Hybrid Effectiveness-Implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.
Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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Duke University Site Investigator:

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Name:

Title:

Affiliation:

University of Florida Site Investigator:

Signed: _____ Date: _____

Name:

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Affiliation:

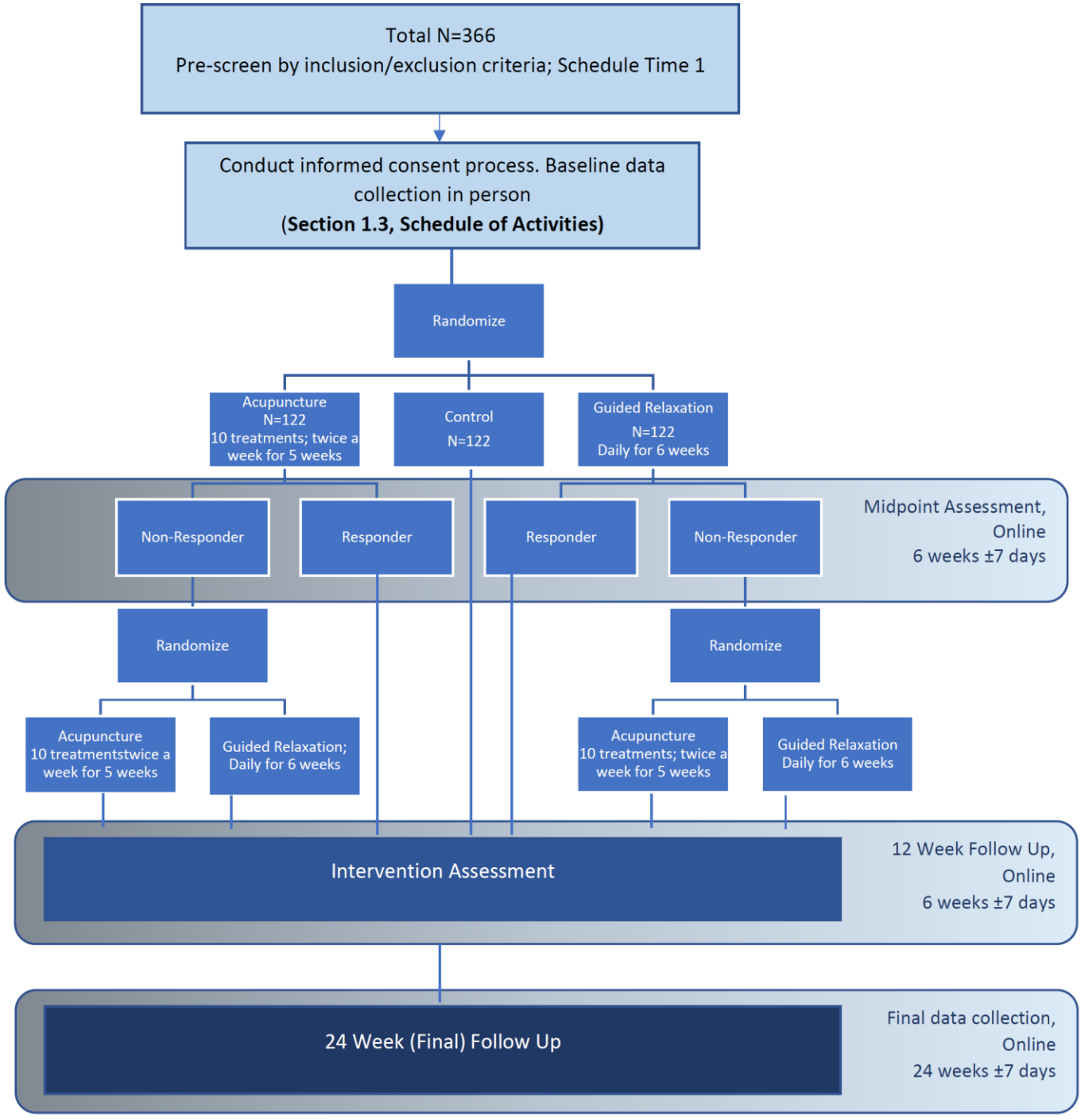
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Hybrid Effectiveness-Implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain
Grant Number:	UG3 AT011265
Study Description:	This pragmatic randomized clinical trial will explore the effectiveness of two complimentary integrative therapies, acupuncture and guided relaxation, for helping reduce chronic pain in individuals living with sickle cell disease. As a pragmatic trial, this study will also assess the implementation barriers and facilitators of including these interventions in real world healthcare settings.
Objectives*:	**Primary Objective**: Determine if each intervention reduces pain impact compared to usual care based on Pain Impact Scores **Secondary Objectives**: Determine the impact of each intervention on all other patient reported outcomes, including opioid use, anxiety, depression, sleep, quality of life, pain catastrophizing, pain self-efficacy, patient activation, as well as measuring patient experience with the interventions.
Endpoints*:	**Primary Endpoint**: Change in pain impact score and PEG **Secondary Endpoints**: Opioid Use, Anxiety, Depression, Sleep, Pain catastrophizing, Global impression of change, Substance use, and Constipation
Study Population:	366 people, aged 18 and up, living with chronic pain resulting from Sickle Cell Disease
Phase* or Stage:	Phase 2
Description of Sites/Facilities Enrolling Participants:	The study sits will include 3 university hospital systems in the US, University of Illinois Hospital & Health Sciences System, Duke University Health System and University of Florida Health.
Description of Study Intervention/Experimental Manipulation:	The study interventions are acupuncture and guided relaxation. Participants randomized to the acupuncture group will receive treatments on-site twice a week for 10 sessions for 30 minutes per session, and the guided relaxation group will use a web-based app remotely on a daily basis with sessions ranging from 2 to 20 minutes each.
Study Duration*:	41 months
Participant Duration:	24 Weeks

