Published in final edited form as:

Contemp Clin Trials. 2017 June ; 57: 51–57. doi:10.1016/j.cct.2017.04.001.

Optimizing Delivery of a Behavioral Pain Intervention in Cancer Patients Using a Sequential Multiple Assignment Randomized Trial SMART

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Abstract

Background/aims—Pain is common in cancer patients and results in lower quality of life, depression, poor physical functioning, financial difficulty, and decreased survival time. Behavioral pain interventions are effective and nonpharmacologic. Traditional randomized controlled trials (RCT) test interventions of fixed time and dose, which poorly represent successive treatment decisions in clinical practice. We utilize a novel approach to conduct a RCT, the sequential multiple assignment randomized trial (SMART) design, to provide comparative evidence of: 1) response to differing initial doses of a pain coping skills training (PCST) intervention and 2) intervention dose sequences adjusted based on patient response. We also examine: 3) participant characteristics moderating intervention responses and 4) cost-effectiveness and practicality.

Methods/design—Breast cancer patients (N=327) having pain (ratings 5) are recruited and randomly assigned to: 1) PCST-Full or 2) PCST-Brief. PCST-Full consists of 5 PCST sessions.

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Trials registration: ClinicalTrials.gov, NCT02791646, registered 6/2/2016

Declaration of conflicting interests: None declared. Authors Kelleher, Dorfman, Plumb Vilardaga, Majestic, Winger, Gandhi, Nunez, Van Denburg, Shelby, Reed, Murphy, Davidian, Laber, Kimmick, Westbrook and Abernethy have no disclosures or financial or personal conflicts of interest to report.

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PCST-Brief consists of one 60-minute PCST session. Five weeks post-randomization, participants re-rate their pain and are re-randomized, based on intervention response, to receive additional PCST sessions, maintenance calls, or no further intervention. Participants complete measures of pain intensity, interference and catastrophizing.

Conclusions—Novel RCT designs may provide information that can be used to optimize behavioral pain interventions to be adaptive, better meet patients' needs, reduce barriers, and match with clinical practice. This is one of the first trials to use a novel design to evaluate symptom management in cancer patients and in chronic illness; if successful, it could serve as a model for future work with a wide range of chronic illnesses.

Keywords

SMART; novel trial designs; breast cancer; pain; pain coping skills training; symptom management

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Introduction

Patients with cancer report pain as their most distressing and feared symptom.^{1, 2} The incidence of moderate-to-severe pain in cancer patients remains greater than 50%. Patients with high levels of pain have poor physical functioning, more physical symptoms, higher levels of depression, increased financial difficulty,^{3, 4} and decreased survival time.⁵ While analgesics are the primary therapy for cancer-related pain,⁶ behavioral pain interventions are an efficacious adjuvant therapy.^{7, 8} Behavioral pain intervention protocols teach patients strategies for managing psychosocial factors that contribute to pain.⁹ Randomized clinical trials (RCT) have supported the efficacy of these interventions; meta-analyses report patients experience significant pain reduction in 65–86% of RCTs.⁷ NIH guidelines recommend that behavioral interventions be integrated into treatment for cancer patients experiencing pain;¹⁰ however, implementation remains low.

Pain Coping Skills Training (PCST) is a behavioral pain intervention that has demonstrated efficacy for reducing pain.¹¹ Traditionally, PCST has been delivered to patients having persistent pain in weekly sessions, in a predetermined dosage or set number of hour-long, face-to-face sessions. PCST protocols train patients in multiple cognitive-behavioral skills (e.g., relaxation, imagery, activity pacing) with the goal of enhancing their abilities to manage pain by changing thoughts, feelings, behaviors, and body responses. PCST protocols vary with regard to the numbers of sessions, duration of sessions, and variety of skills taught. Nevertheless, these protocols have shown success in reducing pain, physical and psychological disability, and improving self-efficacy for pain management and quality of life.^{8, 9, 12–14}

