimal.
2. Timely and appropriate reporting of informed consent process deficiencies, protocol deviations, privacy breaches, conflicts of interest, and/or changes in personnel.
3. Ongoing soliciting, monitoring and appropriate reporting of adverse event activities.
4. Timely and appropriate IRB submission of safety-related documents such as audit reports, sponsor progress reports, ISM reports, and other materials or communications that might impact the safe conduct of this study.
5. Active cooperation with the IRB, ACO, sponsor, and other applicable entities in the event of a random or for-cause internal or external audit.

Institution-Wide Assurances

This protocol will be conducted fully in keeping with the signed MUSC IRB Principal Investigator Statement of Assurance and Department Chair's Statement of Assurance, when submitted to the IRB as a required component of the MUSC IRB Human Research Review Application. An application will be submitted to the MUSC IRB if/when this project is approved and funded by NIH/NINR. Assurances include the following safety-related agreements, signed and dated by the PI.

3) Protecting Confidentiality of Participant Data

Participant Screening and Enrollment. All data from participants screened for the study will be entered into electronic study database. Designated research staff will collect, gather, and enter required data (written informed consent, HIPAA Authorization, medical history and demographics) onto study data forms. Screened patients who do not meet study eligibility will have specific screening data entered into the study database. The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include gender, age, race and reason for exclusion. All dates will be shifted and other Personal Health Information (PHI) will be removed from the study database upon study completion. All data obtained from this study will be used for research purposes only and will comply with Federal HIPAA regulations. Master Screening and Enrollment Logs will be maintained by the PD and will be used to prepare reports on accrual and attrition for the PI and SMC.

Case Report Forms. All proposed study specific case report forms (source documents) for data collection will be designed by the PD in concert with the PI and BS, and transferred by the PD into electronic Case Report Forms (eCRFs) for use in the study's REDCap database. These study specific eCRFs source documents (study logs for correspondence, contact with provider, compensation and other forms such as pre-eligibility screens) will be coded by the participant's unique study ID# for all data collected including study instruments will be maintained in the participant research record and/or their electronic medical record that will be made accessible to study monitors. Completed instruments that require signature on a paper CRF will be scanned and uploaded into the study database to all for remote electronic safety monitoring as well as maintained on file in accordance with MUSC policies and applicable Federal Regulations for the Conduct of Human Participant Research.

Binders. The PD will prepare and maintain a participant-specific binder for each participant containing all non-eCRFs records. A regulatory file will also be maintained to include the IRB-

approved Protocol, original Informed Consent documents, HIPAA forms and other study-related regulatory documents. All paper research records and CRFs will be maintained in a locked file cabinet, stored in a room for research files that is accessible only via a password protected entry system that features security cameras, within the College of Nursing. Access to the research records, study database and PHI's will be restricted to study personnel as approved by the PI and MUSC IRB. As with all studies conducted at MUSC, this study is also eligible for a random audit by MUSC Office of Compliance.

Data Processing. This study will use Research Electronic Data Capture (REDCap) for data capture and management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The study-specific REDCap electronic database will be designed and developed by the PD in concert with the BS. The provision of REDCap is made available through the South Carolina Clinical & Translational Research (SCTR) Institute at MUSC with NIH Grant awards UL1RR029882 and UL1TR000062.

Data Security. Ensuring data security, compliance with 45 CFR 46 and maintaining the integrity of PHI is a top priority. MUSC has Standard Operating Procedures (SOP) to ensure a high level of data security while coordinating electronic and paper data management activities for clinical research trials. The REDCap study database will be hosted in the Biomedical Informatics secure data center at MUSC, a secure environment for data systems and servers on campus, and includes firewall, redundancy, failover capability, backups and extensive security checks. The secure data center has strict access control; only authorized core personnel may access the facility un-escorted. Only authorized users are allowed to connect to the network, and the security of the network is actively monitored. Power and environmental controls have several layers of backups, from interruptible power supplies to alternate and redundant feeds to the local utility company. The REDCap system administrator contributes to the maintenance of institutional disaster recovery and business continuity plans. Load balancers and a highly fault tolerant SAN infrastructure contribute to high availability.