1.2 SCHEMA

Flow Diagram Pragmatic Randomized Clinical Trial



1.3 SCHEDULE OF ACTIVITIES

Construct	Operational Measure	Time Point					
		Pre-screen	Baseline Day 1	Week 6 (mid-point) Day 42 ±7 days	Week 12 (intervention end) Day 84 ±7 days	Week 24 (follow-up) Day 168 ±7 days	Source
EHR for screening		✸					
Informed Consent			✸				
	PRIMARY OUTCOME (PAIN)						
Pain impact score	A composite measure of PEG average pain intensity, pain interference 4a, and function 6b		✸	✸	✸	✸	SRS
	SECONDARY OUTCOMES (MENTAL AND PHYSICAL WELL-BEING AND SATISFACTION WITH CARE)						
PEG	0-10 rating on pain intensity, enjoyment of life and general activity		✸	✸	✸	✸	SRS
Opioid use, morphine milligram equivalent (MME)	Based on participant report of # opioid pills per day using Timeline Followback method with a 14-day look-back period (pill number will be converted to MME/day)		✸	✸	✸	✸	SRS
Opioid MME change (continuous)	Change from baseline to 12 and 24 weeks				✸	✸	Calculated
Opioid MME change (categorical)	Movement from high (> 90 MME), to medium (90–50 MME), to low (< 50 MME), to off opioids			✸	✸	✸	Calculated

Anxiety	GAD–7		✸	✸	✸	✸	SRS
Depression	PHQ-9		✸	✸	✸	✸	SRS
Sleep	PROMIS sleep disturbance 8a and sleep duration question		✸	✸	✸	✸	SRS
Pain catastrophizing	Pain Catastrophizing Scale (PCS)		✸	✸	✸	✸	SRS
Global impression of change	PGIC		✸	✸	✸	✸	SRS
Substance use screener	TAPS1		✸	✸	✸	✸	SRS
Constipation	PROMIS GI Constipation 9a		✸	✸	✸	✸	SRS
	OTHER MEASURES						
Clinical data	Hospitalizations and length of stay		✸			✸	SRS, confirm with EHR
Demographic data	Age, sex, race, employment status, comorbidities, marital status, number of household members, annual income, educational attainment		✸				SRS
Other	Use of non-study behavioral or other non-pharmacologic treatment for pain		✸	✸	✸	✸	SRS
Implementation Survey			✸		✸(Intervention arms only)		SRS
Randomization			✸	✸			
See specific intervention tables for schedules of events							

ACUPUNCTURE INTERVENTION	First randomization	Second randomization
Session 1	Day 3±1	Day 43±1
Session 2	Day 7±1	Day 47±1
Session 3	Day 10±1	Day 50±1
Session 4	Day 14±1	Day 64±1
Session 5	Day 17±1	Day 67±1
Session 6	Day 21±1	Day 71±1
Session 7	Day 24±1	Day 74±1
Session 8	Day 27±1	Day 77±1
Session 9	Day 31±1	Day 81±1
Session 10	Day 34±1	Day 84±1

GUIDED RELAXATION INTERVENTION	First randomization	Second randomization
Intro video	Day 2	Day 43
Pre-video stress and pain tracking	Day 3-42	Day 44-83
Video session	Day 3-42	Day 44-83
Post-video stress and pain tracking	Day 3-42	Day 44-83

QUALITATIVE INTERVIEWS	First focus group	Second focus group	Third focus group	Final focus group
Hospital Staff	6 months after study initiation	12 months after study initiation	18 months after study initiation	24 months after study initiation

2 INTRODUCTION

2.1 STUDY RATIONALE

Nearly 100 people die every day from a prescription opioid overdose in the United States (US). Over-reliance on opioids for those with chronic pain is one of the factors that led to this crisis. Pain, both acute and chronic, that is so severe that it requires opioids to attempt to keep it to tolerable levels, is a constant companion to the 100,000 people in the United States, mostly of African and Hispanic background, and millions more worldwide living with sickle cell disease (SCD). Pain is SCD's hallmark symptom and is the leading cause for almost 200,000 annual emergency department (ED) admissions and most hospitalizations, with estimated annual health care costs in the US of $2.4 billion. We will conduct a hybrid type 1 effectiveness implementation trial to assess the effectiveness of acupuncture

and guided relaxation on 366 people with SCD while observing and gathering information on implementation in three health systems: University of Illinois Hospital & Health Sciences System, University of Florida Health, and Duke University Health Systems. Each serves a large population with SCD, uses EPIC as their electronic health record, and has a Clinical and Translational Science Award (CTSA), which will help speed the translation of discovery into improved patient care. UG3 1-year Planning Phase: Year 1 comprises milestone-driven planning to prepare the three health systems for the subsequent pragmatic clinical trial (UH3). During the UH3 Implementation Phase, our 3-arm, 3-site randomized controlled trial will follow a quantitative Sequential, Multiple Assignment, Randomized Trials (SMART) design, a pragmatic trial that evaluates adaptive interventions where our guided relaxation and acupuncture interventions responds to patients' characteristics and evolving pain status. We rely on the Consolidated Framework for Implementation Research (CFIR) to plan, execute, and evaluate associated implementation processes. The use of complementary and integrative (CIH) therapies by those with SCD to reduce pain, opioid use, and enable themselves to better cope with their pain is well known, but there are few studies that evaluate the effectiveness of these therapies, and none that also evaluates the implementation across multiple health care systems and patient populations as this study will.

2.2 BACKGROUND

Chronic pain and the opioid epidemic are recognized as public health crises with chronic pain affecting 11% of adults in the US. In 2016 chronic pain was estimated to have an annual cost of $635 billion.[1] While chronic pain is frequently treated with opioid medication, long-term opioid therapy is of questionable benefit for it.[2,3] Unfortunately, the dramatic increase in opioid prescribing for chronic pain has not been associated with measurable decreases in the prevalence of chronic pain or pain-related disability. Since 1999, overdose deaths involving prescription opioids have risen along with total opioid-related deaths.[4,5] In 2017, the U.S. Department of Health and Human Services declared the opioid epidemic a public health emergency and outlined 5 key strategic priorities, including supporting research on pain and addiction and advancing better practices for pain management.[6] In light of the generally unfavorable risk-benefit profile of long-term opioid therapy, consensus guidelines promote increasing pain self-management strategies and non-opioid pain care.[7,8] There is now urgent need to evaluate novel treatment interventions.

