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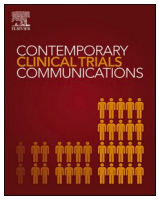

Hybrid effectiveness-implementation trial of guided relaxation and acupuncture for chronic sickle cell disease pain (GRACE): A protocol

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ABSTRACT

Background: People with sickle cell disease frequently use complementary and integrative therapies to cope with their pain, yet few studies have evaluated their effectiveness. The 3-arm, 3-site pragmatic Hybrid Effectiveness-implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain (GRACE) has 3 priorities: (1) evaluate guided relaxation and acupuncture to improve pain control; (2) determine the most appropriate and effective treatment sequence for any given patient based on their unique characteristics; and (3) describe the processes and structures required to implement guided relaxation and acupuncture within health care systems.

Methods: Participants (N = 366) are being recruited and randomized 1:1:1 to one of 2 intervention groups or usual care. The acupuncture intervention group receives 10 sessions over approximately 5 weeks. The guided relaxation intervention group receives access to video sessions ranging from 2 to 20 min each viewed daily over 5 weeks. The usual care group receives the standard of clinical care for sickle cell disease. Participants are re-randomized at 6 weeks depending on their pain impact score. Assessments occur at 6 weeks, 12 weeks, and 24 weeks. The primary outcome is the change in pain impact score and secondary measures include opioid use, anxiety, depression, sleep, pain catastrophizing, substance use, global impression of change, constipation, and hospitalizations. The GRACE study uses the Consolidated Framework for Implementation Research to plan, execute, and evaluate the associated implementation processes.

Conclusion: The results from GRACE will represent a critical step toward improving management of pain affecting patients with sickle cell disease.

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1. Introduction

Black Americans continue to suffer from higher morbidity and mortality rates at younger ages due to a nexus of structural disparities [1], which manifest in high incidence rates and poor health outcomes for many common chronic health conditions [2–5]. Institutional policies and implicit biases have resulted in neglect at the point of care [6], lower rates of insurance [7], and a decreased level of support for diseases primarily impacting Black people [8]. These inequities are evident of care received in the US for sickle cell disease (SCD).

Sickle cell disease (SCD) refers to several hemoglobin disorders, which share a specific mutation in the β-hemoglobin chain. It is the most common genetic blood disorder in the world, with approximately

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Abbreviations

CFIR	Consolidated Framework for Implementation Research
CIH	complementary and integrative health
GAD-7	Generalized Anxiety Disorder-7
GRACE	Hybrid Effectiveness-implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain
HEAL	Helping to End Addiction Long-term
MME	morphine milligram equivalent
NIH	National Institutes of Health
PCS	Pain Catastrophizing Scale
PEG	Pain, Enjoyment of Life, and General Activity
PHQ	Patient Health Questionnaire;
PROMIS	Patient-Reported Outcomes Measurement Information System
SCD	sickle cell disease
SMART	sequential multiple assignment randomized trial
TAPS	Tobacco, Alcohol, Prescription medication, and Other Substance use Tool
US	United States

100,000 people in the United States (US) and millions worldwide living with it [9]. Pain, both acute and chronic, is a constant companion for those with SCD and is the most common reason for their admission to emergency departments and hospitals [10]. Evaluation of alternative therapies that reduce chronic pain and enable those with SCD to better cope with pain is critically needed.

People with SCD often attempt to control their pain and other symptoms by using pharmacological interventions or complementary and integrative health (CIH) therapies [11–14]. Since many people with SCD try 2 or more therapies, there is a need to rigorously test the effects of adding a subsequent therapy when the first does not produce the desired outcomes within a given time period. The Hybrid Effectiveness-implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain (GRACE) is assessing the outcomes of sequencing 2 evidence-based CIH therapies [15,16], acupuncture and guided relaxation, among SCD patients with chronic pain who are being treated in real-world health care systems.

1.1. Selection of therapies

The National Center for Complementary and Integrative Health [17] has identified 5 areas needing greater investigation: mind-body therapies, body-based therapies, biologically based therapies, energy therapies, and alternative medical systems. For this study, we selected 1 body-based therapy (acupuncture) and 1 mind-body therapy (guided relaxation). These 2 therapy groups are most widely used [18] and there is already an evidence base showing that these therapies are safe and effective for reducing pain.

Acupuncture. In Traditional Chinese Medicine, *qi* is the vital energy flowing within and surrounding the body. Meridians are the channels through which *qi* and blood flow in the body. Disorders of *qi* and disorders of blood, whether of deficiency or excess (stagnation or obstruction), can result in pain. Acupuncture needles that are inserted into acupuncture points that access the meridians (pathways for the flow of *qi*) promote the circulation of *qi* and blood, which reduces pain. There is evidence of acupuncture's efficacy for pain conditions. A meta-analysis of 39 high-quality randomized trials of acupuncture examined 20,827 participants for the treatment of 4 chronic pain conditions: nonspecific musculoskeletal pain, osteoarthritis, chronic headache, and shoulder pain. Results indicated that acupuncture was superior to sham acupuncture or usual care for reduction of pain in all 4 pain conditions (all $p < .001$) [19]. A 2019 systematic review and meta-analysis found that acupuncture and/or acupressure was effective for reducing cancer pain [20]. These meta-analyses of acupuncture have established the effectiveness of acupuncture for treating chronic pain conditions other than SCD, and suggest that it may also be effective for the treatment of adults with SCD and chronic pain. There are also promising small studies of acupuncture for the treatment of SCD pain [15,21,22].

Guided relaxation. Mind-body therapies such as guided relaxation use the mind to reduce pain, promote well-being, and alter physical function. Guided relaxation is a state of concentration and focused attention that gives people more control over their pain experience and its impact, as well as an increased sense of well-being [23]. Systematic reviews and meta-analyses reviewing over 48 randomized controlled trials have demonstrated that guided relaxation reduces chronic pain [24–26]. In a systematic study of e-health interventions for SCD published in 2018, the authors identified studies of guided relaxation as an effective stand-alone therapy [27]. One guided relaxation study showed that at the time of the immediate posttest those who did the guided relaxation exercises in the intervention had significantly reduced current pain by 1.1 point on a scale of 0–10 compared with the attention control group [16].

1.2. Research objectives

The objectives of GRACE are to (1) evaluate the effectiveness of 2 nonpharmacological interventions (guided relaxation and acupuncture) compared with usual care for treatment of chronic pain from SCD; (2) identify the best sequence of interventions over a 12-week interval, allowing for adaptation for participants who do not show adequate response; (3) explore study participants' individual characteristics to understand differential treatment response; and (4) identify facilitators as well as challenges and solutions to implementing structures and processes that contribute to integration of CIH therapies into health care systems.

2. Overview of study

2.1. Methods

2.1.1. Study design

This study uses a hybrid type 1 effectiveness-implementation research design. The randomized controlled trial follows a quantitative sequential multiple assignment randomized trial (SMART) design [28], to which we will add a qualitative implementation research component [29]. SMART designs result in pragmatic trials [30] that evaluate adaptive interventions—that is, the selection of interventions responds to participants' characteristics and evolving clinical status [31] (Fig. 1). Use of a SMART design enables the study team to make the following determinations: (1) the relative effectiveness of guided relaxation and acupuncture; (2) the subgroups of participants who do and do not respond to each stage 1 intervention; (3) the most effective intervention sequences; and (4) methods for identifying moderators to operationalize the choice of which intervention to apply at each stage for each individual. This study was approved by the University of Illinois Institutional Review Board (#2021-0065).

2.1.2. Specific aims and hypothesis

The study has the following specific aims and hypotheses:

Aim 1. Determine the effectiveness of guided relaxation and acupuncture as compared with usual care in decreasing pain and opioid use for people with SCD. Hypothesis: At 6 weeks, SCD patients randomized to either CIH intervention will have greater decreases in pain, opioid use, sleep problems, anxiety, depressive symptoms, and pain catastrophizing compared with SCD patients randomized to usual care.

