**Official Title:** Initial Testing of a Mobile App Pain Coping Intervention for Outpatient Oncology Settings (PainPac)

**NCT:** NCT05686122

**Document Date:** 6/3/2024

## Research Summary

### State your primary study objectives

**Aim 1:** Test whether PainPac is feasible (primary aim and outcome), low burden, engaging, and acceptable (secondary outcomes for primary aim).

**Hypothesis:** PainPac will have high feasibility (accrual [N=60]), attrition [<25%], adherence [>75%]), as well as low patient burden (physical, emotional, financial), high engagement (PainPac log in and coping skills practice >3 times/week), and high acceptability (>80% satisfaction) that is at least comparable to PCST-Video.

### State your secondary study objectives

**Aim 2:** Examine the impact of PainPac on pain severity, pain interference, pain self-efficacy, emotional distress, and quality of life (secondary outcomes for secondary aim).
**Hypothesis:** PainPac will demonstrate improvements in pain-related outcomes (e.g., self-efficacy, emotional distress) and quality of life for patients that are at least equivalent to the improvements experienced by PCST-Video participants.

**Aim 3:** Gather quantitative and qualitative post-treatment data on patients' preferences, confidence in using technology, barriers, and facilitators regarding PainPac to update and optimize PainPac for a future large randomized clinical effectiveness trial.
**Hypothesis:** This data will lead to optimization of PainPac to improve pain-related outcomes in cancer patients.

### 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

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**Aim 3:** Gather quantitative and qualitative post-treatment data on patients' preferences, confidence in using technology, barriers, and facilitators regarding PainPac to update and optimize PainPac for a future large randomized clinical effectiveness trial.
**Hypothesis:** This data will lead to optimization of PainPac to improve pain-related outcomes in cancer patients.

This work has the potential to create a paradigm shift for behavioral pain intervention practice. This project will be one of the first to demonstrate that a theory-based standalone mobile app (PainPac) with wide implementation potential is feasible and beneficial to cancer patients. PainPac may drastically increase the availability of behavioral pain interventions. PainPac may be particularly likely to benefit patients in low-resourced areas with no or limited access to trained behavioral pain specialists and patients unable to engage in interventions during business hours. If PainPac is feasible and shows promise for benefits, this work will result in a larger RCT (R01) optimizing and testing the effectiveness of PainPac.

## Background & Significance

- Should support the scientific aims of the research

**SIGNIFICANCE.** Pain is one of the most common, interfering and distressing symptoms for patients with cancer.[1,2] Pain has been identified as a significant problem that does not improve with time in cancer patients.[3] A meta-analysis of studies (N=52) reported that more than half of patients with cancer report pain, with over 1/3 of patients reporting moderate to severe pain.[4] Studies have routinely found that cancer patients report high levels of pain that are distressing and persistent across the cancer spectrum.[4-6] Research has shown cancer patients with pain are more likely to experience psychological distress, physical disability, physical symptoms, lower quality of life, and increased financial difficulty than patients without pain.[3,5-9]

Decades of work have shown behavioral pain interventions are efficacious for cancer-related pain.[10-12] Teaching patients cognitive and behavioral strategies (i.e., relaxation, activity pacing, cognitive restructuring) for managing psychosocial factors related to pain can lead to decreased pain severity, increased pain coping self-efficacy, and decreased psychological distress.[13] These interventions are traditionally delivered in person at a medical center by a trained masters or doctoral level behavioral pain specialists over 8-12 weekly sessions, all of which presents system, provider, and patient access barriers (e.g., availability, time, cost, burden). Our group and others have shown brief behavioral pain interventions (3-6 sessions) reduce pain and improve aspects of quality of life.

We have developed and tested numerous cognitive behavioral pain coping skills training protocols that enhance the abilities of patients with chronic disease to manage their pain, leading to improvements in pain and other important pain-related outcomes.[14,17-25] Our group has extended this research by designing and testing pain coping skills protocols that use mobile health (mHealth) technology for cancer patients with pain.[26-28] These protocols focus on decreasing patient burden and increasing patient accessibility and engagement by creating shorter protocols (4-6 sessions), using hybrid in person and videoconferencing methods, and using mHealth strategies (e.g., websites, smartphones, text messaging, real-time data collection with personalized feedback) to reduce intervention barriers (e.g., in person sessions).[24,27-29] These mHealth pain coping skills interventions have shown high patient acceptability, feasibility, and efficacy.[24,27-30] We published a large trial (N=178) showing a 4 session behavioral cancer pain intervention delivered with home-based videoconferencing is just as efficacious as a protocol delivered in person at the medical center.28 Importantly, the videoconferencing protocol showed significantly greater feasibility (i.e., attrition [16% vs. 30%], adherence) than the in person protocol.

Use of mHealth strategies and videoconference delivered behavioral pain interventions can improve patient access and decrease patient burden. However, videoconference delivered protocols retain some access barriers for many patients due to the therapist-led delivery model and resources required (e.g., expert pain therapist, scheduled appointments). Much more is needed to improve access for the greater than 22 million cancer survivors expected over the next 10 years.[31,32] Developing additional behavioral approaches to cancer pain management is critical. A standalone behavioral cancer pain mobile application that uses efficacious cognitive and behavioral pain management strategies is likely to dramatically increase access to such interventions. A standalone app would eliminate the need for a therapist, be available to the patient at all times, and be easily accessible on a smartphone or tablet. Mobile apps also offer increased options for real-time personalization (e.g., messaging based on daily pain assessment) which can increase engagement and improve overall outcomes.