Potential Harms from Long-Term Opioid Therapy

While we are acutely aware of the dangers of opioid therapy for pain, including the lack of significant improvement in pain, the potential for addiction, overdose, death, and multiple other side effects also can occur, and may be dose limiting. These include opioid induced hyperalgesia,[9] tolerance, hypogonadism, infection,[10] osteoporosis, falls, fractures, motor vehicle accidents, opioid use disorder, intermittent withdrawal symptoms,[11] glycemic control in diabetics,[12] cognitive dysfunction,[13] somnolence and sleep disordered breathing,[14] to name just some. Critically, many of these occur with other medical conditions that are increase in prevalence, as is pain, increasing the possibility of additive or more effect. Clearly effective opioid sparing therapies are need.

Sickle Cell Disease and Pain Management

The term SCD refers to several hemoglobin disorders that have in common a mutation in the β-hemoglobin chain. It is the most common lethal genetic blood disorder in the world. In the US, approximately 100,000 people, mainly of African and Hispanic background have it, but there are millions with it worldwide.[15] Pain is a constant companion for those with SCD. They are so intertwined, that

ancient African tribal words are onomatopoeic for it.[16] Pain is the most common admitting diagnosis to both the Emergency Department (ED), as well as to the hospital. In 2009, the annual medical care costs for SCD in the US were estimated at $2.4 billion.[17] For many years, SCD disease pain was thought to be only acute; it has now become increasingly clear that adults with SCD also experience chronic pain,[18,19] in addition to acute worsening of their pain. Pain in sickle cell disease is a complex process and is often associated with anxiety. In order to attempt to keep their chronic pain to acceptable levels, those with SCD require opioid therapy. One study reported that in a sample of 219 adult patients with SCD during the study period, 78% of the patients used opioids. These included both long acting with or without short acting opioid (38.8%), as well as 47% used only short-acting opioids. Only about 10% used only non-opioid analgesics, and about 5% used no analgesics.[20] In another study of adults with SCD, 85% were taking step 2 opioids, and 65% were taking step 3. This study also reported pain barrier scores similar to or greater than those reported by people with cancer.[19]The evaluation of alternative therapies that reduce chronic pain and the need for opioid medication among individuals with SCD, and to enable patients to better cope with pain, is critically needed to address the lack of adequate pain control, high opioid use, and their negative sequelae.

Safe and Effective Complementary and Integrative Health (CIH) Therapies and Pain Management

The National Pain Strategy has called for a cultural shift in how chronic pain is managed.[21] The use of complementary and integrative health (CIH) therapies is widespread in the US, with a significant increase in its use for common chronic conditions over a 7-year time span.[22] The last updated National Health Interview Survey (2008) reported that 38% of Americans use some type of CIH therapy.[23] The research literature also indicates that there is use of CIH among SCD patients.[24]

Due to the chronicity of pain in SCD and concerns with opioid therapy, patients and families with SCD often attempt to control pain and other symptoms with traditional medicine or CIH therapies.[25] Studies have reported that 89% to 92% of patients with SCD use CIH therapies or cognitive behavioral therapy to control pain, with use higher among females, singles, and patients with more education and higher household income.[26] Prayer and meditation, relaxation techniques, massage, herbal products, heat application, and alternative medical systems are the leading therapies used by people with SCD, followed by warm baths, exercise, and mind-body interventions.[26–28] Since many SCD patients try using 2 or more therapies, there is also a need to rigorously test the effects of adding another therapy when the first does not produce the desired outcomes in a given period of time. This study will assess the outcomes of sequencing 2 evidence-based CIH therapies among SCD patients treated in real-world health care systems.

Selection of Therapies

The National Center for Complementary and Integrative Health[29] identified 5 areas for investigation: mind-body therapies; body-based therapies; biologically based therapies; energy therapies; and alternative medical systems. For this study, we selected one body-based therapy (acupuncture) and one mind-body therapy (guided relaxation), because these 2 therapy groups are the most widely used by patients,[30] and there is evidence that the therapies are safe and effective for reducing pain.

Acupuncture

Acupuncture use is on the rise in the United States. In 2012 (last updated), Americans received 3,484,000 acupuncture sessions, which was a significant increase from the years 2002 to 2007.[31] There is also evidence of its efficacy for pain conditions. American men and women frequently seek acupuncture

for pain whether or not they tell their physicians; almost 8% of those using CIH do not tell their physicians.[32] Acupuncture has demonstrated physiologic analgesic effects. It has been shown to help relieve pain by (1) deactivating the limbic-paralimbic-neocortical network system;[33] (2) activating mu opioid receptors;[34] (3) increasing serum β endorphins;[35] (4) down-regulating M1 macrophages, interleukin-1β, interleukin-6, interleukin-18, and tumor necrosis factor;[36] and (5) regulating central and peripheral blood flow.[37]

Rationale for acupuncture to address pain

A meta-analysis of 39 high-quality randomized trials of acupuncture examined 20,827 patients for the treatment of 4 chronic pain conditions: nonspecific musculoskeletal pain, osteoarthritis, chronic headache, and shoulder pain. Study designs included acupuncture needling versus either sham acupuncture or no acupuncture as a control. Results indicated that acupuncture was superior over sham acupuncture or usual care for reduction of pain in all 4 pain conditions (all $p < .001$).[38] A second meta-analysis examined duration of the acupuncture treatment effect.[39] Long-term follow-up data was analyzed for 20 of the aforementioned trials with 6,376 patients.[39] In trials comparing acupuncture to no acupuncture, effect sizes were reduced by a nonsignificant 0.011 SD per 3 months post acupuncture completion (95% CI, -0.014 to 0.037, $p = 0.4$). In trials comparing acupuncture to sham acupuncture, effect sizes were reduced 0.025 SD per 3 months post acupuncture completion (95% CI, 0.000–0.050, $p = 0.050$). The central estimate suggested that approximately 90% of the acupuncture effect as compared to usual care and approximately 50% of the acupuncture effect versus sham acupuncture would be sustained at 12 months post acupuncture completion. A third 2019 systematic review and meta-analysis examined acupuncture and/or acupressure for reducing cancer pain.[40] Seventeen randomized controlled trials (RCTs) of 1,111 patients for the systematic review and 14 RCTs of 920 patients for the meta-analysis compared acupuncture to sham control, analgesic therapy, and usual care for reducing cancer pain. The primary outcome was pain intensity as measured by the Brief Pain Inventory (BPI), a numerical rating scale, a visual analog scale, or a verbal rating scale. In 7 sham controlled RCTs, verum (traditional) acupuncture as compared to sham acupuncture was found to be associated with reduced pain intensity (mean difference [MD], −1.38 points, 95% CI, −2.13 to −0.64 points, I2 = 81%).