Aim 2. Identify the best adaptive intervention for improved outcomes by comparing the outcomes of the following adaptive intervention

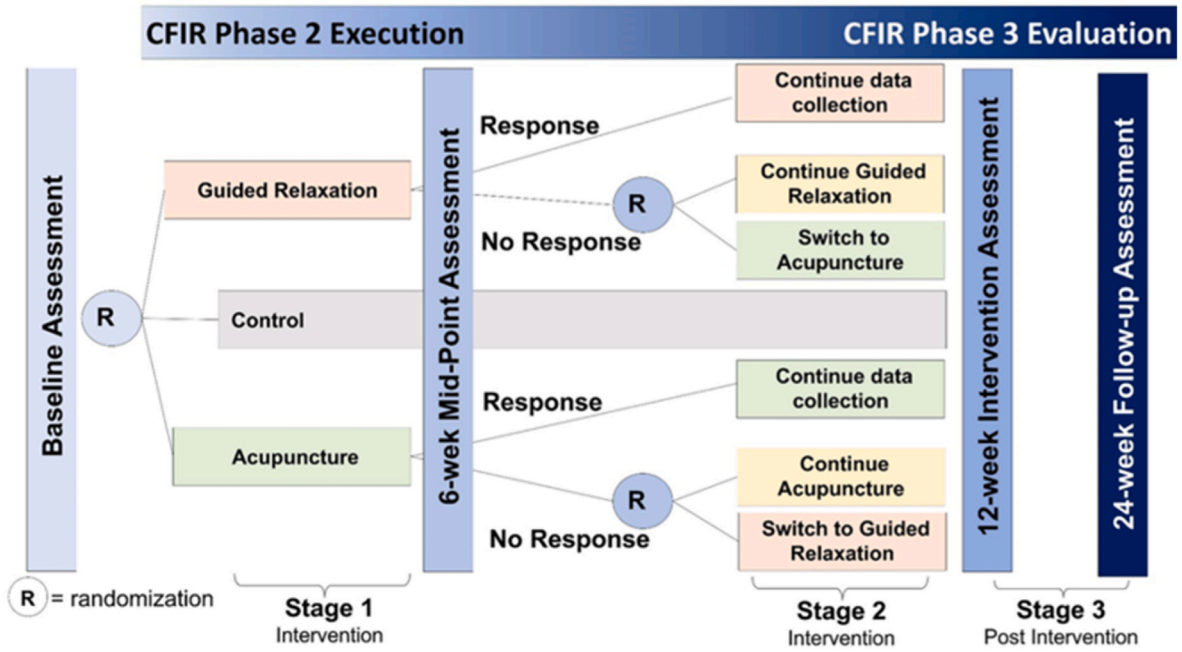

Fig. 1. SMART Study Design showing randomization and measurement time points.

sequences: (1) initiate guided relaxation and switch to acupuncture for nonresponders at midpoint; (2) initiate guided relaxation and continue with guided relaxation for nonresponders at midpoint; (3) initiate acupuncture and switch to guided relaxation for nonresponders at midpoint; or (4) initiate acupuncture and continue with acupuncture for nonresponders at midpoint.

Aim 3. Explore differences in responses to the adaptive interventions by age and sex.

Aim 4. Identify facilitators as well as challenges and solutions to implementing structures and processes that contribute to the seamless integration of CIH therapies into health care systems. To do so, we will conduct individual interviews with 4 participants in each intervention-group who respond to the intervention and 4 who do not respond. We will also conduct interviews with health care system personnel each year.

2.1.3. Setting

GRACE is being implemented in 3 different health care systems: The University of Illinois Hospital & Health Sciences System (UI Health), Duke University Health System (Duke), and University of Florida Health (UF). UI Health is made up of several facilities, that together provide access to multiple levels of care. These include a 495-bed tertiary hospital, an outpatient clinic, an immediate care clinic, and 12 Mile Square Health Centers, which are Federally Qualified Health Centers. UI Health serves a diverse population with 48% of patients identified as African American, 24% Hispanic or Latino, 20% Caucasian, and 8% Asian or Pacific Islander. The entire UF Health system is comprised of two premier academic medical centers, one Children's Hospital, four community hospitals, two specialty hospitals, and more than 80 affiliated primary care and medical specialty practices staffed by physicians on the faculty of the UF College of Medicine. Duke University Health System (DUHS) is a non-profit, integrated, academic health system comprised of many facilities throughout the North Carolina region. DUHS facilities include 1) Duke University Hospital – a full-service tertiary and quaternary care hospital licensed for 957 beds, offering regular and intensive care inpatient units, a regional emergency -trauma center with a separate pediatric emergency department and a major surgery suite with four dedicated open-heart operating rooms; 2) Duke Regional Hospital – a 335 bed acute care community hospital serving residents of Durham and surrounding counties, offering tertiary care services in an 8 contiguous county area; 3) Duke Raleigh Hospital – a 186 bed acute care community hospital serving Raleigh and Wake County; 4) Duke Primary Care (DPC) – a network of primary care physicians and clinics, formed in 1994 and covering 20 locations in eight counties; 5) Private Diagnostic Clinic (PDC) – the PDC offers pediatric and adult specialty services, urgent care facilities, and prevention and wellness services; and 6) Duke Home Care and Hospice – an integrated service providing home care, infusion management, hospice, and bereavement care. We expect UI Health and UF are expected to randomize 120 participants each and Duke is expected to randomize 90 participants.

2.1.3.1. Acupuncture settings. For UI Health, all acupuncture sessions are delivered at the UI College of Nursing Acupuncture Research Laboratory which consists of 4 private acupuncture rooms with massage tables used for acupuncture treatments. For Duke, acupuncture sessions are delivered at the Duke Integrative Medicine Clinic and at two other community acupuncture practices in Siler City and Raleigh, North Carolina to ensure SCD patients minimize travel time. For UF, acupuncture sessions are delivered at two community acupuncture practices, both in Gainesville, Florida.

2.1.4. Participant eligibility criteria

As this is a pragmatic trial, we are using broad inclusion and exclusion criteria to include most of the SCD patients with chronic pain seen in one of our participating health care systems. *Inclusion criteria* are: (1) age of at least 18 years; (2) SCD diagnosis by hemoglobin electrophoresis; (3) ability to speak and understand English; (4) chronic pain defined as a response of "Some days," "Most days," or "Every day" to the question "In the past 3 months, how often have you had pain?" (answer options: Never, Some days, Most days, Every day), as we found that people with SCD desired pain interventions when they had rated their pain as occurring some days; and (5) current pain interference score of 3 or more on a 0 to 10 scale, using the general activity question from the Pain, Enjoyment of Life and General Activity (PEG) scale. *Exclusion criteria* are: (1) receipt of a stem cell transplant for SCD; (2) a known diagnosis of moderate or severe opioid use disorder by *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria, which was assessed by documentation in the EHR and/or self-report during

screening; (3) current incarceration; and (4) participation in a chronic transfusion/exchange program. See Fig. 2 for participant flow diagram.

2.1.5. Screening, consent, and baseline assessments

Potential participants are recruited from the population of patients with SCD and pain who receive care at the University of Illinois Hospital & Health Sciences System, Duke University Health System, or University of Florida Health. Each patient's health care provider, at the time of a clinical visit, determines if the patient is a candidate for non-pharmacological pain care (both acupuncture and guided relaxation). Research staff encourage providers to refer patients to this project via flyers posted in each provider exam room; there are also flyers in the waiting rooms as well as research staff present and available to answer any questions about the study.

Inclusion criteria have been kept intentionally broad so that this study can adhere to its pragmatic goal. Some exclusion criteria can be determined through the EHR, such as patients who receive regular transfusions for their sickle cell disease or those who have had stem cell transplant for their sickle cell disease and are not approached. All patients who are not excluded based on items in their medical record are approached and, if interested in participating in the study, asked screening questions, which include the following.