Traditional RCTs of behavioral pain interventions evaluate outcomes achieved with a “one size fits all” approach in that they test a set intervention time and dose with response assessed post-treatment. This approach poorly matches actual clinical practice where intervention response is assessed in an ongoing fashion, intervention dose and techniques are adapted based on response, and patient characteristics influence intervention choices. There is growing interest in novel RCT designs that can provide information to optimize

behavioral pain interventions. The importance of study designs that are adaptive, better meet patients' pain needs, and match approaches used in clinical practice has been recognized. We utilize a novel treatment approach to conduct a controlled clinical trial, the sequential multiple assignment randomized trial (SMART) design. A SMART design is a study design that allows evaluation of adaptive interventions in which the type or dose of treatment is individually tailored based on the patient's needs.¹⁵ The purpose of this paper is to describe the rationale, design, methods and analyses of a novel RCT that aims to inform treatment efficacy and whether an adjustment to the dose of an initial intervention can improve patient response when a significant pain reduction is not achieved.

Methods

This study was approved by the Institutional Review Board. Recruitment procedures comply with HIPAA guidelines.

Study Aims

Our *first aim* is to provide comparative evidence of response to differing initial doses of a behavioral pain intervention (i.e., PCST-Full vs. PCST-Brief). Our *second aim* is to provide comparative evidence of intervention dose sequences of PCST, which adjust dose based on patient response. Our *third aim* is to determine participant characteristics that moderate responses to initial and secondary doses of PCST following each dose and at 6-months and to derive an optimal adaptive treatment strategy for personalizing selection of initial and secondary interventions based on patient characteristics. Our *fourth aim* is to evaluate the incremental cost-effectiveness and practicality of alternative intervention dose sequences of PCST.

Study Design

This study uses a SMART design (Figure 1). Patients with breast cancer (stage I–IIIC; N=327) who have pain are recruited and randomly assigned to either: 1) PCST-Full or 2) PCST-Brief. Patients will be identified from a pain report in their electronic medical records and screened at recruitment to assess a pain intensity rating of ≥ 5 out of 10. Randomization will be 1:1 with equal allocation to each initial intervention; no stratification will be used. Participants randomized to PCST-Full receive 5 weekly sessions in pain coping skills training with a trained therapist. The PCST-Brief condition consists of one 60-minute, in-person, PCST session (i.e., rationale for training in pain coping skills, progressive muscle relaxation, imagery). Five to 8 weeks following randomization, participants are asked to rate their pain intensity during the past week; all participants are then re-randomized based on their pain rating. Participants in the PCST-Full arm who respond to the intervention by reporting a $\geq 30\%$ reduction in their pain intensity level are re-randomized to receive either a maintenance dose or no further intervention. Participants who do not respond ($<30\%$ pain reduction) are re-randomized to receive an increased dose or maintenance. Participants in PCST-Brief who report at least a 30% reduction in their pain intensity level are re-randomized to receive either a maintenance dose or no further intervention; participants who do not respond to PCST-Brief are re-randomized to receive an increased dose or a maintenance dose. Upon determining response, secondary randomization will also be 1:1

with equal allocation into one of the two appropriate response sequences. All participants receive an intervention condition that is expected to lead to pain reduction; participants are not provided with information on which condition is hypothesized to lead to greater pain reduction.

As shown in Figure 2, all participants complete assessments at baseline, pre-secondary randomization, post-treatment, and six-months post-treatment. Assessments include measures of pain intensity, pain interference, and pain catastrophizing. The baseline assessment also includes measures of depression, social support, and physical performance.

Careful attention has been given to minimize study attrition. Our eligibility criteria include only through cancer stage IIIC, which may minimize attrition due to health or death. We have also very carefully trained study staff, including recruiters, coordinators, and therapists, to communicate expectations to participants and to decrease breaks in communication with participants (e.g., at second randomization) to minimize attrition. For example, we've created study "road map" worksheets that are used to aid in discussion with participants. Our study team meets weekly to track each participant's progress in the study. Finally, we send text messages to participants (3 times per week) to remind them to practice skills, but also view this as a strategy to keep participants engaged. Text reminders for appointments are available to participants who indicate they would be helpful.