Acupuncture and/or acupressure were combined with analgesic therapy for reducing pain intensity in 6 RCTs (MD, −1.44 points; 95%CI, −1.98 to −0.89; I2 = 92%) and for reducing opioid dose in 2 RCTs (MD, −30.00mg morphine equivalent daily dose; 95%CI, −37.5mg to −22.5mg). These 3 large meta-analyses examining acupuncture for the treatment of 4 chronic pain conditions establish the effectiveness of acupuncture for the treatment of other chronic pain conditions including SCD. In summary, acupuncture treats a wide range of pain conditions within the body therapy category and was selected because it (1) has been a highly utilized CIH therapy and (2) is effective in reducing pain.

Acupuncture for the treatment of SCD

There have been 5 studies of acupuncture for the treatment of SCD. Three were pediatric studies: a case study,[41] a study of 2 patients,[42] and a retrospective uncontrolled trial of 12 patients.[43] Two additional studies examined the use of acupuncture for the treatment of adults with SCD. One study, which was an uncontrolled retrospective review, treated a total of 24 inpatient and outpatient adults during acute vaso-occlusive crisis with individualized acupuncture point prescriptions.[44] In this study, 9 inpatients received a median of 3 treatments and had a reduction in pain of 2.1 on a 0–10 pain rating scale, and 15 outpatients received a median of 4 treatments and had up to a 75% reduction in pain. Another uncontrolled study treated 10 adults with a total of 16 acute vaso-occlusive crises; participants reported a decrease in pain in 15 of 16 acute vaso-occlusive crises.[45] All studies reported pain reduction, and

several examined the implementation effect of acupuncture for the treatment of SCD.[44–46] In summary, acupuncture is a significant body-based therapy selection because it: (1) is low risk; (2) does not interfere with any other treatment the patient is receiving; and (3) is proven popular, acceptable, and effective.

Guided Relaxation

Mind-body therapies such as guided relaxation use the mind to reduce pain, promote well-being, and improve physical function. Guided relaxation is a state of concentration and focused attention that gives people more control over their pain experience and its impact and an increased sense of well-being.[47]

Rationale for guided relaxation to address pain

Systematic reviews and meta-analyses reviewing over 48 RCTs have demonstrated that guided relaxation reduces chronic pain,[48–50] as well as reducing acute pain following surgical procedures.[48] Guided relaxation has also been shown to help with sleep,[51] anxiety,[52] and reduce cardiac events.[53] Guided relaxation that is delivered via web app can be provided in any location at any time, so it is less costly and more convenient than delivery by an experienced clinician. In a systematic study of eHealth interventions for SCD published in 2018, the authors found studies that evaluated guided relaxation as a stand-alone therapy showed intervention participants had lower current anxiety and pain scores and continued reductions in pain at follow up.[54]

Guided relaxation for treatment of SCD

Our previous studies have demonstrated that guided relaxation is an effective CIH therapy for reducing pain.[55] The goals for the first feasibility study were to determine (1) acceptability, (2) frequency and issues related to tablet use, (3) data completion rates, and (4) attrition rate. The study also explored the potential efficacy of the intervention on pain, among people with SCD ≥18 years old with a moderate to severe level of pain (>3 on a 0–10 scale). Participants were stratified by worst pain intensity and randomly assigned to either control or guided relaxation. The tablet-based guided relaxation intervention included a 12-minute guided relaxation video that was administered at baseline, plus 6 additional video clips ranging from 2 to 20 minutes. All video clips had similar content. Participants were asked to watch any of the video clips at least once daily. Of the eligible patients who were approached, 59% agreed to be part of the study, and of these, 96% completed the study. Participants receiving the guided relaxation intervention, 72% (n = 20) used the tablet daily during the 2-week intervention period. The guided relaxation lowered current pain [mean = -1.8, 95% CI (−3.3, −0.4)] at immediate posttest. Guided relaxation also demonstrated short-term effects (Day 14) where the intervention group had lower chronic pain scores [mean = -9.0, 95% CI (−17.9, −0.4)] than the control group.[56] Further, we evaluated the proportion of patients who reported a clinically significant reduction in pain, defined as a 2-point reduction on a 0–10 scale, and found that 36% of intervention and 17% of control group patients had a clinically significant reduction in pain over a 2-week period. In a confirmatory study conducted in different geographic region using the same guided relaxation protocol, we found that in immediate posttest, guided relaxation exercises significantly reduced current pain by 1.1 on a scale of 0–10 in the intervention group compared to the attention control group.[55] At the 2-week posttest, the guided relaxation group had significantly lowered composite pain index scores. These findings demonstrate the feasibility of implementing a guided relaxation intervention among adults with SCD experiencing pain and indicate that a tablet-based guided relaxation intervention is effective in reducing pain. In summary, guided relaxation represents a wide range of options within the mind-body therapy category and was

selected because it (1) has been a highly utilized CIH therapy, (2) has been shown to reduce pain, and (3) can be economically delivered and is feasible for adults with SCD to use on their own.

Rationale for Sequencing of the 2 Therapies

Our past work has demonstrated significant improvement in pain from both acupuncture and guided relaxation. While there are likely several contributing physiological mechanisms involved, the benefits derived from acupuncture as a direct body therapy are primarily physically mediated, whereas the effects derived from guided relaxation are cognitively mediated. In this study we will test one strategy, and if it is inadequate, randomize to continue with that therapy or switch to the other therapy, recognizing that benefits may be cumulative alone or by targeting another pathway and be synergistic to the sought benefits. Given potential beneficial systemic effects, the benefits of acupuncture and guided relaxation are not limited to immediate results and may be cumulative over time. The use of 2 therapies that reduce pain via different pathways optimizes the potential for therapeutic benefit. In addition, some people may prefer a mind-body strategy over direct physical contact, and the optimal intervention choice and sequencing may need to account for individual differences. A critical step to determine how to integrate these therapies into evidence-based practice is to complete a pragmatic clinical trial. This trial can inform clinicians, patients, administrators, and policymakers about integrating guided relaxation and acupuncture into real-life clinical settings to increase access to non-opioid treatments, decrease opioid need, and improve health outcomes.