- Have you had a stem cell transplant for sickle cell disease
- Have you been diagnosed with sickle cell disease
- Are you 18 or older
- Do you speak and understand English
- Have you been diagnosed with moderate or severe opioid use disorder based on DSM5 criteria?
- Are you on a chronic transfusion or exchange program
- What number best describes how, during the past week, pain has interfered with your general activity (0–10 scale)
- In the past 3 months, how often have you had pain? (Every day, Most days, Some days, Never)

Patients who express interest in the study first meet with a research assistant who explains the study, answers any questions, and determines if the patient meets the inclusion criteria and is willing to participate. Every potential participant has the opportunity to carefully review the consent form and ask questions prior to consenting. A link to the baseline assessment in Research Electronic Data Capture (REDCap) is sent to each patient upon consent [32,33].

2.1.6. Randomization and second randomization

After baseline data are collected, patients are randomized 1:1:1 to the guided relaxation intervention, the acupuncture intervention, or usual care, stratified on baseline PROMIS pain interference (<60, ≥60) and opioid use (yes, no), and implemented separately at each site. The allocation schedule was created in Excel using permuted blocks of 6 for each stratum and uploaded into the REDCap randomization module where upcoming assignments are concealed until baseline data have been completed and the randomization is executed. Research staff execute the randomization by pushing a button in REDCap where the assignment is automatically recorded. Non-intervention staff, including the statistician, cannot access treatment arm assignment through REDCap.

The second randomization, for those not in usual care, occurs at the midpoint assessment (week 6). Only those participants identified as nonresponders to their assigned stage 1 intervention will be included in the second randomization. This is implemented in a similar manner, separately by site, using a second REDCap randomization module without stratification.

2.2. Interventions

Acupuncture. Acupuncturists' qualifications are recorded for all study acupuncturists in the GRACE Trial Acupuncturists Intake Form on REDCap. Study acupuncturists are required to be License Acupuncturists (LAc) or Acupuncture Physicians and must be certified by the National Certification Commission on Acupuncture and Oriental Medicine; or they must be Medical Doctors (MDs) and hold certification through the American Academy of Medical Acupuncture (AAMA). Years practicing acupuncture will be noted but there is no minimal time in practice required for study acupuncturists. There is 1 study acupuncturist at UIC,

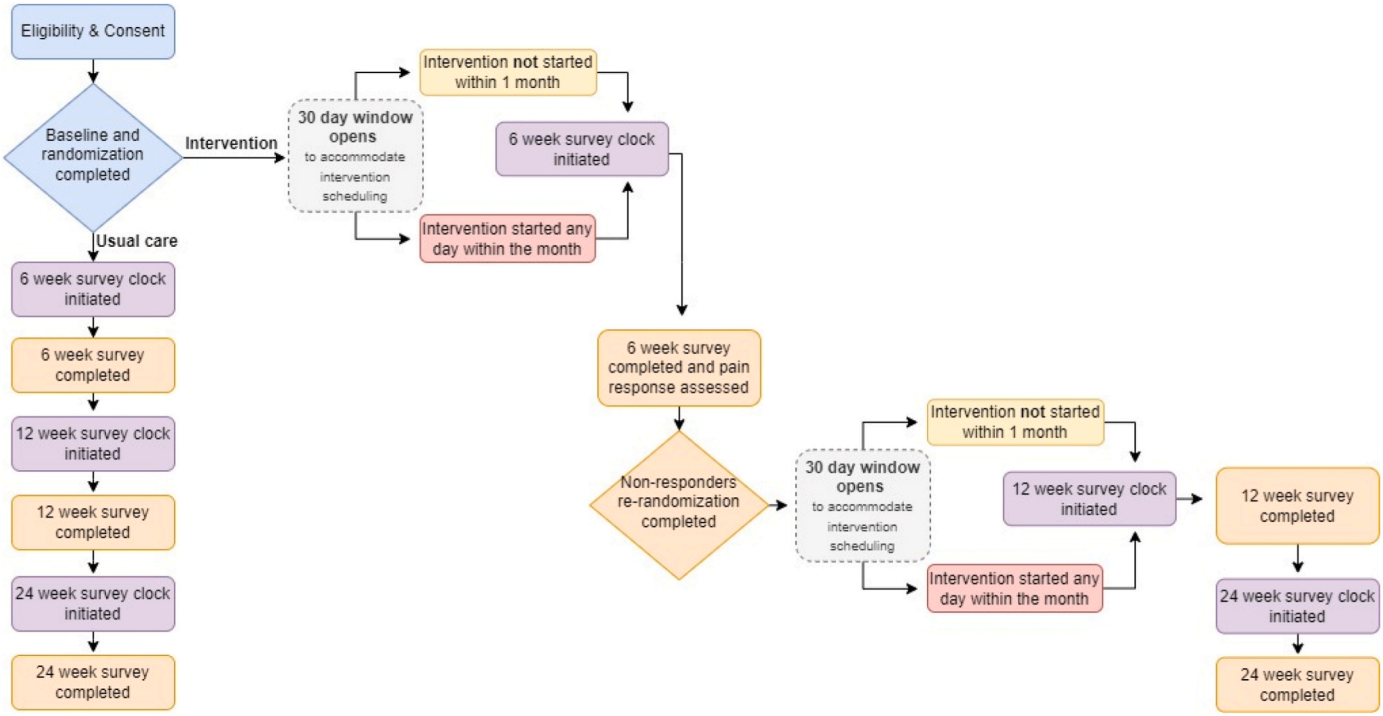

Fig. 2. Participant flow diagram.

4 at Duke, and 2 at UF.

In acupuncture, a set of standardized points is referred to as a point prescription. The GRACE acupuncture intervention includes a standardized point prescription that was developed for this study based on a licensed acupuncturist's Traditional Chinese Medicine assessments of SCD patients (Fig. 3). This point prescription can be replicated easily by any acupuncturist and can be used for the treatment of SCD pain. The needles will be retained (left in place) for 30 min. All needles will be rotated evenly to stimulate the movement of *qi* every 10 min. Participants will receive 2 acupuncture treatments each week for 5 weeks, for a total of 10 treatments.

The Acupuncture Protocol Checklist on REDCap is a step-by-step acupuncture protocol that all study acupuncturists have been trained to use. Fidelity of the Acupuncture Intervention is self-monitored by each acupuncturist for every acupuncture session through completion of the Acupuncture Protocol Checklist on REDCap. Also, fidelity of the acupuncture intervention for each study acupuncturist is monitored every 6 months in real time via video conference call and recorded in the Fidelity Checklist on REDCap.

Guided relaxation. The GRACE guided relaxation intervention includes two components, self-monitoring and use of video banks. Patients monitor their stress and pain levels by providing a rating of stress and pain and then select appropriate video clip based on reported stress and pain levels, and time available to watch the video clip. Patients also monitor their stress and pain levels after watching the video. These steps can be repeated multiple times throughout the day. The video clips, which were developed and validated in psychoneuroimmunology studies in patients with cancer or HIV [34–38], and SCD [16,39,40] are platform independent, so that patients can access them anytime anywhere to manage their pain. The clips include a 12-min guided relaxation video (administered at baseline) and 6 additional video clips ranging from 2 to 20 min. The videos include colorful smoke-like images that slowly change shapes against a dark background. All video clips have similar content, with longer ones having additional positive statements and more repetitions of the same content. Every day, participants will complete pain and stress tracking, watch 1 of 6 videos, and complete the stress and pain tracking again. Sessions will be self-initiated and accessed remotely. Participants are instructed to engage in guided relaxation daily for 5 weeks.

As a measure of intervention fidelity, use of the guided relaxation will be documented by the application software that automatically writes time-stamped data to a Structured Query Language (SQL) database. The fidelity of this protocol is rigorous because the program is computerized and is consistently implemented. In addition, we monitor mobile device use; and time of use is documented in the database to determine intervention dose.