Participant Eligibility Criteria

Eligible participants include patients with a diagnosis of breast cancer (initial or recurrence) within the past two years. Other eligibility criteria are: 21 years old, a life expectancy of at least 12 months, a pain intensity rating ≤ 5 . Exclusion criteria include: cognitive impairment,¹⁶ presence of a severe psychiatric condition, or current or past (<6 months) engagement in PCST for cancer.

Interventions

Initial randomization

Pain Coping Skills Training Full (PCST-full): PCST-full consists of a 5-session intervention delivered to participants at the medical center by their therapist.

Session 1: Participants are provided with a brief overview of the session format and given an opportunity to talk about their cancer diagnosis. Participants are then presented with the rationale for training in pain coping skills and the role that thoughts, feelings, behaviors, and body responses can play in the pain experience. This rationale highlights the multidimensional nature of pain through discussions of the gate control theory¹⁷ and neuromatrix¹⁸ theory of pain. Participants are trained in 1) Progressive muscle relaxation (PMR), which involves concentrating on muscle tension signals and using them as cues to relax, and 2) Pleasant imagery, which involves using one's imagination to focus on a pleasant scene using multiple senses to evoke the image (sight, hearing, touch, taste). Relaxation and pleasant imagery are key to start with because they are considered the most widely used and effective pain coping skills.^{7, 8, 19–21} Behavioral rehearsal, modeling, guided practice, and feedback are used to teach both skills. An audio-recording of PMR and

guided imagery (MP4 player) is provided for daily home practice. Home practice assignments are set at the end of every session for each of the pain coping skills; assignments are written down, specific, and graduated in terms of difficulty.

Session 2: Participants are taught to manage their pain by changing their activity patterns. Skills to cope with pain related to activity are important for participants with persistent pain as pain often increases as they attempt to increase activity; paradoxically, inactivity to avoid pain can lead to more pain. This session focuses on two skills: activity rest cycling and pleasant activity scheduling.²⁰ The skill of activity/rest cycling teaches participants to pace their activities and to increase their activity level over time. Activity-rest cycling helps patients remain productive and active but avoid extreme pain. Pleasant activity scheduling is designed to increase patients' abilities to engage in pleasant and meaningful activities. Brainstorming and goal setting are used to help patients identify and set pleasant activity goals and gradually increase the level and range of such activities. Pleasant activities are important for several reasons: they can provide pain distraction, increase fitness and activity tolerance, and decrease psychological distress. Finally, participants are taught a brief applied relaxation exercise – the mini-relaxation practice.

Session 3: Using techniques drawn from the cognitive therapy literature, participants are taught to recognize how pain-related thoughts, such as pain catastrophizing, can negatively influence their pain and their ability to cope with pain. The therapist works through common examples of overly negative pain-related thinking. Participants are encouraged to think of examples from their life. The therapist and participant work to identify common overly negative thoughts that arise in response to pain and distress, describe the negative consequences of these thoughts, and generate more adaptive thoughts to decrease distress.

Session 4: To provide a rationale for learning to use pleasant imagery, the gate control and neuromatrix theories of pain are reviewed. Using behavioral rehearsal, the therapist guides participants through mini-relaxation, PMR, and imagery practices. Daily practice of relaxation skills is emphasized.

Session 5: Participants are taught a systematic approach to problem solving related to their pain and goal setting for continued skills use. Patients then work to develop a maintenance plan that includes their intentions/goals for daily practice of coping skills, a plan for dealing with pain flares, and a list of short- and long-term goals.

Pain Coping Skills Training Brief (PCST-Brief): PCST-Brief consists of one 60 minute, in-person session followed by 5 weeks (3x/week) of caring text/email reminders (based on patient preference) to practice PMR and imagery. Participants are provided with audio recordings of PMR and imagery for home practice. Session content mirrors that of session 1 in the PCST-Full condition.

Assessing Response Following Initial Randomization

Participants are asked to rate their pain intensity one week following their final PCST-Full session, or approximately 5 weeks following their PCST-Brief session.