We have developed a mobile application – PainPac – that has been used only as an adjunct to in person and videoconferencing interventions. PainPac is a comprehensive mobile app program that provides patients four coping skills modules of efficacious cognitive-behavioral theory (CBT) based pain

management strategies (i.e., relaxation, activity pacing, cognitive restructuring). PainPac is a downloadable app available through iOS or Android. PainPac has been designed using information from three decades of research applying cognitive- behavioral pain management strategies to patients with chronic diseases including cancer.[33-37] It uses Social Cognitive Theory[38] to promote behaviors to improve self-efficacy for pain management and, in turn, improve pain and pain-related quality of life indices.[39] PainPac's therapeutic elements are modeled after efficacious cognitive- behavioral interventions designed and tested by our group of behavioral pain experts (PI: Kelleher, Co-I: Somers, Mentor: Francis Keefe, PhD). Further, Drs. Kelleher and Somers completed a qualitative project with 33 national stakeholder interviews (e.g., policy makers, organization leaders, providers) that generated data to inform PainPac (see Preliminary Data); this is expected to improve our ability to generalize PainPac to settings outside of Duke.[40] Importantly, PainPac's content is extended to patients in their daily life through interactive components like text messaging to improve skills engagement. Daily assessment of pain and skills practice will inform personalized messaging to further promote engagement. Finally, an engagement tool based on a reward system will be used for skills use engagement. We are currently using it as an adjunct to a videoconferencing intervention in two NIH funded trials (1R21CA235083, R01CA237892); we have not tested it as a standalone intervention.

PainPac is innovative as it is designed to be implemented through automated, electronic submission to patients via text, email, and/or MyChart when a patient reports pain at $\geq$4/10 at a clinical oncology appointment. PainPac has been carefully designed by our expert team of behavioral pain clinical scientists, a healthcare and research mobile app firm, and our institutional technology teams (see letter of support from Matthew Roman, Chief Digital Strategy Officer at Duke). PainPac is expected to be beneficial to patients as a standalone intervention for the following reasons. PainPac has been designed to exploit three factors that, according to Social Cognitive Theory,[38] strongly influence self-efficacy for pain control. First, PainPac enhances patients' mastery of pain coping skills by allowing them to access the intervention, practice skills, and receive encouragement on their own time, in their own environment, when they need it. Patients learn skills in short sessions (8 min) and receive daily prompts to apply the skills based on their symptom report (e.g., pain of 6/10 prompts a message to practice relaxation) – in this way patients are also getting what they need, not a static protocol. With traditional models, skill mastery can be difficult as patients are taught at the medical center and asked to go home and remember to practice, with assessment only at their next appointment and little personalization. Second, PainPac provides vicarious learning (i.e., modeling) experiences for each coping skill. Skills modeling takes place through videos and patient stories. Patients can access content any time via their smartphone; to increase salience of vicarious learning, the content has been targeted to cancer patients with pain. Third, patients will receive encouragement or corrective feedback personalized to their skills practice and symptom report (e.g., your pain is higher than normal, try practicing a skill that has worked for you in the past). These prompts are intended to provide feedback for patients that is psychoeducational and lends to a better mastery of self-management of pain.

A technology-based mobile application like we are proposing has the potential to drastically advance cancer patient behavioral pain management access. There is a time sensitive and critical need to optimize the impact of modern technology-based behavioral pain interventions to reach the growing number of cancer patients in the US. PainPac has been used only as an adjunct to our in person and videoconferencing interventions and the next step in this line of work is to test PainPac as a standalone intervention. This work could create a paradigm shift for behavioral pain intervention practice. If PainPac is feasible and acceptable to patients and shows promise for benefits, PainPac has the potential to drastically increase the availability of behavioral cancer pain interventions and lead to improved pain management for a greater number of cancer patients with pain.

## 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 and Design.** We will use a pilot RCT to examine PainPac feasibility (primary aim and outcome), patient burden, engagement, acceptability, and initial pain-related outcomes, compared to a therapist led videoconference delivered behavioral pain intervention (PCST-Video) in colorectal cancer patients with pain (N=60). We will use quantitative and qualitative data to optimize PainPac. Participants will complete assessments at pre-treatment (A1), post-treatment (A2; 4 weeks post-A1), and 1 month follow-up (A3; 1 month post-A2) (months 5-22). Assessment contents can be found in the attached document, Data Dictionary, and will be distributed to both study groups. These assessments contain items that will be used to assess Aim 2 for both study groups. The pain management strategies are relevant and efficacious across cancer types. Due to the pilot nature of this work, we will enroll an opportunity sample of colorectal cancer patients. Dr. Kelleher (PI) has tested behavioral symptom management protocols in colorectal cancer patients and has an established relationship with Dr. Uronis (Co-I) and the GI cancer clinic teams, all of which allows for an efficient start up. Further, colorectal cancer is associated with significant pain, impacts men and women, and spans a large age range, making it a good population for this early work. The preliminary work for PainPac has been in cancer patients including breast, prostate, lung, and stem cell transplant patients. If PainPac is feasible and shows promise, this project will lead to effectiveness testing in diverse cancer patients.

**Participants and Recruitment.** Participants will include (N=60) colorectal cancer patients at the Duke Cancer Institute (DCI) that report pain $\geq$4 at a clinical oncology appointment. Standard care is to record a 0=no pain to 10=worst imaginable score at every clinic appointment and pain $\geq$4 represents clinically significant pain and allows for pre- to post clinically significant change.[46,47] Patients' pain will be re-assessed at enrollment to confirm eligibility. Other eligibility criteria: 1) $\geq$18 years and 2) stage I-IV colorectal cancer diagnosis <2 years. Exclusion criteria: 1) cognitive impairment, 2) brain metastases, 3) severe psychiatric condition (e.g., psychosis) that would contraindicate safe participation, or 4) participation in behavioral pain management in the past 6 months.