Usual care or control condition. Participants randomized to the usual care arm are instructed to continue their usual care with their providers.

2.3. Measures

All participants will be scheduled to complete assessments at 4 time points: baseline (at study enrollment), week 6 (midpoint), week 12 (intervention end), and week 24 (follow-up). The rationale for the 6-week assessment time point is based on our clinical knowledge and our pilot studies [15,39], which have shown positive effects of CIH therapies after 5 weeks of intervention.

2.3.1. Pain and opioid use measures

Pain impact score. The primary outcome to be assessed in this study is

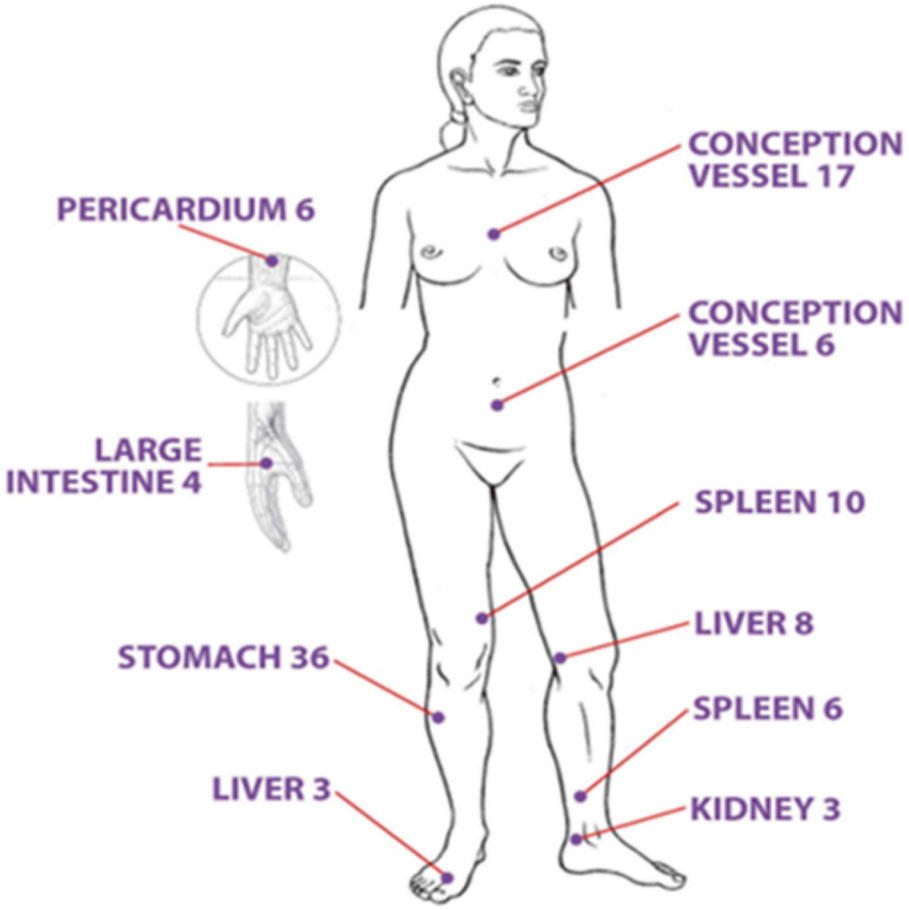

Fig. 3. Acupuncture point prescription. Permission was obtained from the Journal of Chinese Medicine to reproduce this figure.

the pain impact score, a validated composite measure of pain intensity, pain interference, and function [41]. All other outcomes will serve as secondary outcome measures.

PEG scale. The PEG scale is a 3-item version of the Brief Pain Inventory, which assesses pain and its interference with enjoyment of life and general activities. PEG has been shown to be nearly as responsive to improvement as the full Brief Pain Inventory (area under ROC curve: PEG 0.78 versus Brief Pain Inventory 0.81) [42].

Opioid use. Opioid use will be measured in 2 ways, based on participants' reports of number of opioid pills they take per day using the, National Institute of Drug Abuse Clinical Trials Network recommended common date element, the Timeline Followback method [43] using a 2-week look-back period (pill number will be converted to morphine milligram equivalent [MME]/day). The change in MME will be calculated in 2 ways: (1) as a continuous change score between baseline, 12, and 24 weeks, and (2) the categorical MME change—that is, movement from high (>90 MME) to medium (90-50 MME) to low (<50 MME), to 0-MME opioids (no opioids) between baseline, 12, and 24 weeks.

2.3.2. Additional survey measures

Patient-Reported Outcomes Measurement Information System (PROMIS) measures. PROMIS, which was developed by the National Institutes of Health, contains a large, validated data bank of surveys. All PROMIS measures are administered using computerized adaptive testing, which has been programmed into EPIC and ensures a low patient response burden. These measures all have a recall period of 7 days.

The PROMIS *pain interference* [44] item bank specifically focuses on pain interference—defined as the interference of pain in daily activities involving physical, psychological, and social functioning—rather than the more commonly measured pain intensity.

The PROMIS *sleep disturbance* [45] item bank assesses perceptions of sleep quality, sleep depth, and restoration associated with sleep; perceived difficulties and concerns with getting to sleep or staying asleep; and perceptions of the adequacy of and satisfaction with sleep.

The PROMIS *gastrointestinal constipation* [46] item bank is a 9-item measure of constipation, which specifically assesses the symptoms of incomplete evacuation, straining, infrequent stools, and hard stools. The scale also examines rectal pain and need for manual maneuvers to evacuate stool. The items in the constipation domains assess frequency, intensity, bothersomeness, and/or the impact of these factors together in the past 7 days.

Generalized Anxiety Disorder-7 (GAD-7) scale. The GAD-7 scale is a 7-item measure of generalized anxiety disorder. In a criterion-standard study of 15 primary care clinics with 2740 adult patients, the GAD-7 self-report scale demonstrated excellent psychometric characteristics, including internal-consistency reliability (Cronbach $\alpha = 0.92$), test-retest reliability ($r_{icc} = 0.83$), sensitivity (ROC = 0.92), specificity (ROC = 0.76), and factorial validity (factor loadings = 0.69–0.81) [47]. Higher scores on the GAD-7 are associated with higher levels of functional impairment, more disability days, and more physician visits [47,48].

Patient Health Questionnaire-9 (PHQ-9) [49]. This 9-item version of the Patient Health Questionnaire (PHQ) is used to assess depression symptoms. The PHQ-9 has been validated against diagnostic interviews conducted by mental health professionals (K = 0.65; overall accuracy, 85%; sensitivity, 75%; specificity, 90%). It has been positively associated with lower functional status, more disability days, and higher health care utilization. The PHQ-9 also provides an index of depression severity; this index has correlated significantly and highly ($r = 0.84$) with mental health professionals' assessments of depression symptom severity [50–52].

Patient's Global Impression of Change [53]. One of the HEAL common data elements [54], the Patient's Global Impression of Change measures the extent to which a patient's pain status has improved or worsened since the start of a treatment. A clinically important change in pain intensity has been highly associated with the Patient's Global Impression of Change in patients with diverse pain conditions who participated in a number of placebo-controlled trials of gabapentin for reducing pain. Pain scientists have used the Patient's Global Impression of Change extensively as a standard outcome and for comparison with other outcomes [55].

Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) Tool. The TAPS tool consists of 4 questions about use in 4 substance categories in the past 12 months. TAPS can identify, with a high level of accuracy, unhealthy substance use in primary care patients [56].

Pain Catastrophizing Scale (PCS) [57]. The PCS is a 13-item, 3-dimension survey of catastrophizing that includes items that measure a patient's tendency for (1) rumination, (2) magnification, and (3) helplessness. The PCS demonstrates excellent discriminant validity in the context of both experimental pain and clinical pain. Higher PCS scores are strongly correlated with negative pain-related thoughts, emotional distress, and greater perceived pain [58,59].

