mHealth Behavioral Cancer Pain Intervention for Medically Underserved Patients

Pro00103527

NCT04175639

Study Protocol and Statistical Analysis Plan

Protocol Version Date: 1/27/2025

Research Abstract

Please type your Research Abstract here:

The Research Abstract should summarize the main points of your study in one paragraph. The following guidelines may help you:

1. Purpose and objective (1-2 sentences)
2. Study activities and population group (2-4 sentences)
3. Data analysis and risk/safety issues (1-2 sentences)

The efficacy of a mobile health (mHealth) behavioral cancer pain intervention designed to decrease pain and disability for breast cancer patients in medically underserved areas has not been investigated. The long-term goal of this work is to use mHealth technologies to facilitate wide-spread implementation of an

efficacious behavioral cancer pain intervention – a non-pharmacological approach to pain management. The proposed project's objective is to demonstrate the efficacy of an innovative mobile health Pain Coping Skills Training (mPCST-Community) designed to meet the needs of breast cancer patients with pain in medically underserved areas. mPCST-Community addresses intervention barriers for patients in medically underserved areas as it is delivered with video-conferencing in the patients' community based oncology clinic by a remote therapist, is extended to the patients' home environment using simple mHealth technology, and is low-literacy adapted. The central hypothesis is that mPCST-Community will result in decreased pain compared to a mHealth education attention control group (mHealth-Ed). The rationale of this proposal is that if mPCST-Community is shown to be efficacious it will rapidly increase intervention access for individuals who receive their oncology care in medically underserved areas and ultimately reduce pain-related suffering. Guided by strong preliminary data, a randomized controlled trial will be used to pursue three specific aims: 1) Test the extent to which the mPCST-Community intervention reduces pain, fatigue, disability, and distress, 2) Examine self-efficacy and pain catastrophizing as mediators through which the mPCST-Community leads to reductions in pain, fatigue, disability, and distress, and 3) To evaluate the cost-effectiveness of mPCST-Community. For Aim 1, based on the study team's extensive work demonstrating the efficacy of in-person pain coping skills training protocols and pilot work showing promise for mPCST-Community, it is expected that mPCST-Community will lead to decreased pain as well as fatigue, disability, and distress compared to mHealth-Ed. For Aim 2, it is expected that the effects of mPCST-Community will be mediated by increased self-efficacy for pain control and decreased pain catastrophizing. For Aim 3, it is expected that mPCST-Community will demonstrate cost-effectiveness as assessed by all-cause medical resource use, participant and therapist time, and health utilities as well as successful overall accrual, high subject retention, and high intervention adherence.

Research Summary

State your primary study objectives

Aim 1: Test the extent to which mPCST-Community reduces breast cancer patients' pain severity (primary outcome), pain interference, fatigue, physical disability, and psychological distress. **Hypothesis:**mPCST-Community will lead to decreases in these pain-related outcomes compared to a Health-Ed control condition.

State your secondary study objectives

Aim 2: Examine mediators through which mPCST-Community leads to benefits. **Hypothesis:**The effects of mPCST-Community on pain severity, pain interference, fatigue, physical disability, and psychological distress will be mediated by increased self-efficacy for pain management and decreased pain catastrophizing.

Aim 3: Evaluate the cost and cost-effectiveness of mPCST-Community. **Hypothesis:** mPCST-Community will be cost-saving or cost effective in terms of its incremental cost per quality-adjusted life-year from a societal perspective, inclusive of healthcare, intervention and patient-time costs. Its sustainability will be further demonstrated by documenting successful accrual, retention, and protocol adherence.

Please select your research summary form:

Standard Research Summary Template

This is the regular (generic) research summary template which is required for all regular applications (unless your protocol fits under the other research summary templates in this category). Use of these instructions is helpful for ensuring that the research summary contains all necessary elements.

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

Guided by extensive prior work, we have designed an innovative mHealth behavioral pain coping skills training (PCST) intervention to reduce pain and disability in cancer patients in medically underserved areas (mPCST-Community). Our prior work has tested PCST protocols through in-person sessions at major medical centers where resources and literacy levels are relatively high. mPCST-Community is different and innovative; it uses mHealth technology (e.g., videoconferencing) to decrease access barriers for patients in medically underserved areas. The protocol is brief (4 sessions) and delivered in the community clinic by a remote well-trained pain therapist. Importantly, this protocol has been carefully adapted for low literacy patients.Beverly Thorn, PhD, a nationally recognized expert in strategies for adapting pain coping interventions to low literacy, medically underserved patients, was instrumental in developing the mPCST-Community protocol. mPCST-Community extends to the patient's daily life through use of a simple mobile application that provides low literacy text/audio protocol summaries, relaxation audio, daily assessment and personalized feedback, and coping messaging.