Re-randomization (1:1) is as follows:

PCST-Full Condition—Participants who report at least a 30% reduction in their pain intensity level are re-randomized to either PCST-Full Maintenance or no further intervention. Participants who do not respond (<30% pain reduction) are re-randomized to receive PCST-Full Plus or PCST-Full Maintenance.

PCST-Brief—Participants who report at least a 30% reduction in their pain intensity level are re-randomized to either PCST-Brief Maintenance or no further intervention. Participants who do not respond (<30% pain reduction) are re-randomized to receive PCST-Full or Maintenance for PCST-Brief.

Re-randomized conditions:

PCST-Full Plus—Participants receive two additional in-person sessions where pain coping skills are practiced and adherence is emphasized. Participants also receive three weekly calls to review their skills practice, problem solve around any challenges with pain and/or skills practice, and assess progress.

PCST-Full Maintenance—Participants receive five weekly 20-minute booster phone calls from their therapist to review their skills practice and problem solve around any challenges with pain and/or skills practice. Each booster call also entails a therapist-guided mini-relaxation practice and PMR or imagery practice.

No Further Intervention—Participants do not receive further contact from their study therapist.

PCST-Full—Participants receive the intervention described above.

PCST-Brief Maintenance—Participants receive five weekly 20-minute booster phone calls from their therapist to problem solve around any challenges with their PMR practice and to do a brief PMR practice by phone.

Assessing Response Following Secondary Randomization

Participants are asked to rate their pain intensity approximately 5 weeks following their second randomization.

Measures

Pain Intensity—Pain intensity is assessed with the Brief Pain Inventory (BPI).²² This measure asks patients about their pain at its “worst,” “least,” “average,” and “now,” based on a 10-point scale from 0=“no pain” to 10=“pain as bad as you can imagine.” Reference is to the past 7 days.

Pain Interference—Pain interference is assessed with the BPI.²² This measure asks patients how much their pain has interfered with daily activities (e.g., work, sleep) within the

past 7 days. Answers are on a 0=“does not interfere” to 10=“completely interferes” scale; items are averaged.^{23, 24}

Pain Catastrophizing—Pain catastrophizing is assessed with 5 items from the Coping Strategies Questionnaire.²⁵ These items ask about patients’ tendencies to catastrophize when faced with pain (e.g., “When I feel pain it is awful and it overwhelms me”) and are answered on a 0=“never” to 6=“always scale.” Items are summed for a total score.²⁶

Practicality—Practicality is assessed by examining accrual, retention, and adherence. Accrual is measured by meeting the recruitment goal (N=327 participants during 48 recruitment months). Retention is indicated by 80% of participants completing the study. Adherence is examined by calculating the proportion of assigned intervention sessions successfully completed.

Cost-Effectiveness—To examine the expected costs and health outcomes associated with each of the PCST intervention sequences, four types of information are collected throughout the trial. 1) *All-Cause Medical Resource Use*. Information on medical resource use is collected through self-report and available electronic medical records, and focuses on expected cost-drivers and resources that may be differentially affected by the study interventions, including hospitalizations, emergency department and urgent care visits, and outpatient visits. 2) *Participant Time*. Participants are asked to estimate their travel time from home to the facility where PCST sessions take place. Therapists record the time spent in each contact. Indirect costs associated with patient time are valued using the average hourly wage in the US.²⁷ 3) *Health Utilities*. To incorporate potential differences in health-related quality of life experienced by patients in the differing randomization patterns into the cost-effectiveness analysis, health status is measured using the 5-level EQ-5D (5L-EQ-5D) at each assessment.²⁸ 4) *Required Resources for Pain Coping Skills Training*. Information on time spent by staff involved in the delivery of the study intervention is collected to estimate intervention costs. A costing tool is used to estimate costs associated with the pain coping skills.²⁹

Treatment Adherence, Therapist Competence, and Treatment Credibility Ratings—Ratings of therapists’ protocol adherence and competence are made by two licensed clinical psychologists who have expertise in behavioral protocols.³⁰

Descriptive Variables—Participants’ electronic medical records provide information on cancer characteristics and treatments (e.g., surgery, chemotherapy, radiation, hormonal therapy), medical comorbidities, height and weight, and use of antidepressant, anxiolytics, and pain medications. Participants are asked about their cancer treatments and medication use in the past week. These descriptive variables will be examined at baseline; any significant differences between randomization conditions in cancer stage, treatments (e.g., surgery, chemotherapy, radiation, hormonal therapy), and past or current medication (i.e., antidepressant, anxiolytics, pain) will be described and considered in analyses.