2.3.3. Implementation measures

Implementation barriers questionnaire. An implementation barriers questionnaire will ask participants at baseline about MyChart use, access to internet, technology and transportation, current insurance, and previous experience with acupuncture or guided relaxation. A follow-up implementation questionnaire will be given to intervention participants at 6 and 12 weeks (1) to identify which barriers to acupuncture they have experienced, (2) to identify which barriers to guided relaxation they have experienced, and (3) to provide 1 open-ended response for each intervention for barriers not listed in the questionnaire.

Qualitative implementation interviews. To understand the impact of the interventions, we will conduct semi-structured qualitative interviews with participants, providers, and staff. We will use interview guides with questions that reflect the five domains and select constructs of the Consolidated Framework for Implementation Research (CFIR) to capture experiences related to the use and implementation of the 2 CIH therapies [60,61].

We will interview 4 *intervention participants* (2 responders and 2 nonresponders) annually from each intervention arm (n = 48) at each site, after their intervention completion and before the second randomization, about their experiences with the specific intervention(s). We will ask about their perception of what factors hindered or facilitated participating in the intervention. Interview questions will also elicit feedback on which aspects of the intervention they found particularly helpful and what might be changed for future iterations. These semi-structured 60- to 90-min interviews will collect detailed information in a relatively conversational style, which will allow us to delve deeply into a topic and explore experiences with the therapies. We will use interview probes to help ensure we receive complete and consistent information across interviews. Each interview will be digitally audio-recorded and transcribed verbatim by a professional transcriptionist. Interviews will be conducted at clinic visits or, if necessary, online via zoom or by phone.

We will also interview *hospital and clinic personnel* (staff, providers, and interventionists [n = 10 at each site]) to capture details about facilitators and barriers to integrating CIH therapies into current practice. At study completion, the same clinic personnel will be asked to participate in 1 implementation group interview to document shared and unique experiences with integration and to identify suggestion and solutions for moving forward. Together, these qualitative data will provide insight from all perspectives on the integration of guided relaxation and acupuncture into patient care for those living with pain associated with SCD.

2.4. Analyses

Power considerations. Our goal is to recruit 366 participants and retain 330, accounting for 10% attrition by the end of the study. Based on our previous work, we anticipate 5% attrition at 6 weeks, yielding a

sample size of 116 per treatment arm. Conservative minimal detectable differences in group means (standard deviation units) were estimated for the 2 primary endpoint comparisons using a 2-sided test, $\alpha = 0.025$, and 80%–90% power and ranged from 0.46 to 0.051 for our proposed sample size of 116 per group, adjusting for clustering effects due to acupuncturists. To adjust for clustering effects in the acupuncture arm we adjusted the variance of the treatment arm using a range of plausible intraclass correlations and average group sizes per acupuncturist. Pragmatic trials commonly have intraclass correlations ranging from 0.01 to 0.05. We assumed a range of 6–9 acupuncturists across the 3 sites; more than 9 acupuncturists are possible, which would further increase study power. Based on a published effect size of 0.50 for acupuncture [19], we estimate that this sample size will have adequate power to detect a true difference between groups. Power will be enhanced if pre-post measures are correlated greater than $r = 0.5$. These minimum detectable differences are based on a single primary outcome (pain impact score) measured at 6 weeks.

Aim 1: Main effectiveness analysis. We will use the same modeling approach to analyze the primary and secondary outcomes, using all interval-level measures obtained at baseline and 6 weeks. We will investigate mean differences at 6 weeks, controlling for the baseline level of the measure and stratification variables used for randomization. Clustering due to common acupuncturists will be addressed by including indicators for each acupuncturist as a repeated factor in a generalized estimating equations model. We will assume 13 to 19 participants per acupuncturist, but this may vary given the logistical differences at each site. Least square (adjusted) means will be estimated for each treatment arm as well as standard errors and 95% confidence intervals. Analyses will be repeated for intention to treat and per protocol population subsamples. All variables will be assessed for amount of missing data and predictors of missingness. Models will be estimated using full information maximum likelihood, weighted generalized estimating equations, and multiple imputation to determine robustness of parameters using these missing data approaches. If missing data appear to be missing not at random, a pattern mixture approach will also be examined [62]. Among the secondary outcomes, a Benjamini-Hochberg approach will be applied using a false discovery rate of 0.05.

Aim 2: Adaptive intervention analysis. Rerandomization creates underrepresentation of non-responders in the dataset, therefore we will restructure and weight the data as recommended by SMART developers [63] and use the generalized estimating equations approach described above with an additional weight variable to account for the restructured dataset. We will estimate the adjusted mean outcome for each embedded sequence and control condition at 12 weeks. We will compare the sequences and control conditions using contrast statements to select the sequence with the greatest improvement.

Aim 3: Exploratory analyses for moderators. We will use a Q-learning approach to explore moderating variables—such as age and sex response—to stage 1 treatment [63]. Although our SMART results will provide evidence for a best sequence, we can use Q-learning to develop decision rules for more extensive tailoring of therapy combinations—for example, if responses to an intervention differ by sex or age. This approach uses regression models, and for this study will involve 2 stages. In the first stage, we will work backward from the final outcome and explore variables that predict the best response to the stage 2 interventions among those who do not respond to stage 1. The goal is to determine explicit decision rules for assigning a stage 2 intervention by predicting the best outcome based on baseline patient characteristics, stage 1 treatment, and initial response to the stage 1 intervention at week 6. In the next stage, we will examine moderators of response for the stage 1 intervention, controlling for the optimal stage 2 intervention for nonresponders. Confidence intervals estimated for the predicted response will suggest which tailoring decisions will lead to reliable differences in outcomes. We will explore the quality of these decision rules for the pain reduction outcome at week 12 (end of intervention) and week 24 (follow-up) in order to recommend additional tailoring of the combinations of guided relaxation and acupuncture tested by this SMART design. These analyses will be implemented in SAS PROC QLEARN (Methodology Center, Pennsylvania State University) [63].

Aim 4: Implementation analysis. The 5 CFIR domains provides selected constructs that have identified as having a strong influence on implementation or highly relevant to the clinics. We will extract contextual factors (events or statements) from observations (study notes) and interviews to document what facilitates or acts as a barrier to implementation (e.g., challenges, resolutions, and the impact of champions and naysayers). We will then categorize factors according to the CFIR domains and constructs initially using the published online codebook.

We will use a deductive-inductive qualitative analysis to evaluate implementation of the interventions. The first round of coding will be guided by the CFIR domains and constructs (the deductive component), which include (1) intervention characteristics, (2) inner setting (i.e., implementing organization), (3) outer setting (i.e., external environment), (4) individual characteristics (i.e., knowledge and beliefs of the individuals involved in the implementation), and (5) process (i.e., strategies and tactics used in the implementation). Within each domain, specific constructs may influence implementation. We will also capture emergent themes in the data (the inductive component), which will allow for discovery of themes not included in a priori CFIR codes. We will follow an iterative process, whereby analysis will begin at the time of first observation and will inform the direction and content of future data collection.