Implementation Science Using the Consolidated Framework for Implementation Research (CFIR)

The development of our implementation protocol (UG3) and its execution and evaluation (UH3) combine our team's clinical and research experience to advance implementation science by identifying barriers to and facilitators that affect the integration of effective CIH therapies into health systems under real-world conditions. Our study relies on the Consolidated Framework for Implementation Research (CFIR) to inform implementation across the 5 years of the UG3/UH3: planning, execution, and evaluation. This is a novel approach that goes beyond examining effectiveness to also document what affects implementation in 3 different health care systems.[57,58]

We will use CFIR tools, such as interview guides and outcome metrics to guide implementation and increase the potential for scalability from launch to execution and evaluation. The CFIR is a conceptual framework developed to guide multilevel assessment of factors that may influence an intervention's implementation and effectiveness. The core CFIR domains are (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. The final product of the UG3 milestones is a flexible and evidence-based implementation blueprint prototype that will guide and support each health system's capacity to implement the intervention.[59,60] Technical assistance and support by the research team will gradually decrease as each health care system builds capacity to sustain these therapies at the local level. Our blueprint can then be used by others to integrate these and other evidence-based CIH therapies into health care systems. This study is the first to assess these interventions in 3 hospital systems among SCD patients with chronic pain. We will analyze key implementation facilitators and challenges and link these to effectiveness. This work will result in an evidence-based set of recommendations to guide future implementation across different health care settings, with the long-term goal of establishing CIH therapies as part of the standard of care.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

These are low risk interventions, but as with all research, there are potential risks.

- **Emotional Distress**. During the study, participants will be asked to answer questions about sensitive topics that may be upsetting.
- **Acupuncture**. The risks from acupuncture needle insertions include soreness, minor bleeding, bruising after acupuncture needle removal, and fatigue after acupuncture.
- **Loss of confidentiality**.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no guaranteed benefits for being in the research study; however, it is possible that participants will experience a reduction in pain as part of this study.

Participation in this research study may also contribute to the development of treatments for chronic pain management in sickle cell disease patients and may benefit the future health of the community at large.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Emotional distress. The research team will help in identifying additional care, if needed. It will also be emphasized that they have to right to withdraw from the study at any point in time without any negative impact on their healthcare or relationship with the hospital system.

Acupuncture. Participants will be encouraged to rest if necessary and will be provided with a light snack or juice following the acupuncture session.

Loss of confidentiality will be mitigated through methods outlined through the protocol, including hosting the survey data on REDCap, an encrypted server, storing physical files in a locked cabinet and locked office at each site, among others outlined in **Section 10.1.3**.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Test effectiveness of 2 non-pharmacological interventions (Guided Relaxation and Acupuncture)	Pain impact at 6 weeks is the primary endpoint. Secondary outcomes include opioid use, PEG, sleep,	Both guided relaxation and acupuncture have shown positive changes in pain impact at 6 weeks

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
compared to usual care for treatment of sickle cell pain	anxiety, depressive symptoms, and pain catastrophizing	
Secondary		
Identify the best sequence of interventions over a 12 week interval, allowing for adaptation for participants not showing adequate response.	Same primary and secondary outcomes measured at 12 weeks.	Pain impact will determine the effectiveness of intervention sequences. Secondary outcomes may show improvements, possibly as sequelae related to pain relief. Treatment sequence, i.e., initial treatment and second line treatment if poor response, will comprise 4 options (see design) and usual care, will be the independent variable of interest. 12 weeks is the amount of time needed to complete two treatment sequences.
Tertiary/Exploratory		
Explore characteristics to understand differential treatment response.	Pain Impact is the primary endpoint	Moderators of treatment response will be explored from among age, sex, and initial treatment assignment
Patient CIH Therapy Experience	Following completion of the 24 week follow up, patient participants from either of the intervention arms will be interviewed to gain feedback on barriers and facilitators	These qualitative data will be used to better inform how these therapies might be successfully introduced in hospital settings

4 STUDY DESIGN

4.1 OVERALL DESIGN

This Phase 2 pragmatic trial is for the purpose of determining the effectiveness of CIH therapies to reduce pain in SCD patients. Following Baseline data collection (see above table for an outline of all measures), participants will be randomized into one of three arms: usual care, acupuncture or guided relaxation (see **Section 4.3** for a fuller description of these interventions). At 6 weeks, participants complete the midpoint assessment. Utilizing a SMART design (discussed in more detail in **Section 4.2**), we will be able to test for the most effective sequence of intervention, as participants in either of the intervention arms who are not showing improvement in pain scores will be re-randomized to either continue with the CIH therapy they were initially assigned or to switch to the other intervention. At 12 weeks, all participants will complete another assessment (see above for all measures collected at this time point). A final assessment will occur at 24 weeks. Each of the

follow up assessments (6 weeks, 12 weeks and 24 weeks) will occur online through REDCap. As the study continues, we anticipate having the ability to capture patient-reported outcomes in EPIC.

Aim 1: Determine the effectiveness of guided relaxation and acupuncture as compared to usual care in decreasing pain and opioid use for SCD patients. **Hypothesis**: At 6 weeks, SCD patients randomized to either CIH intervention will have a greater decrease in pain, opioid use, sleep, anxiety, depressive symptoms, and pain catastrophizing compared to SCD patients randomized to usual care.
Aim 2: Identify the best adaptive intervention for improved outcomes by documenting outcomes among adaptive intervention sequences: (1) initiate guided relaxation and switch to acupuncture for non-responders at midpoint; (2) initiate guided relaxation and continue with guided relaxation for non-responders at midpoint; (3) initiate acupuncture and switch to guided relaxation for non-responders at midpoint or (4) initiate acupuncture and continue with acupuncture for non-responders at midpoint.
Aim 3: Explore differences in response to the adaptive interventions by age and sex.
Aim 4: Identify implementation facilitators, challenges, and solutions for structures and processes that contribute to the seamless integration of CIH therapies into the 3 health systems by conducting individual interviews with participants in the intervention group who responded to the intervention and those who did not. We will also conduct focus groups with hospital personnel at 4 timepoints.