*Recruitment (months 4-18).* Dr. Steven Patierno, Deputy Director of DCI, and Dr. Hope Uronis, oncologist and Co-I, will assist with recruitment. In 2021, there were 1,457 unique patients with colorectal cancer seen at DCI. This suggests more than adequate numbers to complete the proposed work. We will use our established screening procedures that use electronic medical records (EMR) to identify eligible patients and the same Duke IRB-approved, direct-to-patient recruitment method that has resulted in high rates of enrollment in our previous work. Under a HIPAA waiver, staff will use DEDUCE to query the Duke EMR and identify potential participants. After chart review to verify eligibility, staff will mail patients a study brochure and introductory letter. The letter includes a number to call if the patient is interested (or to opt out) and explains that a staff member will contact them soon. All patients who meet eligibility criteria will be contacted unless they opt out. If interested and eligible, patients will complete electronic consent. We have successfully recruited for many trials using this well-developed EMR-based system and remote, direct-to-patient approach.

**Randomization.** Following consent and baseline assessment, patients will be randomized with equal allocation to: 1) a mobile app behavioral cancer pain intervention (PainPac) or 2) a therapist led videoconference delivered behavioral cancer pain intervention (PCST-Video). For patients randomized to PainPac, eligibility will result in electronic push of study information to the patient through MyChart, email, and/or text, and research staff will confirm app download. All participants will continue to receive standard care from their medical team. No participant will be asked to change pain management strategies. Data from 2021 suggests the majority of Americans (85%) own a smartphone,[48] and similar statistics are reported in cancer patients.49,50 Participants who do not have a smartphone will be loaned one with a data plan to access the PainPac app or PCST-Video sessions. Participants will receive instructions for PainPac or PCST-Video technology, handouts with FAQs and troubleshooting strategies, and contact information for the study team and tech support. Therapists and staff will check in with participants regarding technology usability and tech assistance will be available within 24 hours.

**PainPac.** PainPac is a patient-focused intervention developed using cognitive-behavioral theory and empirically supported strategies to enhance patients' ability to manage their pain. Dr. Francis Keefe (mentor to Drs. Kelleher and Somers) first developed and tested Pain Coping Skills Training (PCST) intervention protocols for patients with arthritis;[45,51] he has conducted many trials demonstrating the efficacy of these protocols. Drs. Kelleher and Somers have applied their experiences working with Dr. Keefe to work with cancer patients with pain, and have developed and tested PCST interventions for cancer patients and focused on making them more accessible.[24,26] PainPac is a logical extension of this work and expected to be an efficacious and innovative option for a highly scalable, implementable, and efficacious behavioral pain management intervention for patients with cancer. PainPac is a mobile app available to patients on a smartphone or tablet. PainPac uses Social Cognitive Theory to promote behaviors to improve pain, self-efficacy for pain management, and pain-related quality of life indices. It also uses real-time data to personalize the intervention and messaging to participants. PainPac contains 4 modules, each including a skill that has shown efficacy for reducing pain in patients with cancer. The 4 skills modules are: 1) progressive muscle relaxation (PMR), 2) imagery relaxation, 3) activity rest cycling and pleasant activity planning, and 4) cognitive restructuring. Patients are prompted to complete one module each week for 4 weeks; each module requires patients to attend to content for 8 minutes and includes text, video, and audio presentation of skill rationale and expected outcomes, skill modeling and tips for daily use, and a patient story about skill use. The first 3 minutes include a rationale for the pain coping skill and expected outcomes of skill mastery and use delivered through audio with text on screen. The next 3 minutes include video with skill modeling and tips for use/practice. The final 2 minutes include a patient story about their experiences (challenges/benefits) with the skill. Each module has complementary content designed to lead to skills practice and mastery. For example, the PMR module has PMR audio clips for full (15min), medium (5min), and short (2min) practice. Importantly, the app also has interactive components to improve coping skills engagement. App messaging includes: 4/week coping messages encouraging practice; daily assessment of pain and skills use that informs personalized messaging to further promote engagement; reminders for skills practice / module completion. PainPac includes an engagement tool with rewards based on completion of modules, assessments, and skills practice. Pattern Health (Durham, NC) specializes in patient-centered apps for medical research with expertise in patient engagement. Pattern Health has a portfolio of funded work with NIH researchers and an established relationship with the study team and Duke, and will be contracted for this study.

**Videoconference Delivered Pain Coping Skills Training (PCST-Video).** Participants randomized to PCST- Video will receive 4 behavioral cancer pain intervention sessions delivered by videoconferencing by

a pain therapist in the medical center to the patient in their natural environment (e.g., home). Sessions will be scheduled weekly for 45-60 min and mimic in person sessions. In rare circumstances when the participant is not able to connect via videoconferencing, the PCST-Video sessions can be delivered via phone. This is a backup option that will rarely if ever be used due to extenuating circumstances. PCST-Video session content is based on Pain Coping Skills Training (PCST) designed by Dr. Francis Keefe (mentor to Drs. Kelleher and Somers) and matches the PainPac skills modules described above. PCST-Video participants will complete assessments at the same intervals as PainPac participants. Interventionist Training (months 2-4). PCST-Video will be delivered by a masters or doctoral level psychologist with experience delivering behavioral pain interventions. Drs. Kelleher and Somers will provide training and therapists will be certified (>90% ratings of competence and protocol adherence[52]) to deliver the intervention. Therapists will follow a manualized protocol; treatment strategies will be taught through didactic instruction, audio-/video-recorded illustration from model cases, and role-play of common scenarios. Sessions will be recorded and reviewed in supervision by Dr. Kelleher. Procedures to Ensure Consistency of Treatment. 1) The therapist will follow a manual; 2) Weekly supervision will occur; 3) Session recordings will be reviewed and feedback provided; and 4) Ratings of treatment adherence and competence will be conducted. Treatment Adherence and Therapist Competence.[52] Ratings of protocol adherence will be made by Drs. Kelleher and Somers. Protocol adherence criteria will be developed for each session with satisfactory adherence ≥90% on the rating scale. Ratings of therapists' competence52 will be used to evaluate 20% of PCST-Video sessions.[52]