We will use qualitative data organizing software to code the data, using a codebook keyed to the interview questions and designed around the CFIR constructs, which will be supplemented with emerging codes as analysis proceeds. At least 2 individuals will code the data independently and discuss with other team members until an intercoder agreement rate of 80% is reached for 15% of the data. To maximize intercoder reliability, the team will meet regularly during data collection and analysis to review emerging themes, reconcile differences in coding, and determine whether modifications to the interview guide are needed for remaining interviews. Discrepant interpretations of interview data during the coding phase will be resolved by consensus during team meetings. We will keep a decision log to document all coding and analytic decisions made during the study [64,65]. We will conduct between-case analysis using replication logic, in which we will compare cases to look for similarities in processes that promote implementation among similar cases and differences in processes that promote sustainment among different cases. We will analyze coded data by constructing causal diagrams that link the coded elements, logically minimizing the diagrams to produce a parsimonious set of pathways and using explicit decision rules to guide the analysis. Quantitative data, from patient logs of session completion and the tracking database, will be integrated with the qualitative data from observation and transcripts of semistructured interviews with participants, providers, staff, and other key stakeholders. We will address Aim 4 using a continuous, iterative process that brings together direct observation and interview data. We will also use mixed-methods analyses to integrate the qualitative data collected about factors (implementation facilitators or barriers) with the quantitative data collected for Aims 1 to 3 (intervention effectiveness) [66]. Preliminary results will be presented to each Collaborative Implementation Council for feedback; any suggested changes will be incorporated into the results and further confirmed until consensus on the results is reached. Triangulating our data sources will allow us to corroborate evidence, prevent researcher bias in interpretation, and increase the confirmability of our interpretations [67].

3. Discussion

New approaches to caring for patients with SCD are needed. The GRACE study aims to address the challenge of chronic pain management among patients with SCD by providing evidence on the effectiveness of CIH therapies as alternatives to opioids. Our goal is for people with SCD

to experience less pain and reduce their use of opioids.

To date, little is known about implementing CIH therapies in clinics caring for patients with SCD. This study will advance the evidence base for these CIH therapies by moving from efficacy research to implementation science. Because implementation science examines effectiveness in real-world conditions, variations in intervention implementation are expected. The GRACE study maximizes scientific rigor by using a hybrid study design to address both the implementation process and intervention effectiveness. Rigor in analysis of the implementation process is enhanced by using the CFIR evidence-based framework to systematically identify key influences (both facilitators and barriers) that affect implementation success and effectiveness at each site and across sites. Rigor in implementation is enhanced by a harmonized implementation strategy for all sites and careful attention to each intervention's fidelity and any adaptations.

Interpretive rigor is strengthened by our mixed-methods approach to obtain in-depth understanding of complex processes and outcomes, as well as by rigorous qualitative data management techniques, a multidisciplinary team approach toward analysis, and an audit trail that reflects the investigators' analytical thought process. A 3-site Collaborative Implementation Council and clinician workshop will be held to incorporate each group's perspectives into interpretation. Transferability is enhanced by detailed identification of similarities and differences across sites and participants [68].

Meanwhile, characterization of patient factors that predict response to the interventions will support further tailoring of strategies and ensure that they are person-centered. Identification facilitators and barriers to the use of these strategies will inform health care systems that are using a transformational paradigm of respectful patient-centered care in their efforts to generalize and broadly implement CIH strategies for patients with SCD across the US.

Our settings (University of Illinois Hospital & Health Sciences System, Duke University Health System, and University of Florida Health) are large health care systems that are geographically diverse and include both rural/urban and hospital/clinic variations. Collectively, these sites represent a large sample of the SCD patient population in the US. Interventions that succeed in these broadly distributed organizations should be amenable to implementation in any US health care center. In addition, the implementation data will inform health insurance and Centers for Medicare & Medicaid Services policy decisions about expanding coverage of CIH therapies for SCD and other chronic pain conditions.

Widespread implementation of CIH therapies will result in a major change in clinical practice and a high national public health impact that will improve pain management, reduce opioid use, and reduce health care utilization, as measured by emergency department use and hospitalization costs [69]. Benefits will include improved health outcomes, reduced stress, and reduced costs for patients' families through the substantial indirect societal benefits related to reduced health care utilization [70]. The results from GRACE will represent a critical step toward improving management of pain affecting patients with SCD.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Center for Disease Control and Prevention, African American Health, 2017. https://www.cdc.gov/vitalsigns/aahealth/index.html. (Accessed 4 November 2022).
[2] D.R. Williams, R. Wyatt, Racial bias in health care and health: challenges and opportunities, JAMA 314 (2015) 555–556, https://doi.org/10.1001/jama.2015.9260.
[3] L.J. Akinbami, J.E. Moorman, A.E. Simon, K.C. Schoendorf, Trends in racial disparities for asthma outcomes among children 0 to 17 years, J. Allergy Clin. Immunol. 134 (2014) 547–553.e5, https://doi.org/10.1016/j.jaci.2014.05.037, 2001-2010.
[4] L.L. Barnes, D.A. Bennett, Alzheimer's disease in African Americans: risk factors and challenges for the future, Health Aff. Proj. Hope. 33 (2014) 580–586, https://doi.org/10.1377/hlthaff.2013.1353.
[5] M.K. Jang, C.G. Park, S. Hong, D. Laddu, H. Li, E. Rhee, A.Z. Doorenbos, Skeletal muscle mass loss during cancer treatment: differences by race and cancer site, Oncol. Nurs. Forum 47 (2020) 557–566, https://doi.org/10.1188/20.ONF.557-566.
[6] Association of American Medical Colleges, How We Fail Black Patients In Pain, 2022. https://www.aamc.org/news-insights/how-we-fail-black-patients-pain.
[7] H. Sohn, Racial and ethnic disparities in health insurance coverage: dynamics of gaining and losing coverage over the life-course, Popul. Res. Pol. Rev. 36 (2017) 181–201, https://doi.org/10.1007/s11113-016-9416-y.
[8] N.C. Bahr, J. Song, The effect of structural violence on patients with sickle cell disease, J. Health Care Poor Underserved 26 (2015) 648–661, https://doi.org/10.1353/hpu.2015.0094.
[9] Center for Disease Control and Prevention, Data & Statistics on Sickle Cell Disease, 2022. https://www.cdc.gov/ncbddd/sicklecell/data.html. (Accessed 16 March 2019).
[10] S. Lanzkron, C.P. Carroll, C. Haywood, The burden of emergency department use for sickle-cell disease: an analysis of the national emergency department sample database, Am. J. Hematol. 85 (2010) 797–799, https://doi.org/10.1002/ajh.21807.
[11] S.L. Yoon, S. Black, Comprehensive, Integrative management of pain for patients with sickle-cell disease, J. Altern. Complement. Med. N. Y. N. 12 (2006) 995–1001, https://doi.org/10.1089/acm.2006.12.995.
[12] W.E. Thompson, I. Eriator, Pain control in sickle cell disease patients: use of complementary and alternative medicine, Pain Med, Malden Mass 15 (2014) 241–246, https://doi.org/10.1111/pme.12292.
[13] A.A. Busari, M.A. Mufutau, High prevalence of complementary and alternative medicine use among patients with sickle cell disease in a tertiary hospital in Lagos, South West, Nigeria, BMC Compl. Alternative Med. 17 (2017) 299, https://doi.org/10.1186/s12906-017-1812-2.
[14] S. Majumdar, W. Thompson, N. Ahmad, C. Gordon, C. Addison, The use and effectiveness of complementary and alternative medicine for pain in sickle cell anemia, Complement, Ther. Clin. Pract. 19 (2013) 184–187, https://doi.org/10.1016/j.ctcp.2013.05.003.
[15] H. Li, C.L. Patil, R.E. Molokie, F. Njoku, A.D. Steffen, A.Z. Doorenbos, J. M. Schlaeger, Acupuncture for chronic pain in adults with sickle cell disease: a mixed-methods pilot study, Acupunct. Med. J. Br. Med. Acupunct. Soc. 39 (2021) 612–618, https://doi.org/10.1177/09645284211017303.
[16] M.O. Ezenwa, Y. Yao, M.-N.T. Nguyen, M.W. Mandernach, C.T. Hunter, S.L. Yoon, D. Fedele, R.J. Lucero, D. Lyon, D.J. Wilkie, Randomized pilot study: a mobile technology-based self-management intervention for sickle cell pain, west, J. Nurs. Res. 42 (2020) 629–639, https://doi.org/10.1177/0193945919878821.
[17] National Institutes of Health, National center for complementary and alternative medicine, complementary, alternative, or integrative health: what's in a name? Natl. Inst. Health Natl. Cent. Complement. Altern. Med. (2014). http://nccam.nih.gov/health/whatiscam/.
[18] G. Deng, B. Cassileth, Complementary or alternative medicine in cancer care-myths and realities, Nat. Rev. Clin. Oncol. 10 (2013) 656–664, https://doi.org/10.1038/nrclinonc.2013.125.
[19] A.J. Vickers, E.A. Vertosick, G. Lewith, H. MacPherson, N.E. Foster, K.J. Sherman, D. Irnich, C.M. Witt, K. Linde, Acupuncture trialists' collaboration, acupuncture for chronic pain: update of an individual patient data meta-analysis, J. Pain 19 (2018) 455–474, https://doi.org/10.1016/j.jpain.2017.11.005.
[20] Y. He, X. Guo, B.H. May, A.L. Zhang, Y. Liu, C. Lu, J.J. Mao, C.C. Xue, H. Zhang, Clinical evidence for association of acupuncture and acupressure with improved cancer pain: a systematic review and meta-analysis, JAMA Oncol. 6 (2020) 271–278, https://doi.org/10.1001/jamaoncol.2019.5233.
[21] K. Lu, M.-C.J. Cheng, X. Ge, A. Berger, D. Xu, G.J. Kato, C.P. Minniti, A retrospective review of acupuncture use for the treatment of pain in sickle cell