Randomization
We will use the REDCap randomization module to manage randomizations within site, stratified on PROMIS pain interference and opioid use. The study statistician will create the allocation schedule for each site using permuted blocks of six within each stratum. Staff can randomize participants by entering the answers to stratification questions and pushing a button. This approach conceals the upcoming treatment arm assignments from staff, and the study statistician will remain blinded to the meaning of treatment arm indicators within the REDCap data management system. We will randomize one-third of participants to the usual care arm and one-third of participants to each intervention arm. If randomization is warranted due to non-response at week 6, a re-randomization form is completed in REDCap.

Planned Interim Analysis
Use of the SMART design provides an interim measure of study outcome. We will summarize the number of participants requiring an additional six weeks of intervention due to non-response. Other planned analyses will include enrollment progress, adherence and protocol deviations, and a summary of adverse events.

To assess implementation barriers and facilitators (Aim 4), 2 non-responder patient participants and 2 responder patient participants at each site will be interviewed about their experiences with CIH therapies, and focus groups involving hospital personnel will occur every 6 months after initiation of the trial to determine if issues have come up and how they were resolved. In addition, all participants will complete an implementation survey assessing technology ownership, use, and acumen as well as previous exposure to acupuncture/guided relaxation, and insurance status. The survey will be administered through REDCap at Baseline for all participants, and at the 12-week timepoint for those participants in either intervention arm.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Pragmatic trials are designed to maximize external validity to determine effectiveness of interventions in real-world settings while also providing information about the generalizability of an intervention within the context of routine practice. Pragmatic trials and implementation research designs are useful for testing flexible and broadly applicable evidence-based interventions across multiple settings and within diverse populations. In keeping with the intent of this HEAL initiative: Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM), we are determining the effectiveness of two CIH therapies, guided relaxation and acupuncture to improve outs of adults with SCD. The PRECIS 2 was used to guide the design of the proposed research, which measures the relationship of the intervention, setting, and study design with the health care systems where the intervention will be delivered.

This study uses a hybrid type 1 effectiveness-implementation research design. The RCT will follow a quantitative SMART design, to which we will add a qualitative implementation research component. SMART design results in pragmatic trials that evaluate adaptive interventions where the selection of interventions responds to the patient's characteristics and evolving clinical status. Using this design, the study team will make the following determinations:
(1) the relative effectiveness of guided relaxation and acupuncture;
(2) the subgroups of patients 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.

The primary objectives of the trial are (a) to compare guided relaxation with usual care and (b) to compare acupuncture with usual care, rather than to compare guided relaxation to acupuncture. This is our rationale for choosing, as the primary objective, to determine whether either intervention has benefit rather than comparing the effectiveness of the 2 interventions:
(1) There is strong evidence for the effects of each intervention, but it is not yet known whether either intervention can be implemented in the context of SCD clinical care.
(2) Outside of the trial setting, the infrastructure and/or personnel required for implementing each intervention differ and may not be uniformly available. Thus, knowing whether each intervention is effective will allow post-trial implementation to be based on available resources.
(3) Outside of the trial setting, the uptake of the interventions may depend on patient preferences. Thus, knowing if an intervention has benefit may be more important than knowing if it is more effective than an alternative that might not be as appealing to an individual patient.

If the effectiveness of guided relaxation and acupuncture is confirmed in this pragmatic trial, then our findings could change practice for treating adults with SCD by reducing prescription of drugs, including opioid, in favor of referral for CIH interventions like guided relaxation and acupuncture with far fewer adverse effects.

4.3 JUSTIFICATION FOR INTERVENTION

Acupuncture intervention.
In Traditional Chinese Medicine, qi is the vital energy flowing within and surrounding the body. The channels through which qi and blood flow in the body are called meridians. Disorders of qi and disorders of blood, whether deficiency or excess (stagnation or obstruction), can result in pain. Acupuncture

needles are inserted into acupuncture points that access the meridians (pathways for the flow of qi) and promote the circulation of qi and blood, which reduces pain. In acupuncture, a set of standardized points is referred to as a point prescription. Dr. Schlaeger has developed this standardized and efficacious point prescription through her Traditional Chinese Medicine assessments of SCD patients. This point prescription can be easily replicated by any acupuncturist and can be used nationally and internationally for the treatment of SCD pain. The needles will be retained (left in place) for 30 minutes. All needles will be evenly rotated to stimulate the movement of qi every 10 minutes. Participants will receive 2 acupuncture treatments each week for 5 weeks, for a total of 10 treatments. While a full treatment would be 10 sessions, our other work has shown that participants can experience some reduction in pain after 7 sessions.

Guided relaxation intervention.
The video clips were developed and validated in psychoneuroimmunology studies in patients with cancer or HIV. The video includes colorful smoke-like images that slowly change shapes against a dark background. The guided relaxation intervention includes a 12-minute guided relaxation video (administered at baseline) and 6 additional video clips ranging from 2 to 20 minutes. All video clips have similar content, with longer ones having more repetitions of the same content. For example, the clip on Breathing out worry, breathing in light begins with

> *"Notice the cloud-like formations on the screen. Observe how the images drift and change. As you breathe deeply, your concerns and tensions, which worry you, go out into the atmosphere where they can dissolve just as the cloud-like formations on the screen dissolve and vanish from view. It is all right to let go of your worries. In fact, it is important to your health that you do so. Just breathe out problems and worries. See them drift off, walking by and off the screen, no longer a part of you."*

The video a participant selects will only play after the pain score has been entered. Participants will be encouraged to watch at least one of the 6 video clips daily for the first two weeks. In on our previous work, after 2 weeks utilizing these videos, a reduction of pain ratings occurred. Ideally, a participant would complete the guided relaxation sessions daily until the assessment. As this is a pragmatic trial, we will also be assessing the use of these interventions in real world conditions, which might mean that a participant does not complete all the sessions leading up to the assessment.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline, 6 week, 12 week and 24 weeks assessments.