We propose a randomized controlled trial (RCT) to test the efficacy of the developed mPCST-Community protocol in breast cancer patients with pain receiving cancer care in medically underserved areas (N=190). We have done careful and extensive pilot work to prepare for the proposed trial. Our pilot work (*Journal of Psychosocial Oncology*) was conducted in breast cancer patients with pain in three medically underserved rural community clinics. First, focus group data (3 groups; n=19) were used to further refine the adapted protocol. Second, the mPCST-Community protocol was evaluated in a single-arm trial with 20 patients. We found high feasibility (i.e., recruitment met), low attrition and high adherence (90% completion), and high acceptability. Importantly, impressive and positive pre- to post-intervention changes were found for pain severity (t=-2.52, p=0.01,g_{av}=0.62; 30% change), pain interference (t=-2.62,p=0.01, g_{av}=0.62), and self-efficacy for pain management (t=3.57, p=0.0004, g_{av}=0.98; 30% change).[8]Study specific aims are:

Aim 1: Test the extent to which mPCST-Community reduces breast cancer patients' pain severity (primary outcome), pain interference, fatigue, physical disability, and psychological distress. **Hypothesis:**mPCST-Community will lead to decreases in these pain-related outcomes compared to a Health-Ed control condition.

Aim 2: Examine mediators through which mPCST-Community leads to benefits. **Hypothesis:**The effects of mPCST-Community on pain severity, pain interference, fatigue, physical disability, and psychological distress will be mediated by increased self-efficacy for pain management and decreased pain catastrophizing.

Aim 3: Evaluate the cost and cost-effectiveness of mPCST-Community. **Hypothesis:** mPCST-Community will be cost-saving or cost effective in terms of its incremental cost per quality-adjusted life-year from a societal perspective, inclusive of healthcare, intervention and patient-time costs. Its sustainability will be further demonstrated by documenting successful accrual, retention, and protocol adherence.

Background & Significance

- Should support the scientific aims of the research

B. Significance.*Patients with cancer report pain to be their most distressing and feared symptom.*[9,10]We have shown that higher pain scores in patients with breast as well as lung, prostate, and colorectal cancers (N=4781) are related to higher levels of physical disability, physical symptoms, and distress.[11]Cancer pain is also related to lower overall health-related quality of life, poor physical

functioning, more physical symptoms, higher levels of depression, and increased financial difficulty.[12,13]Higher levels of pain are related to decreased survival time in breast and other cancers.[14,15]***Patients with cancer experience high levels of pain.*** Two meta-analysis have found cancer pain prevalence to be greater than 50%, with over 1/3 of patients reporting moderate to severe pain.[16,17]A population-based study in 11 countries reported > 50% of cancer patients (N=5084) experience moderate-to-severe pain.[18] High pain incidence is noted across the cancer spectrum.[16]***Women diagnosed at each breast cancer stage experience pain challenges due to both the tumor itself and/or treatments.***[19-23]Breast surgeries and lymph node dissection can lead to site related pain and neuropathic pain.[24]Radiology and chemotherapy treatments can result in painful skin lesions, residual plexopathy pain, and neuropathic pain.[25,26]Lymphedema pain is common and related to breast surgeries, axillary lymph node dissection, and radiation.[27]Antihormonal treatment for breast cancer is related to joint pain and arthralgia that can lead to medication nonadherence or discontinuation.[28-32]

Women with breast cancer in medically underserved areas are at a particularly high-risk of persistent pain.[33,34,35,36,37] Medically underserved areas are defined as US regions where there is a relative or absolute deficiency of healthcare resources. Compared to the general population, patients receiving care in medically underserved areas are more likely to be racial minorities and have low literacy levels. Persistent breast cancer survival disparities continue between racial minority women and white women;[38]racial minority women are more likely to experience delays in breast cancer treatment and/or inadequate treatment.[39]These factors contribute to increased pain experience by women with cancer in medically underserved areas. Later stage diagnosis and treatment increases women's risk for both disease-related pain and treatment related pain (e.g., mastectomy vs. lumpectomy). Further, women in medically underserved areas are much more likely to have comorbid health problems (e.g., obesity, arthritis, diabetes) which contribute to increased pain. Empirical work has found that women with breast cancer in medically underserved areas report higher pain severity and pain interference across the cancer spectrum.[33]Research has also found that disparities in breast cancer treatment and symptom burden (i.e., pain) are maintained by several system factors including poor quality care in geographical isolated locations (i.e., medically underserved areas) and disparities in supportive cancer care (e.g., behavioral pain management).[38]Even general behavioral interventions (e.g., weight management, smoking cessation) are lacking in medically underserved area with behavioral cancer pain interventions being almost non-existent.[40]