Potential Tailoring Variables—Tailoring variables are participant characteristics that are important for individualized selection of an intervention at each treatment decision point.

Potential tailoring variables assessed at baseline are: 1) *Depression* is assessed with the Center for Epidemiologic Studies-Depression Scale (CES-D).³¹ 2) *Social support* is assessed with an 8-item³² Medical Outcomes Study Social Support Survey³³ (MOS-SS) that was recently validated in cancer patients. 3) *Physical activity* is assessed with the Rapid Assessment of Physical Activity (RAPA).³⁴ 4) *Physical performance* is assessed with the Functional Status Questionnaire physical function subscale.³⁵ These scales have demonstrated good reliability and validity.^{32, 34, 35} Potential tailoring variables assessed post-baseline but prior to selection of secondary intervention are: pain interference, cancer stage, and pain catastrophizing. These variables will be used to inform Aim 3.

Statistical Analyses

Analysis of Aim 1

The primary hypothesis is that participants initially randomized to PCST-Full will report a significantly greater reduction in pain intensity from baseline than participants randomized PCST-Brief following their assigned interventions. We define the primary endpoint as a percent reduction in pain from baseline at Assessment 2. We expect that both intervention conditions will lead to a reduction in pain but that PCST-Full will produce a 10% greater reduction in pain than PCST-Brief. Average percent reduction in pain will be compared between the two intervention conditions using a standard two-sided, two-sample t-test. For determining sample size, we base calculations on the results of Kwekkeboom et al.¹⁹ Assuming that the standard deviation of percent reduction in pain is 30% under each condition, using an effective sample size of 142 per group (N=327 allowing for 15% attrition) will provide 80% power to detect a 10% difference in percent reduction in pain using this statistical test at a 0.05 level of significance.

To define response to initial intervention condition at Assessment 2, numerical percent reduction in pain from baseline will be dichotomized as being $\geq 30\%$ or $< 30\%$, with $< 30\%$ reduction corresponding to non-response. A secondary analysis will compare the proportions of participants responding to the assigned initial intervention condition. A standard two-sided, two-sample test of proportions based on this sample size will have power 80% to detect a difference in response rates of 16.5% at level 0.05. Empirical evidence suggests using a 30% reduction in pain as a marker of clinical significance when using 11-point numerical pain rating scales like the one in this study.³⁶ There is no single consensus approach on how to power for a SMART trial; in this study power was determined based on the up-front comparison of pain following the initial randomization.

An additional secondary analysis is to compare average percent reduction in pain from baseline between the two initial intervention conditions (i.e., PCST-Full and PCST-Brief) following completion of both the assigned initial and secondary intervention condition. This can be interpreted as comparing intervention sequences starting with PCST-Full versus those starting with PCST-Brief, averaged across intermediate response and secondary intervention conditions. Using a standard two-sided, two-sample t-test will provide 80% power to detect a 10% difference in average percent reduction in pain at level 0.05.