The REDCap system itself has several additional layers of protection including password protection. Access to the data and its security is managed institutionally by sponsored login IDs through a Shibboleth login with an MUSC issued NetID and features a user account management filter that controls who can access the data and to what degree. All personnel must pass an employment background check before being issued an ID. Password complexity, history and expiration standards are implemented at the institutional level. Access to individual REDCap projects and their data is managed by the owner of the project. All transactions are securely delivered to the application using Secure Sockets Layer (SSL – SHA-1 with RSA Encryption; 2048-bits). It is then transmitted internally (behind the firewall) to the database server. All transactions are logged at the server layer (httpd logging), application layers (REDCap logs activity to a database table), and the database layer, using both query and binary logging. This feature provides audit trails for all changes, queries, data exports and reports. MUSC Information security policies are available at: https://mainweb-v.musc.edu/security/policy/

Data Entry. Only MUSC IRB approved study personnel that are authorized to have access to the REDCap study database will be granted password access. Study personnel using computers that are connected to the Internet will directly enter data into the remotely housed database. As such, no electronic study data will be stored on hard drives and/or any portable electronic devices. Additionally, all personnel with access to the database will have current University of Miami CITI training in the

Conduct of Human Subject Protections, and their respective institution's HIPAA and Information Security trainings that are completed annually. Each participant will be assigned a unique study identifier, all PHIs will be masked, and data exports will be limited to the PI, the PD and the BS for generating reports and the conduct of statistical data analysis.

Data Monitoring. Ongoing quality control procedures will be implemented for data collection, storage and processing. The PD will conduct monthly monitoring of the study database and generate a report for the PI to review at team meetings. Standing agenda items for these meetings will include participant recruitment and retention, AE's, protocol deviations, data integrity and overall study conduct. The PD will work to resolve and validate discrepant data. Discrepancies that warrant clarification will be sent to appropriate parties for review and resolution. All data entry and changes made in the study database by authorized study personnel will be automatically logged by REDCap, and provide a transparent visible audit trail for reviewers.

SECTION C.
Procedures for Identifying, Reviewing and Reporting Adverse Events
1) Identifying. Potential minimum risks identified for participants are outlined in the Protection of Human Participants and will also be outlined in the IRB-approved informed consent document. Additional unknown risks may occur and, if so, will be identified through diligent monitoring by the PD and the frontline research team throughout the conduct of this study. During the informed consent process, participants will be advised of the potential minimum risks of participation as identified in the IRB-approved informed consent document and reminded throughout the study that the researchers should be promptly informed about any concerns regarding potential side effects, adverse events, or clinical deterioration. Participants will also be instructed to immediately notify the PI and/or designee of any suspected adverse events, if possible. Throughout the course of study, at each study contact, the researchers will elicit information about experienced AEs and monitor participant progress. The PD will maintain an electronic record of all reported adverse events and notify the PI and GE of all reportable events as they occur. The PD will generate and provide de-identified semi-annual administrative human participant safety reports for the SMC to review participant progress, accrual and attrition rates. Additionally, the BS will generate semi-annual safety reports for the SMC to provide for the monitoring of the frequency of all reported side effects and AEs.
2) Reviewing. Adverse events will be assessed and evaluated by the members of the SMC according to the following MUSC's IRB Adverse Event Reporting Policy http://academicdepartments.musc.edu/research/ori/irb/HRPP/HRPP%20Guide%20Section%204.7:

- Expected/Anticipated—Identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
- Unexpected/Unanticipated—Not identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
- More Prevalent—Occurs more frequently than anticipated or at a higher prevalence than expected.
- Serious—Results in death, is life threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity, cancer, overdose, or causes a congenital anomaly/birth defect.