Behavioral interventions help alleviate cancer pain. Medication management of cancer pain is critical.[41]Yet, due to a number of persistent challenges (e.g., inadequate dosing, side effects, patient beliefs, addiction concerns[42-45]) there is a need for adjunctive pain management strategies. Procedural strategies for cancer pain management have shown some efficacy (e.g., acupuncture, massage, neuromodulation)[46,47]; these strategies are limited by their reliance on a healthcare provider at each event, lack of attention to psychosocial pain factors, and absence of skills training to improve patients' pain self-management. In a review of psychosocial and/or behavioral cancer pain management strategies by Dr. Keefe (Co-I) and colleagues,[48]evidence of efficacy was found for hypnosis, relaxation with imagery and meditation training, cognitive-behavioral approaches, and education. Cognitive behavioral coping skills training to manage pain and enhance self-efficacy was one of the strategies combined with education showed the strongest evidence for decreasing pain.Our group has conducted a meta-analysis of 21 trials of cognitive behavioral cancer pain interventions; 86% of the trials testing the efficacy of imagery (a behavioral skill) led to significant pain reductions, with 65% of the trials reporting an overall pain reduction.[49]Another meta-analysis of 20 studies using cognitive behavioral interventions to decrease pain in breast cancer patients reported a moderate effect size (d=.49), with 69% of patients reporting less pain relative to control groups. Syrjala et al.[50]reported that behavioral techniques (relaxation, imagery) led to significantly decreased pain compared to active and standard care control groups in cancer patients. Importantly, behavioral interventions that are brief (i.e., 3-6 sessions) can be useful for reducing pain and improving quality of life.[51-53]NIH guidelines recommend that behavioral pain interventions be integrated into cancer treatment.

Behavioral cancer pain interventions are minimal to absent in medically underserved areas.[54]To date, these interventions are typically conducted through in-person sessions with well-trained pain therapist at a major medical center. Primary barriers to accessing in-person behavioral interventions include time constraints, transportation difficulties (e.g., availability, parking), and distance from the medical center.[55]Cost factors (e.g., financial, time, physical) also pose intervention access barriers.[56,57]Additional barriers contribute to the absence of behavioral cancer pain intervention for patients in

underserved areas including lack of trained pain therapists at community-based clinics, prohibitive travel to major medical centers, and low literacy levels. Breast cancer patients who reported higher levels of time, effort, and cost barriers to needed treatment reported lower levels of functional and psychological well-being[58]both of which can increase pain and disability.

mHealth could reduce barriers that limit medically underserved patients' access to behavioral interventions.Advances in mobile health (mHealth) technologies provide new opportunities to implement behavioral interventions that are efficacious. mHealth technologies have the ability to decrease critical barriers (e.g., costs, travel, physical burden) that have been identified as limiting access to in-person behavioral cancer pain interventions. Studies examining mHealth strategies to manage chronic medical illnesses (e.g., diabetes) and psychiatric disorders (e.g., post-traumatic stress disorder) have found that mHealth delivery is feasible and acceptable to patients and can improve outcomes.[59-62]mHealth technologies such as electronic diaries, web-based interventions, and text messaging have shown pain benefits.[63-65]However, the reach of these strategies is limited and they have not been adapted for medically underserved areas. Further, though there are hundreds of pain focused mobile applications that could reach medically underserved areas, there is very little evidence that these applications are efficacious in any population, particularly one with unique needs. The critiques of existing pain mobile applications are consistent stating that the apps are often limited to information and symptom monitoring, not linked to scientifically proven concepts for behavioral pain management, not developed by pain management experts, and not empirically supported or tested.[66,67] mPCST-Community has been designed for patients in medically underserved areas and will provide cancer patients with pain a mobile application that addresses each of these stated problems combined with a four session mHealth videoconferencing intervention.

The proposed mHealth Pain Coping Skills Training protocol (mPCST-Community) for patients in medically underserved areas is significant and innovative.We have designed this protocol to reduce pain and disability in cancer patients in medically underserved areas. mPCST-Community is adapted from a Pain Coping Skills Training protocol developed by our team that is typically delivered through in-person sessions, at our tertiary care medical center. Protocol skills have been shown to be effective for decreasing cancer pain[68-70]including including neuropathy[71]and chemotherapy[72,73]pain. The new mPCST-Community protocol combines 4 videoconferencing sessions delivered to the patient in the community clinic by an well-trained therapist at a major medical center. Further, mPCST-Community extends to the patient's daily life through use of a simple mobile application that includes app based behavior change techniques suggested to enhance outcomes.[1,2]Beverly Thorn, PhD, a nationally recognized expert in strategies for adapting and targeting pain coping interventions, has provided extensive input into the mPCST-Community content based on her pioneering work in applying behavioral pain protocols to low literacy, low-income patients in medically underserved areas.