disease patients: descriptive analysis from a single institution, Clin. J. Pain 30 (2014) 825–830, https://doi.org/10.1097/AJP.0000000000000036.
[22] L.L. Co, T.H. Schmitz, H. Havdala, A. Reyes, M.P. Westerman, Acupuncture: an evaluation in the painful crises of sickle cell anaemia, Pain 7 (1979) 181–185, https://doi.org/10.1016/0304-3959(79)90009-5.
[23] L.H. Eaton, J.P. Hulett, D.J. Langford, A.Z. Doorenbos, How theory can help facilitate implementing relaxation as a complementary pain management approach, Pain Manag. Nurs. Off. J. Am. Soc. Pain Manag. Nurses. 20 (2019) 207–213, https://doi.org/10.1016/j.pmn.2018.12.008.
[24] W. Ju, L. Ren, J. Chen, Y. Du, Efficacy of relaxation therapy as an effective nursing intervention for post-operative pain relief in patients undergoing abdominal surgery: a systematic review and meta-analysis, Exp. Ther. Med. 18 (2019) 2909–2916, https://doi.org/10.3892/etm.2019.7915.
[25] R.B. Hyman, H.R. Feldman, R.B. Harris, R.F. Levin, G.B. Malloy, The effects of relaxation training on clinical symptoms: a meta-analysis, Nurs. Res. 38 (1989) 216–220.
[26] Y. Zhang, L. Montoya, S. Ebrahim, J.W. Busse, R. Couban, R.E. McCabe, P. Bieling, A. Carrasco-Labra, G.H. Guyatt, Hypnosis/Relaxation therapy for temporomandibular disorders: a systematic review and meta-analysis of randomized controlled trials, J. Oral Facial Pain Headache 29 (2015) 115–125, https://doi.org/10.11607/ofph.1330.
[27] S.M. Badawy, R.M. Cronin, J. Hankins, L. Crosby, M. DeBaun, A.A. Thompson, N. Shah, Patient-centered eHealth interventions for children, adolescents, and adults with sickle cell disease: systematic review, J. Med. Internet Res. 20 (2018), e10940, https://doi.org/10.2196/10940.
[28] A.Z. Doorenbos, E.A. Haozous, M.K. Jang, D. Langford, Sequential multiple assignment randomization trial designs for nursing research, Res. Nurs. Health 42 (2019) 429–435, https://doi.org/10.1002/nur.21988.
[29] G.M. Curran, M. Bauer, B. Mittman, J.M. Pyne, C. Stetler, Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact, Med. Care 50 (2012) 217–226, https://doi.org/10.1097/MLR.0b013e3182408812.
[30] A.Z. Doorenbos, Y. Kato, Pragmatic clinical trials: increasing the rate of translating nursing research into practice, Jpn. J. Nurs. Sci. JJNS. 17 (2020), e12350, https://doi.org/10.1111/jjns.12350.
[31] D. Almirall, I. Nahum-Shani, N.E. Sherwood, S.A. Murphy, Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research, Transl. Behav. Med. 4 (2014) 260–274, https://doi.org/10.1007/s13142-014-0265-0.
[32] P.A. Harris, R. Taylor, B.L. Minor, V. Elliott, M. Fernandez, L. O'Neal, L. McLeod, G. Delacqua, F. Delacqua, J. Kirby, S.N. Duda, REDCap Consortium, the REDCap consortium: building an international community of software platform partners, J. Biomed. Inf. 95 (2019), 103208, https://doi.org/10.1016/j.jbi.2019.103208.
[33] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inf. 42 (2009) 377–381, https://doi.org/10.1016/j.jbi.2008.08.010.
[34] I.B. Corless, D. Abrams, P.K. Nicholas, C.A. McGibbon, The use of complementary and alternative therapies, AACN Clin. Issues. 11 (2000) 4–6, https://doi.org/10.1097/00044067-200002000-00002.
[35] I.B. Corless, D. Abrams, B. Biglieri, M. Dodd, View from within Coping with Isolated Thrombocytic Purpura, 1987. Washington, D. C.
[36] I.B. Corless, D. Abrams, E. Biglieri, M. Dodd, Men with Isolated Thrombocytic Purpura:The Impact of a Psychophysiological Intervention on Platelet Count, 1987. Washington, D. C.
[37] I.B. Corless, in: D.C. Washington (Ed.), The Impact of Psychophysiological Intervention on Men with ITP, 1987.
[38] I.B. Corless, For Healthful, Loving Living, Video and Discussion, Chapel Hill, NC, 1988.
[39] M. Ezenwa, Y. Yao, R. Molokie, C. Engeland, Z. Wang, M. Suarez, Z. Zhao, J. Carrasco, R. Angulo, D. Wilkie, Feasibility of an internet-enabled tablet-based guided imagery for stress and pain reduction intervention in adults with sickle cell disease, J. Pain 16 (2015) S101, https://doi.org/10.1016/j.jpain.2015.01.422.
[40] M.O. Ezenwa, Y. Yao, C.G. Engeland, R.E. Molokie, Z.J. Wang, M.L. Suarez, D. J. Wilkie, A randomized controlled pilot study feasibility of a tablet-based guided audio-visual relaxation intervention for reducing stress and pain in adults with sickle cell disease, J. Adv. Nurs. 72 (2016) 1452–1463, https://doi.org/10.1111/jan.12895.
[41] R.A. Deyo, S.F. Dworkin, D. Amtmann, G. Andersson, D. Borenstein, E. Carragee, J. Carrino, R. Chou, K. Cook, A. DeLitto, C. Goertz, P. Khalsa, J. Loeser, S. Mackey, J. Panagis, J. Rainville, T. Tosteson, D. Turk, M. Von Korff, D.K. Weiner, Focus article: report of the NIH task force on research standards for chronic low back pain, Eur. Spine J. Off. Publ. Eur. Spine Soc. Eur. Spinal Deform. Soc. Eur. Sect. Cerv. Spine Res. Soc. 23 (2014) 2028–2045, https://doi.org/10.1007/s00586-014-3540-3.
[42] E.E. Krebs, M.J. Bair, T.M. Damush, W. Tu, J. Wu, K. Kroenke, Comparative responsiveness of pain outcome measures among primary care patients with musculoskeletal pain, Med. Care 48 (2010) 1007–1014, https://doi.org/10.1097/MLR.0b013e3181eaf835.
[43] S.M. Robinson, L.C. Sobell, M.B. Sobell, G.I. Leo, Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use, Psychol. Addict, Behav. J. Soc. Psychol. Addict. Behav. 28 (2014) 154–162, https://doi.org/10.1037/a0030992.
[44] D. Amtmann, K.F. Cook, M.P. Jensen, W.-H. Chen, S. Choi, D. Revicki, D. Cella, N. Rothrock, F. Keefe, L. Callahan, J.-S. Lai, Development of a PROMIS item bank to measure pain interference, Pain 150 (2010) 173–182, https://doi.org/10.1016/j.pain.2010.04.025.
[45] L. Yu, D.J. Buysse, A. Germain, D.E. Moul, A. Stover, N.E. Dodds, K.L. Johnston, P. A. Pilkonis, Development of short forms from the PROMIS™ sleep disturbance and Sleep-Related Impairment item banks, Behav. Sleep Med. 10 (2011) 6–24, https://doi.org/10.1080/15402002.2012.636266.