The relationship of adverse events to study participation will be determined by the DSMC according to the MUSC IRB Adverse Event Reporting Policy:

- Unrelated—There is not a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

- Possibly Related—The adverse event may have been caused by the drug, device, or intervention, however there is insufficient information to determine the likelihood of this possibility.
- Related—There is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

3) Reporting. All reportable AE, SAE and unanticipated problems experienced by participants will be reported to the NIH/NINR and MUSC IRB in compliance with their Adverse Event Reporting Policy requirements, using the IRB's password protected on-line secure server adverse event reporting system. Within 24 hours after a reportable AE, SAE or unanticipated problem has been reported by the participant, it will be initially graded by the PD, forwarded to the study's C for review and approval, and then will be submitted by the PI to MUSC IRB. The Institutional Official(s) will review the event and discuss the report with the IRB Chair and the Director of the Office of Research Integrity. After IRB review and acknowledgement, the PI will further review, and the PD will forward a copy of the reportable AE, SAE or unanticipated problem and IRB acknowledgement letter to the NIH/NINR Program Officer through MUSC's OSRP. The activities will be reported to the NIH/NINR within 72hrs. In addition, all cumulative reportable AE, SAE and unanticipated problems included in the ISM reports will be submitted to the NIH/NINR in the PI's Annual Progress Reports.

4) Examples of Potential Reportable Adverse Events: In accordance with MUSC IRB Adverse Event Reporting Policy, an AE is reportable is it meets all of the following criteria: 1) is unexpected 2) is related and/or possibly related, and 3) is serious and/or suggests that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized. Additionally, per MUSC's policy all participant deaths, protocol deviations, complaints about the research, and breaches of confidentiality are reportable events. From our previous work among this study population, an **example of an AE** would be feeling lightheaded or dizziness while or after performing the yoga breathing exercises. Depending on the severity, the possible steps to be taken include referral to a medical provider, resting in a prone position until the feeling subsides, and/or withdrawing the participant from the study. An **example of an SAE** would be the death of a participant from renal failure, which although would be viewed as unexpected and unrelated to the intervention is nonetheless a reportable serious event. No further steps would be taken except to review, grade and report the event to all applicable agencies. An **example of an unanticipated problem** would be the participant strains his or her neck while performing the yoga breathing. The steps in this case would be to withdraw the participant from the study and invite him or her to restart the study after the strain has resolved. These events and problems will be reported in accordance with the IRB and NIH/NINR policy as noted in Section C.3.

SECTION D. Multi-site Monitoring and Compliance

This is not a multi-site study.

SECTION E. Assessment of External Factors

The PI will conduct a semi-annual assessment of external factors through a review of literature related to new developments in the areas of yoga breathing among older populations, and other approaches that may have an impact on the safety of participants or on the ethics of the study. To determine whether any changes are necessitated to the study protocol, the SMC will review any identified literature or product safety data that may pose as a potential impact to the risk benefit ratio study and/or safety of study participants.

SECTION F. Interim Analysis

Based upon our prior research in this field among this same population and the minimal risk associated with the intervention, there are no stopping rules for this study. Accordingly, interim futility analysis will not be performed. However, the BS and PD will generate semi-annual qualitative interim analysis reports on a) adverse events; and b) data obtained during phone calls and returned end-of-study surveys to understand issues related to the uptake, usability, and adoption of the yoga breathing exercises among this population. We will also evaluate the screening and enrollment procedures, barriers to participation and retention, including, safety, adherence, acceptability, and feedback from the participants.

15.0 Risks to Subjects

The risks associated with this intervention are not considered greater than those that patients would otherwise be exposed to when engaged in an routine physical activity exercise program. Overall, potential risks associated with participation in the study are viewed to be minimal. However, as with all studies, there are inherent risks involved with the conduct of human subject research that gathers Protected Health Information (PHI). Participants will be made aware of these risks during the Informed Consent process. Identified study risks include: Physical discomfort, emotional distress, social wellbeing, Loss of privacy, and randomization.