The end of the study is defined as completion of the final assessment at 24 weeks of our final enrolled participant (n=366), as shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patient-Participants:

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Age ≥ 18 years old
3. Has SCD diagnosed by hemoglobin electrophoresis
4. Ability to speak/understand English
5. Chronic pain defined as a response of "Most days","Every day", or "Some days" to the question, "In the past 3 months, how often have you had pain?" (Answer options: Never, Some days, Most days, Every day)
6. Current pain interference using the general activity question from PEG, score ≥3 on 0-10 scale

Hospital personnel focus group participants:

1. Currently employed in the health system in a capacity that interfaces with SCD patients
2. Able to speak/understand English

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Had a stem cell transplant for sickle cell disease
2. A known diagnosis of moderate or severe opioid use disorder by Diagnostic and Statistical Manual of Mental Disorders-5 criteria
3. Current incarceration
4. Patients who are on a chronic transfusion/exchange program
5. Any other condition that the investigator considers precludes participation in the clinical trial

Hospital staff participants:

1. Any concerns that the investigator considers would preclude or bias participation

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

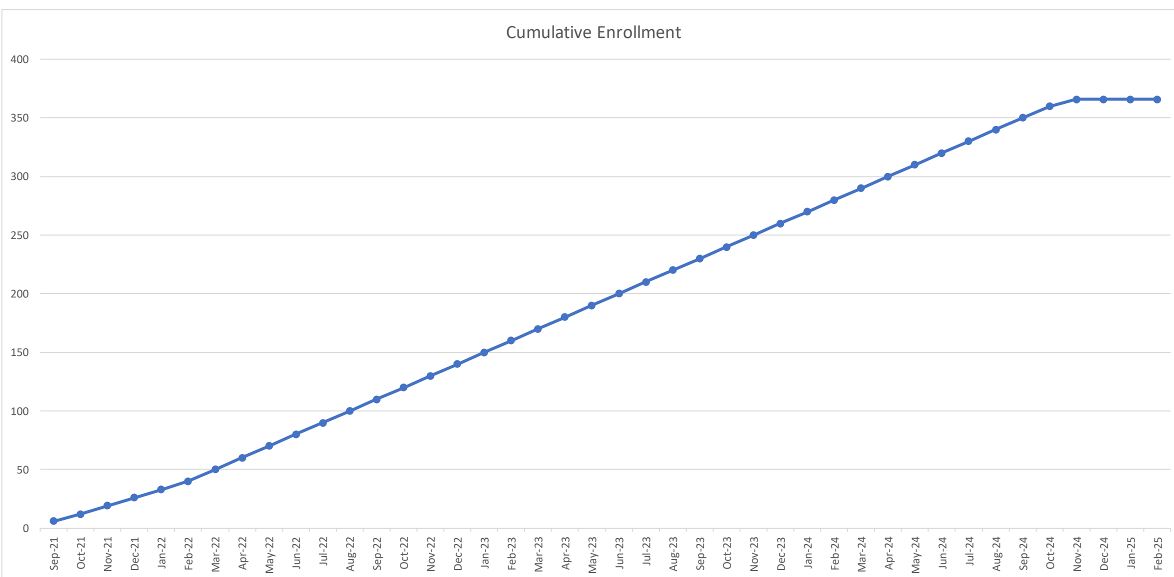
Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria will not be able to participate. We will collect demographic information on these screen failures to determine if there are any common factors among those who do not meet study criteria. Individuals who do not meet the eligibility criteria for one or more reasons can be screened again after 30 days. There is no limit to the number of times an individual can be screened for participation in the trial.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Total Recruitment: 366 participants, 122 per arm after randomization. We anticipate a 5% attrition at 6 weeks and 10% attrition by end of study. Our anticipated enrollment table:

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	199	132	10	7	348
White	0	0	0	0	0
More than One Race	10	7	1	0	18
Total	209	139	11	7	366

Anticipated accrual over time:



Cum. Accrual	6	12	19	26	33	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190
Recruitment	6	6	7	7	7	7	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Study Month	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33

Cum. Accrual	200	210	220	230	240	250	260	270	280	290	300	310	320	330	340	350	360	366			
Recruitment	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	6			
Study Month	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54

Recruitment Strategy. Study participants will be recruited from the population of patients with sickle cell disease with pain who are receiving care at the University of Illinois Hospital & Health Sciences System, the Duke University Health System, and the University of Florida Health. At the time of each patient's clinical visit, the health care provider will determine if the patient is a candidate for non-pharmacological pain care (both acupuncture and guided relaxation). Providers will be encouraged to

refer patients to this project using flyers in each provider exam room. There will also be flyers in the waiting room, as well as research staff who will be present in the waiting room to answer any questions about the study. The study will also utilize printed materials in public spaces, including ads posted on public transportation. Additionally, patients of the sickle cell clinics will be contacted through MyChart ahead of a scheduled appointment or by mail for those not enrolled in MyChart with permission from their provider. Patients who express an interest in the study will meet with the research assistant, who will explain the study and answer any questions. Additionally, patients will be shown an informational website and research assistants will provide the participants with the URL. Since the website is publicly available potential participants will also be able to navigate there via search engines (i.e. Google, Duck Duck Go, Yahoo), review the site, and complete a contact form enabling a member of the research team to answer any questions.

Patients who meet study eligibility criteria will be offered the opportunity to be randomized to either the acupuncture or guided relaxation interventions. The research assistant will emphasize the importance of participating in the full intervention or interventions, and the data collection. Participants will be asked to mark their personal calendar for intervention days and times and data collection dates. These strategies have worked well in our ongoing trials to keep attrition below 20%.

Participants will be assured of the confidentiality of all information and that refusing to participate will not alter their care. Participants will continue to receive standard medical care while participating in the study, so if any health care problems arise, they may seek care from their providers. For patients who refuse the study, the research assistant will seek consent to review their record for demographics and ask the reason for refusal. These data will help us understand who declines and will contribute to external validity and generalizability of the findings.

Research assistant training will occur during the first six months of the study and will include didactic information, role-playing, reviewing problem cases, and return-demonstrations. The research assistant will introduce the study to patients using a script that includes (1) initial randomization to acupuncture or guided relaxation, and the possibility of being re-randomized after 5 weeks of receiving the first intervention to either continuing the same intervention or switching interventions; (2) the complete study lasting a total of 6 months to include all data collection; (3) both interventions being designed to help reduce symptoms and improve physical function and quality of life; and (4) a review of potential risks and benefits.