Social Cognitive Theory. mPCST-Community has been designed to specifically exploit four factors that, according to social cognitive theory,[74]strongly influence self-efficacy for pain control. First, mPCST-Community seeks to enhance patients' mastery of pain coping skills by allowing them to practice and receive feedback on skills in their own environment. For instance, after patients learn the pain coping skill of progressive muscle relaxation (PMR) at their first session, they will be encouraged to share their home experience with their therapist by sending a videotext of their environment and experience. The therapist will provide feedback and problem solve around any difficulties (e.g., barking dog) also through videotext. PMR is typically taught and practiced only in a small room setting at the medical center and patients are asked to imagine their home practice setting and describe potential issues/problems that might arise. Second, mPCST-Community will provide patients with multiple vicarious learning(i.e., modeling) experiences for each pain coping skill. Modeling of skills will take place by the therapist in session and through videos, through a character in a video clip, and through other patients' stories. Patients will be able to access the video clips and stories at any time via their smartphone; to increase the salience of vicarious learning, the content has been targeted to women with breast cancer. Third, patients will receive verbal encouragement from the therapist, personalized to the patients' home skills practice experience. For instance, when a patient learns the pain coping skill of activity/rest cycle they will discuss it with their therapist in the video-session and will then video themselves in the space in their home where they tend to overdo an activity (e.g., dishes, yard work) and describe their plan for not overdoing. The therapist will then provide encouragement about their plan. The therapist will be able to help the patient identify a rest location and problem solve around observed environmental obstacles. Finally, mPCST-Community provides opportunities for patients to receive feedback about any negative physiological or psychological initial reactions when practicing skills in their own environment. For example, if a patient feels increased pain or tension when practicing PMR in a certain chair or in a dimly lit room; problem solving can be used to alter environmental cues.

The focus of this application is a new behavioral cancer pain intervention protocol (mPCST-Community) that is designed to use mHealth technology in medically underserved communities to increase patients' self-efficacy for pain control, defined as confidence in their ability to control pain related to disease,[75] and to decrease their maladaptive coping tendencies such as pain catastrophizing, defined as one's tendency to ruminate about pain, magnify pain sensations, and feel helpless when dealing with pain.[76] This project studies the efficacy of a mobile health pain coping skills training (mPCST-Community) protocol for reducing pain in patients with breast cancer who live in medically underserved areas. Our past work suggests that pain in women with breast cancer is more strongly related to negative outcomes (physical symptoms, function, distress) making the reduction of pain particularly salient for this group. This study also examines increased self-efficacy for pain control and decreased pain catastrophizing as potential mediators through which mPCST-Community leads to benefits. Stanton et al.[77] called for focused attention on mediators of efficacious psychosocial interventions for cancer as a necessary step to develop maximally effective interventions. We have shown low levels of self-efficacy for pain control and high pain catastrophizing to be related to negative outcomes in pain patients.[78-80] A small number of studies in other samples with persistent pain (i.e., back pain[81], jaw pain[82]) have shown treatment-related changes in pain self-efficacy and catastrophizing to be mediators of outcomes.

This project will be the first to test the efficacy of mPCST-Community, a novel mHealth behavioral cancer pain intervention designed for patients in medically underserved areas. Before deploying mHealth technologies for delivery of behavioral cancer pain interventions, the efficacy of this approach must be determined. The proposed research is expected to demonstrate that our mHealth protocol decreases cancer pain and disability for patients in medically underserved communities. This study may result in increased implementation of a potent and accessible behavioral cancer pain intervention for cancer patients.Broad implementation of an efficacious mHealth-based intervention could improve overall quality of life[12-15] among patients who face barriers to accessing in-person interventions (e.g., underserved areas, time constraints).

Design & Procedures

- Describe the study, providing details regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