**Selection of Subjects**

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

**Participants and Recruitment.** Participants will include (N=60) colorectal cancer patients at the Duke Cancer Institute (DCI) that report pain ≥4 at a clinical oncology appointment. Standard care is to record a 0=no pain to 10=worst imaginable score at every clinic appointment and pain ≥4 represents clinically significant pain and allows for pre- to post clinically significant change. Patients' pain will be re-assessed at enrollment to confirm eligibility. Other eligibility criteria: 1) ≥18 years and 2) stage I-IV colorectal cancer diagnosis <2 years. Exclusion criteria: 1) cognitive impairment, 2) brain metastases, 3) severe psychiatric condition (e.g., psychosis) that would contraindicate safe participation, or 4) participation in behavioral pain management in the past 6 months.

*Recruitment (months 4-18).* Dr. Steven Patierno, Deputy Director of DCI, and Dr. Hope Uronis, oncologist and Co-I, will assist with recruitment. In 2021, there were 1,457 unique patients with colorectal cancer seen at DCI. This suggests more than adequate numbers to complete the proposed work. We will use our established screening procedures that use electronic medical records (EMR) to identify eligible patients and the same Duke IRB-approved, direct-to-patient recruitment method that has resulted in high rates of enrollment in our previous work. Under a HIPAA waiver, staff will use DEDUCE to query the Duke EMR and identify potential participants. After chart review to verify eligibility, staff will mail patients a study brochure and introductory letter. The letter includes a number to call if the patient is interested (or to opt out) and explains that a staff member will contact them soon. All patients who meet eligibility criteria will be contacted unless they opt out. If interested and eligible, patients will complete electronic consent. We have successfully recruited for many trials using this well-developed EMR-based system and remote, direct-to-patient approach.

**Subject Recruitment and Compensation**

- Describe recruitment procedures, including who will introduce the study to potential subjects. 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 approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

We will use a pilot RCT to examine PainPac feasibility (primary aim), patient burden, engagement, acceptability, and initial pain-related outcomes, compared to a therapist led videoconference delivered behavioral pain intervention (PCST-Video), in patients with colorectal cancer and pain. This study will be conducted at the Duke Cancer Institute (DCI) and involve 60 colorectal cancer patients with pain. Dr. Steven Patierno, Deputy Director of the Duke Cancer Institute, and Dr. Hope Uronis, GI oncologist physician champion and Co-Investigator, will work closely with Dr. Kelleher and the study team to assist

with recruitment. Drs. Patierno and Uronis are committed to this work; Dr. Kelleher has a history of support from both Drs. Patierno and Uronis, and has worked closely with Dr. Uronis on past trials and successfully recruited cancer patients with pain. All recruitment procedures comply with HIPAA guidelines and will receive approval from the Duke University Health System (DUHS) institutional review board (IRB). During our most active phase of recruitment, we will recruit approximately 12-18 patients per quarter (4-6 patients/month) over the course of 15 months (N=60) of this two-year R21 project.

Patient participants will be recruited through our well-developed recruitment system that uses linked electronic medical records at Duke University Medical Center (DUMC) to identify patients who meet study criteria. We will use the same Duke IRB-approved, direct-to-patient recruitment method that has resulted in high rates of enrollment in our group's previous work, including PainPac preliminary work and trials with patients with colorectal cancer. Under a HIPAA waiver, study staff will use DEDUCE to query the Duke electronic medical records (EMR) and identify potential participants. After a careful chart review to verify initial eligibility (e.g., ≥18 years, colorectal cancer diagnosis, stage I-IV, in the last 2 years), study staff will mail potential participants a study brochure and introductory letter signed by the PI. The letter will state that the patient may be eligible to participate in a research study evaluating a mobile app behavioral cancer pain intervention for patients with cancer and pain. The letter includes a number to call if the patient is interested in learning more about the study (or would like to opt out) and explains that a study staff member will contact them about the study. Patients will then be called by highly trained study staff to assess interest. All patients who meet eligibility criteria will be contacted *unless they opt out*. Consistent with Duke's direct-to-patient recruitment guidelines, we will only attempt to contact patients a maximum of three times if we are unable to reach them. If a patient is interested when contact is made with a study team member, they will be provided with information about the study, its purposes, requirements, and time commitment. Interested patients will complete a scripted telephone screening (e.g., BPI pain severity) compliant with DUHS IRB policies to confirm full eligibility. Those who do not pass the telephone screening but ask for resources will be provided with a list of free resources available through the Duke Cancer Patient Support Program (e.g., financial support, individual and couple counseling). Eligible patients who wish to enroll in the study will complete an electronic consent form; a member of the study team will provide private consent and answer any questions that the potential participant may have. Those who do not have access to the internet for completing the electronic consent form will be mailed a paper copy. This remote, direct-to-patient recruitment approach has allowed us to efficiently reach more patients while reducing numerous obstacles encountered with methods that require physician time and clinic resources. We have successfully recruited for many trials using this well-developed recruitment system.

Participants will complete assessments at pre-treatment (A1), post-treatment (A2; 4 weeks post-A1), and 1 month follow-up (A3; 1 month post-A2) (months 5-22). Participants will receive $30 for each assessment (totaling up to $90 for all 3).

**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?

If patient is cognitively impaired, they will be excluded from the study per study protocol.

**Study Interventions**

- If not already presented in #4 above, 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.

Study interventions presented in #4 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?