Analysis of Aim 2

We will carry out secondary analyses to compare the eight intervention sequences (see Table 1) embedded in the SMART on the basis of average percent reduction in pain achieved at Assessment 3 (post-intervention) and Assessment 4 (6-month follow-up). This will be implemented using specialized methods^{15, 37, 38} that take into account that the actual interventions received by a trial participant may be consistent with having followed more than one of the sequences; this results in improved precision of comparison (e.g., a participant randomized to PCST-Full initially, responded, and then received no further intervention could have experienced these interventions by following either of the sequences, as outlined in table 1: (2) Initial intervention PCST-Full followed by PCST-Plus if the patient does not respond and no further intervention if she does; or (4) Initial intervention PCST-Full followed by PCST-Full Maintenance if the patient does not respond and no further intervention if she does). Thus, this patient's data contribute to assessment of average percent reduction in pain for both of these sequences. We will compare all eight sequences using the approach outlined in Nahu-Shani et al.³⁷ with linear models of percent pain reduction that include main effects for initial and secondary interventions and their interactions. We will also compare pairs of sequences that reflect the least and most intensive approaches overall (i.e., (8) Initial intervention PCST-Brief followed by PCST-Brief Maintenance if the patient does not respond and no further intervention if she does vs. (1) Initial intervention PCST-Full followed by PCST-Plus if the patient does not respond and PCST-Full Maintenance if she does) and starting from the same initial intervention (e.g., (8) Initial intervention PCST-Brief followed by Maintenance for PCST-Brief if the patient does not respond and no further intervention if she does vs. (5) Initial intervention PCST-Brief followed by PCST-Full if the patient does not respond and Maintenance for PCST-Brief if she does).

Analysis of Aim 3

To evaluate pain interference, cancer stage, pain catastrophizing, as moderators of participants' responses at Assessment 2 to initial interventions, we will use standard methods based on linear models for percent reduction in pain as a function of these characteristics as well as standard tests for qualitative interactions³⁹ and more recent variable selection methods for qualitative interactions that adjust for multiplicity.^{40, 41} We will use the estimated models from Q-learning³⁷ and value search estimation^{42, 43} to develop an optimal adaptive treatment strategy to test for moderators of the initial and secondary interventions. Specifically, we will first conduct an overall test of the null hypothesis that there are no moderators at either of the initial or secondary intervention decisions. If the test rejects this null, we will conduct a series of appropriate multiplicity-adjusted statistical tests to identify specific baseline and intermediate moderators of responses at Assessments 3 and 4. Namely, because of the sequential nature of the interventions, standard statistical tests for this purpose are invalid without appropriate modification.^{44, 45} We will use suitable bootstrap methods⁴⁴ to ensure that the tests are valid (i.e., have correct control of Type I error). We will use the methods of Q-learning³⁷ and value search estimation^{42, 43} to estimate an optimal adaptive treatment strategy for selecting initial and secondary interventions.

Baseline demographic and medical characteristics, including cancer stage, pain severity, pain interference, pain catastrophizing, depression, physical activity and performance will be considered as potential tailoring variables for the initial intervention decision in linear models for response (percent pain reduction). Baseline characteristics plus response to initial intervention, adherence to initial intervention, and reassessments of pain severity, interference, and catastrophizing will be considered as potential tailoring variables for the secondary intervention adjustment decision in linear models for response. We will evaluate the potential improvement in percent pain reduction that could have been realized for each trial participant if she had received initial and secondary interventions via the optimal adaptive strategy.

Monte Carlo simulations will be conducted to compare the average percent pain reduction achievable using the optimal adaptive strategy to that achievable using the simpler embedded sequences that do not take account of patient characteristics beyond response to initial intervention to assess the potential benefit associated with the personalized adaptive strategy. Because the proposed SMART is not powered to estimate an optimal adaptive strategy, this analysis will be exploratory and hypothesis-generating, as estimation of an optimal strategy will inform the formulation of adaptive strategies that could form the basis for future investigations.

Analysis of Aim 4

We will use patient-level data on medical resource use, total medical costs, and EQ-5D-derived preference weights to determine whether there are significant differences across PCST strategies and between responders and non-responders. We will use generalized linear models for comparisons: negative binomial/log models for resource use, gamma/log models for costs and normal/identity models for 5L-EQ-5D preference weights. We will evaluate the incremental cost-effectiveness of the PCST interventions by designing a decision analytic model that represents the 8 combinations of initial and subsequent intervention strategies tested in the SMART. The probability of response will be included after the initial and subsequent interventions as defined above (30% reduction in pain scores). For each strategy and response combination, we will assign expected costs, inclusive of intervention costs and non-intervention medical costs, and preference weight-adjusted (i.e., quality-adjusted) survival time. To avoid complexities imposed with multiple comparators in an incremental cost-effectiveness analysis, we will use an equivalent net benefits approach that allows each strategy to be evaluated individually.⁴⁶ To evaluate model uncertainty, we will employ probabilistic sensitivity analysis in which we assign distributions to each model parameter and run thousands of Monte Carlo simulations.