Research Plan.Women with breast cancer(N=190) will be randomly assigned with equal allocation to: 1) mPCST-Community or 2) mHealth-Education. Both conditions (mHealth-Ed) will involve four 50-minute individual sessions conducted over the course of 8 weeks with videoconferencing at the participant's community-based clinic or at the participant's home. Participants in mPCST-Community and mHealth-Ed will receive a smartphone to extend the intervention into their home environment. The study mobile application will provide participants in the mPCST-Community with: a mobile application that provides text and audio of intervention content tailored for low literacy, modeling video-clips, stories from other patients with pain, and other mPCST-Community materials (e.g., relaxation audio). The mPCST-Community participants will also enter daily pain, fatigue, and hassles levels and daily coping skills practice; this data will be used to send personalized messaging encouraging skills use. Innovative components of the mPCST-Community intervention include: new hybrid delivery modality (i.e., videoconferencing in community clinic, smartphone) to make such a protocol accessible to patients in medically underserved communities, adaptation for low-literacy patients, and use of personalized messaging. The therapist delivering the intervention will be at Duke University Medical Center and the participants will be at their community-based clinic. Participants may also choose to complete sessions in their home environment. mHealth-Ed participants will be given smartphones to access education session information, receive cancer education based messaging, and an education app. Participants will complete assessments at baseline, post-intervention, and at a 3- and 6-month post-intervention follow-up.

*mHealth Behavioral Cancer Pain Intervention (mPCST-Community).*Participants will complete 4, 50-minute video-sessions at their community-based clinic; a therapist at Duke will deliver the session. Participants may also choose to complete their 4, 50-minute video-sessions in their home environment. Staff will be present at the community-based clinic to assist. Each site has a private room where the videoconferencing sessions will be conducted; we have used 3 of the proposed sites in our pilot studies and have successfully

set up the videoconferencing systems. mPCST-Community includes a mobile app to extend the intervention into daily life.

The therapist delivering the mHealth behavioral cancer pain intervention will be a doctoral level clinical psychologist. Once the video connection has been established, the patient and therapist will complete a session that mimics an in-person, face-to-face session. mPCST-Community sessions will be scheduled weekly with some flexibility (8 weeks to complete sessions) provided for scheduling conflicts (e.g., sickness, holidays). The content of the mHealth behavioral cancer pain intervention sessions is based on Pain Coping Skills Training (PCST) designed by Dr. Keefe (Co-I). Dr. Somers, along with Drs. Keefe, Shelby, and Thorn, has carefully designed the proposed mHealth protocol choosing particular skills shown to be efficacious in patients with cancer pain; further the protocol has been carefully designed to include content relevant to patients in medically underserved areas. PCST enhances patients ability to cope with their pain by teaching them skills to enhance their ability to manage their pain by changing their behaviors, thoughts, and feelings about pain.[89]Also, based data gathered from focus groups, the intervention protocol has been updated throughout to address fatigue as it relates to pain. We expect that the skills in this protocol will enhance patients' ability (i.e., self-efficacy): a) to use attention diversion techniques to decrease pain and distress, b) manage their pain to engage in activities that will decrease their pain, disability, and distress, and c) to use cognitive restructuring to decrease pain catastrophizing which can result in decreased pain, disability, and distress.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Participants. Participants will be women with a diagnosis of breast cancer within the last three years. Stages I-IV will be included as recently published work suggests increased life expectancy for patients with advanced cancer[87]and significant pain is possible from both the tumor and cancer treatments during this time period.[19-23] Other eligibility criteria are: 1) being ≥18 years old, 2) having a life expectancy of ≥12 months, 3) report experiencing pain on at least 10 days in the last month and rate their pain in the past week as a 4 or greater on a 0-10 scale. The combination of these items assess patients level of persistent pain (in the last month) and pain severity with an accurate recall period (i.e., last week; ≥4). Exclusion criteria include: 1) cognitive impairment as indicated by a baseline Folstein Mini-Mental Status Examination of <25[88] and the Rapid Estimate of Adult Literacy in Medicine, Revised (REALM-R) or through medical chart review indicated by a baseline Folstein Mini-Mental Status of Examination <25 2) brain metastases, 3) presence of a severe psychiatric condition or a psychiatric condition (e.g., suicidal intent) that would contraindicate safe participation in the study as indicated by the medical chart, treating oncologist, or medical/study staff interactions, or 4) current or past (<6 months) engagement in PCST for cancer.

Recruitment. Participants will be recruited from cancer clinics that are part of the Duke Cancer Network (DCN). Each clinic is in a medically underserved area and sites are in mostly rural or highly urban areas of North Carolina, South Carolina, Georgia, and Virginia and has provided a detailed letter of support. These clinics provide oncology care to patients who otherwise would have very limited access to subspecialty cancer care. We will recruit from 8 sites (see Table 2 for site, county consensus, the medically underserved index, primary care physician to patient ratio, annual number of breast cancer patients, and projected annual and total recruitment). Each clinic has staff designated to assist with trial recruitment (see letters of support from site oncologists). During study start-up, the study team will travel to each site to train staff members in procedures. Training may also take place over a videoconferencing platform. Short videos along with written information on study purpose and procedures will be produced and available to clinic staff at each site. Study staff will visit each site at least quarterly and up to twice quarterly. Our team consists of several experienced clinical trials investigators with extensive histories of successful recruitment (Drs. Keefe, Samsa, Reed). Drs. Somers (PI) and Shelby (Co-I) have successfully recruited breast cancer patients to behavioral trials in the DCN clinics. The study team will closely track participant recruitment during the first year of recruitment. If recruitment is not met at 90% overall for Year 1, three of our sites (i.e., Gwinnett, Lexington, Spartanburg) have indicated that they will work with our team to increase recruitment (see letters of support; 40 additional patients annually).