[46] B.M.R. Spiegel, R.D. Hays, R. Bolus, G.Y. Melmed, L. Chang, C. Whitman, P. P. Khanna, S.H. Paz, T. Hays, S. Reise, D. Khanna, Development of the NIH patient-reported outcomes measurement information system (PROMIS) gastrointestinal symptom scales, Am. J. Gastroenterol. 109 (2014) 1804–1814, https://doi.org/10.1038/ajg.2014.237.
[47] R.L. Spitzer, K. Kroenke, J.B.W. Williams, B. Löwe, A brief measure for assessing generalized anxiety disorder: the GAD-7, Arch. Intern. Med. 166 (2006) 1092–1097, https://doi.org/10.1001/archinte.166.10.1092.
[48] K. Kroenke, R.L. Spitzer, J.B.W. Williams, P.O. Monahan, B. Löwe, Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection, Ann. Intern. Med. 146 (2007) 317–325, https://doi.org/10.7326/0003-4819-146-5-200703060-00004.
[49] A. Martin, W. Rief, A. Klaiberg, E. Braehler, Validity of the brief patient health questionnaire mood scale (PHQ-9) in the general population, Gen. Hosp. Psychiatr. 28 (2006) 71–77, https://doi.org/10.1016/j.genhosppsych.2005.07.003.
[50] B. Löwe, R.L. Spitzer, K. Gräfe, K. Kroenke, A. Quenter, S. Zipfel, C. Buchholz, S. Witte, W. Herzog, Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses, J. Affect. Disord. 78 (2004) 131–140, https://doi.org/10.1016/s0165-0327(02)00237-9.
[51] B. Löwe, J. Unützer, C.M. Callahan, A.J. Perkins, K. Kroenke, Monitoring depression treatment outcomes with the patient health questionnaire-9, Med. Care 42 (2004) 1194–1201, https://doi.org/10.1097/00005650-200412000-00006.
[52] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (2001) 606–613, https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
[53] J.T. Farrar, J.P. Young, L. LaMoreaux, J.L. Werth, M.R. Poole, Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale, Pain 94 (2001) 149–158, https://doi.org/10.1016/S0304-3959(01)00349-9.
[54] L.D. Wandner, A.F. Domenichiello, J. Beierlein, L. Pogorzala, G. Aquino, A. Siddons, L. Porter, J. Atkinson, NIH pain consortium Institute and center representatives, NIH's helping to end addiction long-termSM initiative (NIH HEAL initiative) clinical pain management common data element program, J. Pain 23 (2022) 370–378, https://doi.org/10.1016/j.jpain.2021.08.005.
[55] S. Perrot, M. Lantéri-Minet, Patients' Global Impression of Change in the management of peripheral neuropathic pain: clinical relevance and correlations in daily practice, Eur. J. Pain 23 (2019) 1117–1128, https://doi.org/10.1002/ejp.1378.
[56] J. McNeely, L.-T. Wu, G. Subramaniam, G. Sharma, L.A. Cathers, D. Svikis, L. Sleiter, L. Russell, C. Nordeck, A. Sharma, K.E. O'Grady, L.B. Bouk, C. Cushing, J. King, A. Wahle, R.P. Schwartz, Performance of the tobacco, Alcohol, prescription medication, and other substance use (TAPS) tool for substance use screening in primary care patients, Ann. Intern. Med. 165 (2016) 690–699, https://doi.org/10.7326/M16-0317.
[57] M.J.L. Sullivan, S.R. Bishop, J. Pivik, The pain catastrophizing scale: development and validation, Psychol. Assess. 7 (1995) 524–532, https://doi.org/10.1037/1040-3590.7.4.524.
[58] Y. Conti, J.-J. Vatine, S. Levy, Y.L. Meltz, S. Hamdan, O. Elkana, Pain catastrophizing mediates the association between mindfulness and psychological distress in chronic pain syndrome, Pain Pract. 20 (2020) 714–723, https://doi.org/10.1111/papr.12899.
[59] M.J. Lami, M.P. Martínez, E. Miró, A.I. Sánchez, M.A. Guzmán, Catastrophizing, acceptance, and coping as mediators between pain and emotional distress and disability in fibromyalgia, J. Clin. Psychol. Med. Settings 25 (2018) 80–92, https://doi.org/10.1007/s10880-018-9543-1.
[60] L.J. Damschroder, D.C. Aron, R.E. Keith, S.R. Kirsh, J.A. Alexander, J.C. Lowery, Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science, Implement. Sci. IS. 4 (2009) 50, https://doi.org/10.1186/1748-5908-4-50.
[61] M.A. Kirk, C. Kelley, N. Yankey, S.A. Birken, B. Abadie, L. Damschroder, A systematic review of the use of the consolidated framework for implementation research, Implement. Sci. IS. 11 (2016) 72, https://doi.org/10.1186/s13012-016-0437-z.
[62] R.J.A. Little, D.B. Rubin, Statistical Analysis with Missing Data, third ed., Wiley, Hoboken, NJ, 2019.
[63] I. Nahum-Shani, M. Qian, D. Almirall, W.E. Pelham, B. Gnagy, G.A. Fabiano, J. G. Waxmonsky, J. Yu, S.A. Murphy, Q-learning: a data analysis method for constructing adaptive interventions, Psychol. Methods 17 (2012) 478–494, https://doi.org/10.1037/a0029373.
[64] D.G. Cope, Methods and meanings: credibility and trustworthiness of qualitative research, Oncol. Nurs. Forum 41 (2014) 89–91, https://doi.org/10.1188/14.ONF.89-91.
[65] U.H. Graneheim, B. Lundman, Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness, Nurse Educ. Today 24 (2004) 105–112, https://doi.org/10.1016/j.nedt.2003.10.001.
[66] A.Z. Doorenbos, Mixed methods in nursing research : an overview and practical examples, Kango Kenkyu 47 (2014) 207–217.
[67] J.W. Creswell, C.N. Poth, Qualitative Inquiry and Research Design: Choosing Among Five Approaches, fourth ed., SAGE Publications, Inc, Los Angeles, 2017.

[68] C. Teddlie, A. Tashakkori, Foundations of Mixed Methods Research: Integrating Quantitative and Qualitative Approaches in the Social and Behavioral Sciences, SAGE, 2009.
[69] S.B. Zeliadt, S. Coggeshall, H. Gelman, M.H. Shin, A.R. Elwy, B.G. Bokhour, S. L. Taylor, Assessing the relative effectiveness of combining self-care with practitioner-delivered complementary and integrative health therapies to improve pain in a pragmatic trial, Pain Med. Malden Mass. 21 (2020), https://doi.org/10.1093/pm/pnaa349. S100–S109.
[70] T.E. Paterick, N. Patel, A.J. Tajik, K. Chandrasekaran, Improving health outcomes through patient education and partnerships with patients, Proc. - Bayl. Univ. Med. Cent. 30 (2017) 112–113, https://doi.org/10.1080/08998280.2017.11929552.