Not only will the decision model provide useful results about the uncertainty of the magnitude of net benefits (i.e., cost-effectiveness) of each PCST strategy, but it will also allow us to evaluate the value of information (VOI) that could be collected with a larger clinical trial to increase precision for the parameters representing costs and effectiveness. In addition, with additional parameters to represent differential uptake of more or less costly PCST interventions (even if hypothetical), we can use the model to determine cut points at which there would be greater overall benefits to a population of cancer patients through

adoption of a lower-cost, but potentially less-effective PCST strategy in more patients versus a higher-cost, more-effective strategy that is provided to fewer patients.

Accrual will be indicated by meeting the recruitment goal of 327 participants during the 48 recruitment months. Descriptive statistics will be used to report the number of patients screened and determine rates of non-eligibility and refusal. Retention will be indicated by 80% of consented participants completing the protocol. Adherence will be calculated as the proportion successfully completing all intervention sessions during the first randomization and second randomization; 75%-completed sessions and 75%-completed assessments will serve as our benchmark. If less than 45% of patients complete all intervention sessions and assessments, the trial will not be considered feasible.

Discussion

Very little is known about the optimal dosing (i.e., session number, skills) that leads to decreased pain in response to behavioral pain interventions. Optimizing behavioral pain interventions by understanding dose-response, adapting the intervention based on response, and identifying personal characteristics related to response could reduce practical barriers and dramatically increase the use of such interventions in clinical practice. To our knowledge, this study is the first to develop an evidence-based, optimal adaptive strategy for personalized behavioral pain management in cancer patients using state-of-the-art methodology (SMART).^{37, 42, 43} An optimal strategy is one that leads to a reduction in pain that is the greatest that could be expected for the patient based on his or her characteristics. Moving toward optimizing PCST delivery will lead to interventions that work for cancer patients with pain and will lead to greater clinical implementation by improving response rates, increasing uptake by patients and providers, and minimizing burden. Additionally, providing patients with minimally effective dosing decreases burden on both the patient and the overall healthcare system; again, implementation and patient uptake increases when burden is minimized.

This study will answer some questions but likely lead to many others. For instance, this unique study design is being used to examine pain relief as the primary outcome and marker for response or no response. However, the results may suggest that other outcomes such as decreases in pain interference or pain disability and/or self-efficacy for pain management without pain relief should be considered. Perhaps even if pain itself does not decrease, other benefits will be seen from the interventions (e.g., less pain interference).

This study attempts to inform treatment efficacy and to rigorously evaluate how to adjust an initial intervention to improve patient response when a significant pain reduction is not achieved. This is not only one of the first trials to use a novel design to evaluate symptom management in cancer patients but also in chronic illness more generally; if successful, it could serve as a model for future work with a wide range of chronic illnesses.

Acknowledgments

Grant acknowledgement, Source of Support: This work is supported by a grant awarded to the senior author TJS from the NIH/NCI 1R01CA202779-01.

Funding statement: This study is funded through an NIH/NCI grant 1R01CA202779-01 awarded to senior author TJS.

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Figure 1.
Trial design with focus on randomization pattern.

Figure 2.
Basic study procedures.

Table 1

Eight PCST intervention sequences embedded in the SMART design.

1	PCST-Full →PCST-Plus if no response and PCST-Full Maintenance if response
2	PCST-Full →PCST-Plus if no response and no further intervention if response
3	PCST-Full →PCST-Full Maintenance regardless of response
4	PCST-Full →PCST-Full Maintenance if no response and no further intervention if response
5	PCST-Brief →PCST-Full if no response and PCST-Brief Maintenance if response
6	PCST-Brief →PCST-Full if no response and no further intervention if response
7	PCST-Brief →PCST-Brief Maintenance regardless of response
8	PCST-Brief →PCST-Brief Maintenance if no response and no further intervention if response