We will use electronic medical records (EMR), tumor registry information, and clinic staff to identify potential patients. The clinical research coordinator will send an email to the treating oncologist to alert them of potential participants. Participating oncologists have agreed to alert the study team if they estimate a potential participant has less than 1-year to live or there is known psychotic disorder, suicidal

intent, or other conditions that would contraindicate safe study. Potential participants will be mailed a letter from their provider and the research study team with information about the study. The letter will let the patient know that a member of the study team will call them to follow-up; an opt out phone number will also be provided. If a potential participant meets study inclusion criteria they will be scheduled for an appointment at their community based clinic with study or clinic staff, or be scheduled for a telephone appointment with study or clinic staff. All participants will continue to receive standard medical care from their medical team.

Subject Recruitment and Compensation

- Describe recruitment procedures, including what method(s) will be used, when the study will be introduced to potential participants and by whom. If any follow-up contact is planned, describe the proposed method and timing. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about how many DUHS participants will be recruited. If participants are to be compensated and/or reimbursed, provide specific prorated amounts to be provided for expenses such as travel and /or lost wages, and/or for inducement to participate.

Potential participants will be provided with written materials describing the study, its purposes, and its requirements. We have done several pilot and large scale trials that include technology based delivery; we have carefully scripted our study introduction content both with verbal communication and written text /picture content. Consent will take place where patients receive their cancer care. Participants will receive $30 for completing each assessment (total = $120).

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Cognitive impairment as indicated by medical chart review, or by a baseline Folstein Mini-Mental Status Examination of <25 and the Rapid Estimate of Adult Literacy in Medicine, Revised (REALM-R) will be assessed. If patient is cognitively impaired, they will be excluded from the study per study protocol.

Study Interventions

- If not already presented in the Design & Procedures section, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i. e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

Presented above.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant individuals, imprisoned persons or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

3. Potential Risks. The primary risks of this study are those associated with confidentiality. There is some risk attendant to confidentiality of self-report data. Two password protected databases will be used for this study to ensure confidentiality. First, a tracking database will be used for recruitment and follow-up. This data will house information related to tracking the participants in the study, such as phone numbers and addresses. No medically sensitive or outcome data will be stored in this database. This database will also track nonparticipants (i.e., those who have declined participation) only to the barest minimum to ensure that they are not contacted again about participation. At the end of the study, all identifiable data of non-participants such as their names will be deleted. Tracking data on participants will be retained for the usual required period. Second, all study data will be stored in a separate password protected RedCap database without any personal identifiers. Data in this database will be derived from patients' direct input into the electronic patient reported outcomes system which is an onlinesurvey system; data entered into this system is stored on a secure server housed behind the DUMC firewall. Only a unique study identification number will link the electronic data to the study data file. The tracking data and study data will be stored in a file on a secure DUMC psychiatry server which can only be accessed by necessary members of the research team. Access to the Duke network requires a password protected, 128-bit encrypted virtual private network connection provided by Cisco systems.

There is also some risk of loss of confidentiality inherent to the use of video conferencing to conduct the study intervention sessions. To protect patient privacy, we will work with Duke's Institutional Review Board and Duke Medicine's Information Security Office (ISO) to implement the most up to date and secure videoconferencing option available at the time of study conception. The study mobile application may also present some risk of loss of confidentiality. Information input by participants into the mobile application is stored in a MySQL database. This is a standard security feature which allows the database to be kept separate from the web server to protect access to the database. In addition, the hard drive of the database machine will be encrypted, which will provide security in case the hard drive is physically compromised.

The PI has completed Duke University Health System Institutional Review Board's online training course: Protecting Research Subjects, as well as human research subjects' protection training and certification through the Collaborative Institutional Training Initiative (CITI) program, both of which address confidentiality.All other individuals involved in this study will be required to complete these courses and ongoing training. The PI, mentor/co-mentor, and collaborators have conducted research in the proposed area and have not encountered participants who experience significant psychological distress as a result of study procedures. In fact, participation in the proposed interventions, particularly PCST-Community, is associated with few negative side effects and potentially multiple benefits to physical health, mood, and quality of life. The proposed significance of study findings outweighs the limited risk.