**Potential Risks**
In the proposed study, the potential risks to participants are minimal and rare. The potential risks are associated with (1) confidentiality related to the use of smartphones and a mobile app, and self-report data, and (2) potential emotional upset due to questioning about thoughts, feelings, and personal/family history of cancer when completing intervention sessions and assessments. First, breach of confidentiality is a possible risk. This will be clearly stated in the consent form. All efforts will be made to maintain confidentiality. Participants' data and research records will be carefully stored (See protections against risk). Second, participants will be asked about their thoughts and feelings about their cancer, pain, and symptoms; thus, it is possible they may experience distress. The psychological risk associated with answering questions is expected to be minimal. Although some participants may find certain questions or topics to be upsetting, heightened awareness of existing psychosocial and practical needs may be the first step in resolving these concerns. The recruitment letter will clearly acknowledge the voluntary nature of participation and patients will have the ability to decline further contact from study personnel at any time (i.e., to opt out). Participants will be fully informed about the study during the informed consent process and instructed to decline to answer any question or to discuss any issues they find troubling. If a participant reports significant distress during study participation, the study team will consult with Drs. Kelleher and Somers (licensed clinical psychologists). If the participant requires additional treatment, we will initiate the appropriate referral. Out team has extensive experience conducting psychosocial intervention trials with patients with cancer and have not encountered significant psychological distress caused by study participation. Moreover, patients with cancer often report benefits from participating in psychosocial research. Thus, the risk of psychological distress is minimal and these safeguards should be adequate.

**Adequacy of Protection Against Risks**
**a. Informed consent and assent.** Recruitment will take place through the Duke Cancer Institute (DCI), an NCI-designated Comprehensive Cancer Center. Recruitment procedures will receive Institutional Review Board (IRB) approval and comply with HIPAA regulations. This study will follow the same recruitment procedures used in previous RCTs conducted by our team with cancer patients, including colorectal cancer patients, and including multiple federally-funded projects conducted by the Duke Pain Prevention and Treatment Research Program. In March of 2019, Duke implemented a revised Recruitment and Engagement Policy that allows Duke researchers to utilize "direct-to-patient" or "cold contacting" methods. Rather than requiring physician approval before approaching potential participants, Duke researchers can use IRB-approved methods of direct contact. The Duke Notice of Privacy Practices informs all patients that Duke is an "opt-out" institution. That is, patients' medical records may be reviewed for research purposes, and patients may be contacted about research unless they "opt-out" of such contacts. This policy change was largely driven by respect for patients' autonomy (i.e., empowering patients to choose whether to participate in research), need for increased patient awareness of research opportunities, and research demonstrating "op-out" methods result in stronger recruitment rates and more representative study samples.

Under a HIPAA waiver, potentially eligible patients will be identified by study staff using the Duke Enterprise Data Unified Content Explorer (DEDUCE) to query the Duke Electronic Medical Record (EMR) on a weekly basis. After a careful chart review to verify initial eligibility (e.g., age $\geq$ 18 years, English speaking, stage I-IV colorectal cancer diagnosis, pain score of 4 or greater at a Duke clinical oncology appointment), study staff will mail potential participants a study brochure and introductory letter signed by the Principal Investigator. The letter explains that the patient may be eligible to participate in a research study evaluating a mobile app behavioral cancer pain intervention for patients with cancer and pain. The letter includes a number to call if the patient is interested in learning more about the study (or would like to opt out) and explains that a study staff member will contact them in around five days to discuss the study. Patients will then be called by highly trained study staff to assess interest. All patients who meet eligibility criteria will be contacted *unless they opt out*. Consistent with Duke's direct-to-patient

recruitment guidelines, we will only attempt to contact patients a maximum of three times if we are unable to reach them. If a patient is interested when contact is made with a study team member, they will be provided with information about the study, its purposes, requirements, and time commitment. Interested patients will complete a scripted telephone screening (e.g., symptom ratings) compliant with DUHS IRB policies to confirm full eligibility. Those who do not pass the telephone screening but ask for resources will be provided with a list of free resources available through the Duke Cancer Patient Support Program (e.g., financial support, individual and couple counseling). Eligible patients who wish to enroll in the study will complete electronic consent using REDCap. Those who do not have access to the internet for completing the electronic consent form will be mailed a paper copy. A member of the study team will provide private consent and answer any questions that the potential participant may have. This remote, direct-to-patient recruitment approach has allowed us to efficiently reach more patients while reducing numerous obstacles encountered with methods that require physician time and clinic resources. We have successfully recruited for many trials using this well-developed recruitment system.

**b. Protections against risk.** Risks associated with the proposed study are low and not expected, but nonetheless will be carefully monitored. The study investigators, including Drs. Kelleher (PI) and Somers (Co-I), both licensed clinical psychologists, and Dr. Uronis (Co-I), medical oncologist, and the study team will take all precautions possible to avoid and minimize potential risks. The consent form will address all possible risks. Should any of these occur, appropriate emergency care will be provided. The proposed significance of study findings outweighs this risk. Here we detail all procedures for protecting against or minimizing potential risks.

*Confidentiality*. Breach of confidentiality will be a potential risk noted in the consent documents and verbally discussed with the patients during recruitment. Protection of confidentiality is a central priority. All efforts will be made for confidentiality to be maintained by using study ID numbers to identify participants' research records and by having a limited number of individuals who have access to identifying information. As noted, participants' data and research records will be protected using subject identification numbers. A document linking participant names to subject identification numbers will be stored separately from data and research records in a password-protected database. All paper research records (e.g., paper consent documents) will be kept in a locked file cabinet in a locked office. Electronic data files (e.g., audio recordings of sessions) will be stored on an Office of Information Technology (OIT) secured DUMC network drive. This drive will be backed up and secured by the OIT department on a daily basis. Only approved study staff will have access to the research records. There is some risk of loss of confidentiality inherent to the use of videoconferencing to conduct the PCST-Video intervention sessions. To protect patient privacy, we will use Zoom videoconferencing, which has standard internationally-recognized and accepted encryption algorithms. Zoom meetings will have end-to-end encryption (E2EE). In a meeting with E2EE enabled, no one except each participant—not even Zoom's servers—has access to the encryption keys being used to encrypt the meeting. No recording will be conducted within Zoom. Audio-recording of intervention sessions will be conducted using Voice Recorder on the study teams' encrypted Duke-issued and maintained laptops. Audio-recordings will be saved to the DUMC server and deleted from the laptop. All audio-recordings will be deleted at the end of the study. All study staff will be required to complete Duke University Health System Institutional Review Board's online training course (i.e., 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. The anticipated significance of the study results and likely benefits to participants outweigh the minimal risks.