Physical discomfort. Participants with pre-existing medical conditions that would make increase in physical activity dangerous to their health will be excluded from the study. There may be minor physical discomfort from the increase in physical activity; however, the potential risk to all subjects is minimal. The participants' pain and fatigue scores will be assessed on a weekly basis by the PI, who is a Board-Certified Family Nurse Practitioner, which will allow for further determination of any untoward effects of participation in the physical activity program. The PI will be communicating with the participants via telehealth visits on a weekly basis to allow for further follow-up of any physical issues with the program.

Emotional distress*.* Participants will be asked to provide information about their self-reported pain and fatigue, social isolation, depression and demographic data. These questions pose an anticipated low psychological risk, e.g. for anxiety, if participants appear upset by questions about their health issues, they will be instructed that if they do not wish to answer a question, they can skip it and go to the next question.

Social well-being. There is low potential for adverse social effects in this research study. Through bi-weekly telehealth visits with nurses, participants will have social support during their participation.

Loss of privacy*.* PHI from participants will be gathered and stored electronically on secure and encrypted servers and there are risks associated for the loss of privacy and confidentiality. As well as having a comprehensive DSMP that details data safety, handling, monitoring, storage and security procedures, we will further minimize the potential for loss of confidentiality through the physical separation of participant names from their research record.

All participants will be screened for depression using the PROMIS Emotional Distress-Depression Short Form 8a. If a participant scores in the severe depression category (raw score 33 and above) a referral will be placed to a mental health professional which could result in loss of confidentiality. Additionally, participants that score in the moderate depression category (raw score 23 to 32) further screening for suicidal ideation will take place. If the participant would admit to suicidal ideation at any time during the study, an emergent mental health consult will be placed which could also lead to loss of confidentiality.

Randomization. Participants are being assigned to one of three study groups and treatment programs by chance. Each exercise program may prove to be less or more effective or have more or less or unknown side effects than the other or other available treatments. Participation in the study is completely voluntary and participants may withdraw their consent at any time.

If participants should experience any symptoms during physical activity and medical attention is needed, resource numbers of local healthcare providers and hospital system emergency services are provided to all subjects to access in the same manner they would with any emergency that they encountered. The PI is a board-certified Family Nurse Practitioner and will be available as a resource by telephone during regular business hours. This information (contact resources) is provided in writing to all subjects who choose to consent and enroll in the study.

16.0 Potential Benefits to Subjects or Others

There may be no direct and immediate benefit to the participants from this research study. Participants in the study may accrue the benefit of improved mobility, strength and balance and along with the benefits of the yoga and behavioral activiation, more motivation to be physically active which could improve symptoms of chornic pain and/or fatigue. The benefit to others is that if this program is proven effective, other low-income older adults, might benefit as well from its future implementation.

18.0 Drugs or Devices

This study does not involve the use or storage of any drug product. All investigational supplies and materials are readily commercially available and are not industry regulated. All study supplies (tablets) will be inventoried and stored in a locked cabinet, behind a locked door by the researchers. Study supplies will be dispensed individually to each participants after enrollment and group assignment.

A&D Medical Premium Wireless Blood Pressure Monitor is an FDA approved, Bluetooth blood pressure cuff that will be utilized to collect participants blood pressure and pulse and transmit the data to the “Activate for Life” application.

The “Activate for Life” app is an application that will be available on participants tablets. This app has the ability to receive Bluetooth data from the A&D wireless blood pressure monitor. The app will also allow participants to enter there pain and fatigue levels on a “1-10” scale, ask participants to input their PA and their use of pain medication for the day, and record thoughts on a voice recorded daily diary. This information will transmit from the application to a firewall protected server at MUSC where it will be available to the research team. No medical information will be stored on the app.

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