4. Recruitment and Informed Consent. All recruitment procedures will comply with HIPAA guidelines. The recruitment procedure will be as follows: Potential participants will be identified through electronic medical record review or their medical team. Once a potential participant has been identified, their primary oncologist will be contacted for permission to attempt to recruit the participant for this study. If the oncologist agrees, potential participants will be told about the study by a member of the medical staff and asked if they would be willing to talk with a member of the study team. Potential participants will also be sent a letter through postal mail letting them know that someone will call about the study or meet them at their clinic visit or give them a number to call to completely opt out of any further study activities. Once a potential subject agrees, a member of the study team in the cancer clinic will approach them in person or over the telephone. At this time, the member of the study team will describe the study in detail, provide the patient with consent forms, and offer to answer any questions about the study. Once a patient has consented, they will complete the first study assessment at that time or at a time in the future convenient for them.

5. Potential Benefits and Importance of Information to be Gained.This study has several potential benefits. First, cancer patients with persistent pain randomized to the PCST-Community condition that learn ways to enhance their pain coping strategies may experience significant decreases in pain and disability. Cancer patients randomized to the mHealth-Ed condition may also gain important information about how to manage their pain and other aspects of their disease. Second, if the proposed PCST-Community protocol proves to be efficacious, it could be applicable to a number of patient populations with persistent pain who face challenges similar to breast cancer patients with persistent pain. Third, the proposed model of treatment delivery has the potential to be expanded to intervene on a number of other needs faced by patients with chronic illness (e.g., medication adherence, psychosocial distress, caregiver burden). This PCST-Community protocol model has the potential to dramatically increase access to treatment and improve patient outcomes.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

No cost to the subject.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

Statistical Power & Analyses. The approach to the analysis will utilize repeated measures mixed model analysis of covariance. For simplicity of exposition, this is described with the outcome not as a vector of 4 measurements, but instead as the analysis of a series of one-dimensional difference scores, with each difference score taken relative to the baseline measurement. Model covariates will include baseline score, variables unexpectedly unbalanced between groups at baseline (i.e., to account for potential bias), and variables that may be correlated with the outcome (i.e., to increase precision). Potential covariates include depression, social support, physical activity, medical/demographic variables including cancer treatments, and recruitment site.

Aim 1: Test the extent to which mPCST-Community reduces pain severity (primary outcome), pain interference, fatigue, physical disability, and psychological disability. Demographic, medical characteristics and other potential covariates will be summarized. Focusing on pain severity as an illustration of our analytical methods, we will first describe the pattern of missing data over time by group – paying particular attention to the possibility of differential drop-out. We will then analyze three outcome variables: post-intervention minus baseline addresses the mechanistic hypothesis pertaining to immediate effects of the intervention; 3 months minus baseline addresses the (primary) hypothesis of short-to-medium term effects of the intervention; and 6 months minus baseline addresses the hypothesis of longer-term effects of the intervention. Each hypothesis will be tested using the main effect of study group, adjusting for covariates. We anticipate relatively little missing data for the primary and mechanistic hypotheses – the issue of missing data will be addressed through sensitivity analyses using propensity scoring (which would essentially allow us to "compare likes with likes" even in the presence of differential drop-out).[130]**Statistical power**. For purposes of estimating power, we define pain severity as the primary outcome variable. Using the methods of Cohen, and assuming an effective sample size of 72 per group (i.e., 90 per group minus 20% attrition), an unadjusted analysis has 80% power to detect an effect size of approximately 0.48. This is a moderate effect size which is a reasonable estimate of the minimum clinically important difference in patients with pain and practically important and consistent with what will need to be shown for adoption of the intervention in clinical practice.[131-133] Furth er support for this effect size is gained from our pilot work that has been consistent (within the constraints

imposed by study design and sample size) with an intervention having this level of efficacy.[1] In an unadjusted analysis, the effect size equals the difference between the group means divided by the pooled standard deviation. (Consistent with previous data, this could for example be a difference in mean pain scores of 5.0 vs 4.0;SD= 2.0). Such a power calculation is conservative, as the reduction in degrees of freedom associated with the covariates in an adjusted analysis should have less of an impact than the reduction in the mean squared error associated with those same covariates.