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. Identifying information will be kept separate from research records. 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 online survey 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. Patient data that goes into the mobile behavioral pain application (PainPac) will only be identified with a number and the app is designed so that data, like self-report data, is stored on a secure server housed behind the DUMC firewall. 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.

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 risks associated with the proposed study are low. The PI and investigative team have conducted research in the proposed area and have not encountered medical emergencies or significant

psychological distress caused by study procedures. In fact, participation in the proposed study procedures and intervention 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.

*Smartphone Security Measures*. Smartphones used for this study will be configured for minimal use necessary for the purpose of the study and will not be used for personal use by staff or study participants. Specifically, the following steps will be taken: 1) Study staff will keep the operating system on the most current version. 2) We will enable encryption on the device and verify that data protection is enabled, set "require passcode" to immediately, and enable erase data to "automatically erase the device" after 10 failed passcode attempts. 3) We will set Auto-Lock. 4) Study staff will use Restrictions to restrict any unnecessary access including changing account settings. 5) We will reset smartphones between use for different participants. 6) At end of device life, we will send the device to Duke Procurement Surplus & Salvage for secure destruction. Study participants will have the option to use a Duke Health study smartphone or their personal smartphone. The study mobile application will be made available to participants regardless of whether they use a study smartphone or their personal smartphone.

*Mobile App Data Storage and Security*. Pattern Health (Durham, NC) is a digital health company specializing in patient-centered web and mobile products for clinical and medical research and health data tracking and analysis, with expertise working with wireless devices and improving patient engagement. Pattern Health has an established relationship with the PI and study team, as well as other researchers at Duke, the Duke Medicine Information Security Office (ISO), Duke Health Technology Services (DHTS), and the Duke Digital Strategy Office. Pattern Health is contracted for the implementation of a mobile app for use in the current study, which is similar to the mobile app developed and tested *adjunctively* in Dr. Kelleher's prior work. App data 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. Duke ISO, DHTS, and the Duke Digital Strategy Office will review and approve Pattern Health's documents outlining their data collection process, and data storage and security for the proposed study; these Duke entities previously approved Pattern Health's data collection, storage and security for Dr. Kelleher's ACS RSG and previous NIH R21 projects, and these procedures will be the same for the proposed R21 project.

*Emotional Upset*. The risk of emotional upset associated with intervention sessions and assessments is rare, and all interactions with study participants will be under the direction of PI Dr. Kelleher, a licensed clinical psychologist. To address risks related to the possibility of psychological distress, participants will have the option of withdrawing from the study without loss of benefit. Interventionists and study staff in this trial will have experience working with distressed patients with chronic disease. They will be trained, specifically in the context of this trial, to monitor participants' psychological status and 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. Interventionists will be trained to report any concerns immediately and directly to the PI. 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 or extreme distress. As noted previously, intervention sessions will be audio-recorded and reviewed by Drs. Kelleher and Somers to ensure the delivery of effective and ethical treatment. Further, the study Clinical Research Coordinators (CRC) will monitor daily all assessments with particular attention paid to the suicidal ideation item on the Brief Symptom Inventory. The CRC will immediately report all elevated responses on this item to the study PI. Dr. Kelleher (PI) will also be contacted when *any* emotional distress is identified in a participant. The study assessments have been well validated for use with patients with cancer. *Moreover, these assessments were specifically chosen for their brevity in order to reduce patient burden*. Participants will be reminded that they can omit responses to any questions that they do not feel comfortable answering. Again, all research personnel who have direct contact with patients will be trained to observe and immediately report any adverse events to Dr. Kelleher. Dr. Kelleher will report any adverse events to the institutional review board at Duke University and to NIH, and will consult Drs. Somers (licensed clinical psychologist and senior level faculty Co-I), and Uronis (experienced physician) to collaboratively develop a course of action, which may involve facilitating referrals for additional treatment. These referrals may be made to various members of the Duke Cancer Patient Support Program, including psychiatrists, psychologists, and medical family therapists, as appropriate. Participants will be provided with emergency contact numbers as well as access to numerous support services offered through the DCI. Dr. Kelleher 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 pre-doctoral interns) and Dr. Somers (Co-I) directs the clinical psychology training program within the Duke Cancer Patient Support Program at the Duke Cancer Center. Both Drs. Kelleher and Somers are integrated into the psychosocial clinical care program at the Cancer Center and have experience referring cancer patients who are distressed to appropriate psychosocial or psychiatric care within this large team of mental health professionals. Dr. Kelleher will use these same resources when making referrals for distressed participants in this study. The PI and entire investigative team have conducted research in the proposed area and have not encountered significant psychological distress caused by study procedures. In fact, participation in the proposed study procedures and intervention 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. *Finally, it is important to note that all participants will continue to receive usual care from their medical team. Consistent with numerous behavioral pain intervention protocols in our group, no participant will be asked to change or decline any strategies for pain management based on their participation in the study*.

**Potential Benefits of the Proposed Research to Research Participants and Others**
There are numerous potential benefits of the proposed research. Colorectal cancer patients with persistent pain may learn ways to enhance their pain coping and may experience significant decreases in pain and disability; the proposed intervention may lead to improvement in participants' pain and pain-related outcomes. There are currently no evidence-based standalone mobile app behavioral cancer pain interventions for patients with cancer and pain. This study has the potential to be of great benefit to this heavily burdened patient population. We also anticipate the results from this study will spur more research into mobile health-based behavioral symptom self-management interventions for patients with cancer and pain.

## 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 Design and Analyses.** A pilot trial (N=60) will be used to compare PainPac (n=30) to PCST-Video (n=30) on measures of feasibility (primary aim), burden, acceptability, engagement, and initial pain-related outcomes. Sample size was informed by pilot trial guidelines for RCTs of behavioral interventions,[63, 64] and past similar studies,[26,65-67] that suggest 30 participants per condition is sufficient for determining feasibility and acceptability, and feasibility of a future definitive trial. We anticipate no more than 25% attrition by 1 month post- baseline, based on previous psychosocial studies with cancer patients.[65,68-70] Both groups of 30 participants are needed because we aim to demonstrate two types of feasibility: feasibility of the PainPac app, which only requires the 30 PainPac participants, and feasibility of the subsequent larger RCT (i.e., recruitment, assessments), which requires all 60 PainPac and PCST-Video participants. We are recruiting both sexes and all genders, and we expect a nearly equal sample size between sexes. To account for sex as biological variable, we will describe all outcomes disaggregated by sex. We will examine intervention effects and use this data to optimize PainPac. Aim 1. Feasibility (accrual, attrition, adherence), burden, acceptability, and engagement will be assessed post-treatment and descriptive statistics will be produced for PainPac and PCST-Video. Overall trial feasibility benchmarks include reaching target accrual (N=60) within 15 months and <25% attrition by 1 month post- baseline. Descriptive statistics will be used to report non-eligibility and refusal. Data of non-completers will be compared to completers. 75% completed will serve as our feasibility benchmark. If >25% of consented patients drop out, PainPac will not be considered feasible. We do not expect attrition to be greater in the PainPac condition compared to PCST-Video. PainPac feasibility benchmarks include protocol adherence indicated by calculating the degree to which participants are willing/able to complete study assessments (pre, post, follow- up) and the 4 PainPac skills modules or 4 PCST-Video sessions. 75% completed will serve as our benchmark. If >25% of consented patients do not complete the intervention (modules /sessions and assessments), PainPac will not be considered feasible. We expect adherence in the PainPac condition will be at least comparable to PCST-Video. Patient Burden will be measured as a continuous variable by assessing physical, emotional, and financial burden of engaging in the study intervention. We expect burden will not be greater in PainPac compared to PCST-Video. Patient Engagement will be assessed by electronic app data (e.g., PainPac weekly log-ins) and patient self-report defined as the

number of times per week they practice the coping skills. ≥3 times/week will serve as the benchmark; if participants log into PainPac and/or practice the coping skills <3 times/week, PainPac will not be considered engaging. We expect engagement in PainPac will be at least comparable to PCST-Video. Acceptability will be indicated by 80% of patients reporting satisfaction with PainPac and PCST-Video (M=3. 2/4) on the CSQ. Aim 2. Between-group differences at follow-up will be characterized using Cohen's d and 95% confidence intervals. Consistent with recommendations for small pilot RCTs of behavioral interventions,[63,64] we propose a conservative approach that focuses on describing effect size estimates and their variability instead of testing for significant group differences. As this is a small trial intended to provide signals the intervention is promising and data for a larger trial, all pre- to post-intervention and 1 month variables will be characterized using graphs/plots and descriptive statistics (e.g., mean, standard deviations, range). We will examine the pattern of findings to determine the best analytic plan for the subsequent trial. Pain may vary based on pain medications and disease stage/treatment; we will describe these variables and include them, when appropriate, as covariates in future larger trials. The subsequent trial will be fully powered to test two active conditions. Given our proposed sample size (N=60), an a priori power calculation using G-Power suggests we will have >80% power to detect medium-sized effects of d=0.74 (α=0.05, two-tailed). However, as noted above, our analytic plan focuses on describing between-group differences rather than testing for significant effects. Aim 3. We will use methods from applied thematic analysis[71] to analyze interview data. First, we will create a codebook a priori that corresponds to major content areas from the interview guide. The codebook will include a coding matrix with categories, codes, and definitions. The analysts (Dr. Erkanli and a study member) will segment interview transcripts into major content areas using Nvivo and then use an inductive and iterative approach to identify data-driven codes. As new codes emerge, they will be applied to previously coded sections until all relevant information is captured. All codes will be grouped into themes and subthemes. The analysts will meet to discuss coding and resolve discrepancies in interpretation, and maintain an audit trail of coding and analytic decisions. The study team will review the qualitative findings and develop action steps for modifying the protocol. All data will be used to optimize PainPac for a large randomized clinical effectiveness trial. We will optimize areas related to patient preferences, barriers, beliefs, and cultural tailoring to increase usability and engagement and meet user needs.

**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 research study carries minimal risk. All patients in the study will continue their usual care during the course of this 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 (PI). The PI will report any adverse events to the institutional review board (IRB) at Duke University and to NIH. 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 one data safety officer who is a physician (MD) and not associated with this study. The appointed MD officer will have experience with clinical research and trials with oncology populations and have a thorough understanding of adverse events. The appointed data safety officer will also have technology expertise and will have an annual responsibility to evaluate our current methods 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 (PI: Dr. Kelleher). Dr. Kelleher is supported by a strong and experienced team of investigators, including Dr. Somers, a senior investigator and licensed clinical psychologist. 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 or extreme distress. Dr. Kelleher 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 doctoral 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.