Aim 2: Explore potential mediators (i.e., self-efficacy for pain control, pain catastrophizing) through which mPCST-Community leads to reduction in pain severity, pain interference, fatigue, physical disability, and psychological disability. This hypothesis will be explored, for example, by first fitting a model with intervention group as the primary predictor and self-efficacy as an outcome, and then by fitting a second model with self-efficacy as the primary predictor and pain severity as an outcome. Including intervention group in this latter model also allows us to test an interaction between self-efficacy and intervention group and, thus, assess whether the relationship between self-efficacy and pain severity is consistent across study groups. In contradistinction with the other analyses associated with this aim, the test for interaction is likely to have modest power and thus is considered to be exploratory. The same caveat applies to other interactions – for example, for aim 1 a test of whether the impact of the intervention is consistent across gender or other similarly-defined patient subgroup. This approach to mediator analyses is appropriate given the relative lack of maturity of the science examining interactions within behavioral intervention trials; while this study is designed around main effects, Aim 2 provides adequate new knowledge within the practical constraints of this trial. This approach to mediation analyses is consistent with current analysis of RCTs from the biomedical literature.[134-136]

Aim 3: To evaluate cost, cost-effectiveness and practicality of mPCST-Community.**Analyses.**We will use patient-level data to test for differences between mPCST-Community and the Health-Edu conditions on medical resource use, medical costs and productivity costs. We will use generalized linear models specified using negative binomial error distributions and log links for resource use and gamma error distributions and log links for costs. We will apply mixed-effects linear regression models to test for interactions between study interventions and time on EQ-5D-derived preference weights across the 6-month follow-up period. Baseline resource use and EQ-5D weights will be included as covariates in regression models. For each patient will compute quality-adjusted life-years (QALY) using the trapezoidal rule applied to EQ-5D weights at baseline, post-intervention, 3 months and 6 months. Because the mHealth-Ed control was designed to control for patient contact time and does not represent standard care, accounting for the costs of providing this condition and patient time spent participating would inappropriately offset the costs associated with the mPCST-Community intervention. Therefore, we will modify our calculation of the numerator of incremental cost-effectiveness ratio (ICER) in which we will calculate the difference in mean medical costs and productivity costs between the mPCST-Community and mHealth-Ed control groups then add direct costs of resources required to provide mPCST-Community as well as participant time costs. To compute the difference in QALYs, we will subtract mean QALYs in the mHealth-Ed condition from mean QALYs in the mPCST-Community condition. Then, we will divide the estimated difference in mean costs by the difference in mean QALYs and generate a 95% confidence interval constructed using nonparametric bootstrapping. We then will calculate net health benefits (QALY*λ – Cost, where λ represents maximum willingness to pay per QALY) for each patient, and apply linear regression analysis to evaluate whether intervention and patient baseline characteristics are associated with improved cost-effectiveness. In sensitivity analyses, we will evaluate the impact of: (1) applying various durations of sustained benefit beyond the 6-month follow-up period; (2) excluding productivity gains/costs; and (3) assuming patients could participate in videoconferencing at home. To evaluate practicality and sustainability of PCST-Community, we will assess accrual, participant retention, and intervention protocol adherence.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

This behavioral pain intervention trial carries minimal risk. All patients in the trial will continue their usual care during the course of trial, thus their doctors will provide monitoring of the patients' overall medical status. All research personnel who have direct contact with patients will be trained to observe and report any adverse event to the principal investigator. The principal investigator will report any adverse events to the institutional review board at Duke University within 48 hours. An adverse event is defined as any untoward medical occurrence during the clinical investigation that has a causal relationship to the study protocol. A serious adverse event is defined as any event which results in death, is immediately life threatening, results in persistent or significant disability/incapacity, patient hospitalization, or is serious for

any other reason representing significant hazard. We will also appoint two data safety officers. One data safety officer will be a MD who is not associated with this study. The appointed MD officer will have experience with clinical research and trials and have a thorough understanding of adverse events. The other safety data officer will be a senior investigator who has technology expertise and will have an annual responsibility to evaluate our current mHealth system of assessment and intervention and identify any problems. All adverse events will be reported to Duke's IRB and the data safety officer in real time. All data will be stored on a secure server with multiple backups created regularly. All interactions with study participants will be under the direction of a Licensed Clinical Psychologist (Dr. Somers [PI]). Study investigators and staff for this trial will be taught to monitor for any signs that participants are experiencing high levels of physical or emotional distress that need to be addressed outside the context of this trial. If this is determined to be the case, the PI will work directly with the participant to move forward in a way that is in the best interest of the patient. No participant will be kept in the trial if they are experiencing increased extreme distress. Dr. Somers works directly with Cancer Patient Support and Care at Duke Cancer Institute as a practicing licensed clinical psychologist and as a supervisor to psychology trainees (i.e., advanced graduate students, clinical psychology interns); she is integrated into the psychosocial care program at the Cancer Center and has experience referring cancer patients who are distressed to appropriate psychosocial or psychiatric care within this large team of mental health professionals. She will use the same resources when making referrals for distress participants in this study.

Privacy, Data Storage & Confidentiality

- Complete the Privacy and Confidentiality section of the iRIS submission form.