**Potential Risks.** Risks associated with the proposed study are minimal and rare. Psychological risks include anxiety or distress due to questioning about thoughts, feelings, and personal/family history of cancer. There is the possibility of a breach of confidentiality due to the use of mailing of information. The consent form will address this possibility. All efforts will be made for confidentiality to be maintained by using case numbers to identify participants' research records and by having a limited number of individuals with access to identifying information. Identifying information will be kept separate from research records. All research records will be kept in a locked file cabinet and password protected computer files. Only the PI and other trained staff will have access to the research records. To ensure that there are no changes in potential risk during the course of the study and that confidentiality is maintained the PI and sponsors will implement a Data and Safety Monitoring Plan.

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 MRN, name, phone numbers and addresses. No medically sensitive or outcome data will be stored in this database. This database will also track non-participants (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 database without any personal identifiers. Data in this database will be derived from patients' direct input into the electronic patient reported outcomes system (e.g., REDCap), which is an online survey system; data entered into this system is stored on a secure server housed behind the Duke University Medical Center (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.

**Mobile App Data Storage and Security.** Pattern Health (Durham, NC) is a digital health company specializing in patient centered web and mobile products for clinical and medical research and health data tracking and analysis, with expertise working with wireless devices and improving patient engagement. Pattern Health has an established relationship with researchers at Duke and is contracted for the development of a mobile app for use in the current study. Pattern Health will have access to PHI. Study personnel will input participant information including name, phone number, email, birth date, language preference, time zone, and gender to create a profile for the participant. Participants will enter their full name, date of birth and e-mail address to access the corresponding profile. MAG and ISO have reviewed and approved Pattern Health's documents outlining this data collection process, and data storage and security. The RDSP and corresponding exception requests for this will go through full approval. A contract will be executed between Pattern Health and Duke. Patients may enter assessment data via the study mobile app or on their own online or by phone with a study team member. Assessment data entered via the mobile app will be temporarily stored on the cloud-based app platform (Pattern Health) and imported to REDCap via an assigned study ID number. Assessment data will be transported from the cloud-based app into REDCap for storage. Pattern Health uses 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 data base machine will be encrypted, which will provide security in case the hard drive is physically compromised.

**Data Safety Management Reporting**
Monitoring of data and safety procedures will ensure that the protocol is conducted in accordance with Good Clinical Practice (GCP), that data are of high quality and integrity, and that the facilities and staffing are adequate for continued participation in the study.

**Data Safety and Monitoring Plan.** This trial carries minimal risk. All patients in the trial will continue their usual care during the course of the 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 PI (Dr. Kelleher). The PI will report any adverse events to the institutional review board at Duke University and to the NIH. 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 appoint one data safety officer who is a MD and 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 appointed data safety officer will also have an annual responsibility to evaluate our current 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.

**Protection Against Risk.** All interactions with study participants will be under the direction of a Licensed Clinical Psychologist (Dr. Kelleher [PI]). Interventionists in this trial will have experience with distressed

patients with chronic disease. They will be trained, specifically in the context of this trial, 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 or extreme distress. Interventionists in this trial will be carefully trained to monitor participants' psychologist status and report to the PI. Dr. Kelleher (PI) will be contacted when emotional distress is identified in a participant. Dr. Kelleher works directly with the Cancer Patient Support Program at the 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.

There is the possibility of a breach of confidentiality. The consent form will address this possibility. All efforts will be made for confidentiality to be maintained by using case numbers to identify participants' research records and by having a limited number of individuals who have access to identifying information. Identifying information will be kept separate from research records. All research records will be kept in a locked file cabinet and password protected computer files. Only the PI and other trained research staff will have access to the research records. The PI has completed Duke University Health System Institutional Review Board's online training course: Protecting Research Subjects, which addresses confidentiality. All other individuals involved in this study will be required to complete this course and ongoing training.

**The Data and Safety Management (DSM) Report:** In addition to the above monitoring of data safety, there will also be a DSM Report generated quarterly by the CRC and data manager and presented to the PI. A full DSM report will be provided to the Data and Safety Monitoring officers annually or more frequently as needed. DSM Reports will contain the following:

- **Study Overview** with a review of study protocol, purpose of the study, primary outcomes, a description of key study personnel involved, and study timeline.
- **Recruitment Data** with total number of patients approached and screened, total participants enrolled, and data on reasons for inclusion/exclusion of potential participants.
- **Sociodemographic Data** from study participants with reference to expected age, racial, ethnic, sex, gender, and economic profiles.
- **Participant Retention** including a description of reasons for participant attrition.
- **Quality Assurance** including a report on data integrity processes, data transfer, encryption, any issues with paper and electronic data.
- **Regulatory Issues** including a report on IRB changes and protocol changes and the reasons for these changes.
- **Adverse Events** including a report on which events were study-related and which were not, how these AEs were managed and reported. Given that this is a behavioral virtual reality technology-based intervention focused on coping with pain, no medical emergencies are expected. However, if they arise, we will immediately contact the patient's oncologist. Dr. Tamara Somers (Co-I) directs the clinical psychology training program within the Duke Cancer Patient Support Program at the Duke Cancer Center. For psychosocial distress, the PI will contact Dr. Somers immediately to discuss the most appropriate course of action. If additional treatment is indicated, the PI and Dr. Somers will facilitate appropriate referrals. The PI and study team (Drs. Kelleher and Somers [Co-Is]) have conducted research in the proposed area and have not encountered significant psychological distress caused by study procedures.
- **Serious Adverse Events** including a detailed report on the individual(s) for whom this occurred, timing of the event, relationship to study procedures, timing and completion of reporting, and actions of Duke IRB, and the NIH as necessary. For the purpose of this behavioral trial, a SAE is defined as an even that, as a direct result of the study, causes serious harm to the subject (e.g., study involvement caused death or serious injury). We do not anticipate any SAEs.

**Privacy, Data Storage & Confidentiality**

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