Strategies to enhance recruitment. Although we will be using the electronic health record to initially identify eligible patients, using personalized, face to face recruitment methods by research staff and providers have been found to produce the best results in recruiting Black/African American participants. Additional strategies to be used to increase our recruitment will include: 1) establishing contact with any Black/African American or female health care providers located in the sickle cell clinic to gain their support to encourage their patients to participate; 2) reviewing training and recruitment materials to assure that language used is culturally sensitive, clear and simple; and 3) making every effort to hire research staff of female gender and/or Black/African American. We will work to develop a list of benefits, as well as barriers to participating in the research study. This list of benefits can be communicated to potential participants, and specific benefits can be emphasized when speaking to different audiences. A frequently asked questions sheet will be created addressing potential concerns in order to clear up misconceptions.

Participant Retention Strategies. An important retention strategy is to engage the participants as active partners in the research through their understanding of the importance of their contribution. We will

build on existing trusting relationships with the community, as well as encouraging our patients to engage with their networks about the study. We will schedule data collection at times convenient to participants and at a time of day with fewer competing activities. We will collect multiple types of contact information (email, cell phone, and home phone) to maximize our ability to contact participants with reminders the day before and the day of their study appointments. We will also send a thank-you letters upon completion to acknowledge the participant's contribution to the research. Importantly, the implementation side of this study will include patient interviews to gain insight on what barriers and facilitators they observed in participation in the study.

Participants will receive a total of $100 for participation in each of the 4 data time points for Aims 1-3. Participant compensation will be greatest at the end as another mechanism for encouraging continued participation. Participant compensation is as follows:

- Baseline: $20
- 6-week assessment: $20
- 12-week assessment: $20
- Final assessment: $40

Because participants randomized to the acupuncture group will have to go to a clinic site to receive their intervention treatments, people in this arm will receive regionally specific amounts to cover travel costs. Participants at UIHealth and Duke University will receive $10 per session; those at the University of Florida will receive $20 per session, as they have to travel a greater distance to the acupuncture site on average.

Strategies to enhance retention.

1) Research staff will emphasize the importance of participating in the full intervention and the data collection.

2) Patients will be asked to mark their home calendar for study contact times.

3) Patients are called regularly so that the contact is maintained for the entire study and study staff will

be flexible when scheduling appointments.

4) Several phone numbers for participants will be obtained for follow up.

5) Along with incentives, participants will be sent small tokens of appreciation that will remind them of the study: birthday cards, thank you cards, etc.

6) Study updates and results will be shared with participants, families of participants, participating practitioners and the Black/African American community.

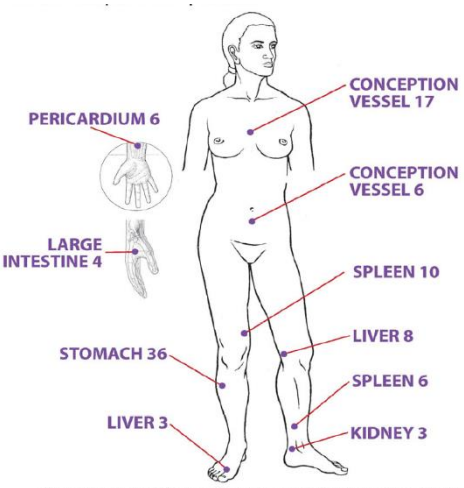
These strategies have worked well in our completed and ongoing trials. Our training of study staff includes topics often expressed by Black/African American people approached for research including: 1) mistrust, 2) the inability to see a clear personal benefit, and 3) a lack of understanding about the purpose of the research. We will also observe for evidence of cultural stereotyping and gender biases in our training session. We will provide booster sessions on sensitivity training as needed and reassess any personnel who appear to need improvement in this area. Recruitment of women will be tracked to ensure adequate recruitment milestones are met. If adequate recruitment milestones are not met, focus groups will be conducted to assess the needs and preferences of potential participants.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Acupuncture. In Traditional Chinese Medicine, qi is the vital energy flowing within and surrounding the body. The channels through which qi and blood flow in the body are called meridians. Disorders of qi and disorders of blood, whether deficiency or excess (stagnation or obstruction), can result in pain. Acupuncture needles are inserted into acupuncture points that access the meridians (pathways for the flow of qi) and promote the circulation of qi and blood, which reduces pain. In acupuncture, a set of standardized points is referred to as a point prescription. Dr. Schlaeger has developed this standardized and efficacious point prescription through her Traditional Chinese Medicine assessments of SCD patients. This point prescription can be easily replicated by any acupuncturist and can be used nationally and internationally for the treatment of SCD pain.



All points except Conception Vessel 6 & 17 needled bilaterally

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 and an increased sense of well-being. Systematic reviews and meta-analyses reviewing over 48 RCTs have demonstrated that guided relaxation reduces chronic pain. Previous work by Dr. Ezenwa has developed a protocol for Guided Relaxation that has shown to help with the management of chronic pain in sickle cell disease patients.

6.1.2 ADMINISTRATION AND/OR DOSING

Acupuncture. Participants will receive the acupuncture treatments in a clinical space designated at each of the study sites. Treatments will be administered by a trained acupuncturist. The needles will be retained (left in place) for 30 minutes. All needles will be evenly rotated to stimulate the movement of qi every 10 minutes. Participants will receive 2 acupuncture treatments each week for 5 weeks, for a total of 10 treatments.

Guided Relaxation. On the first day of the intervention, participants will complete a pain and stress tracking, watch a 12-minute introductory video, and complete the pain and stress tracking again on the first day of the intervention. Every day following, participants will complete the pain and stress tracking, watch one of 6 videos (ranging in duration from 2 to 20 minutes each), and complete the stress and pain tracking again. Sessions are self-initiated and accessed remotely.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Research team training will be provided for team members who recruit participants, collect data, provide the guided relaxation and acupuncture interventions, and conduct interviews. Training will include didactic information, written protocols, role-playing, demonstrations, and return demonstrations, based on our study-specific criteria.

Guided Relaxation. Dr. Ezenwa has developed a protocol for the guided relaxation intervention, which is delivered via web app. The research specialist will be trained on this protocol and will practice explaining how to access the app to participants with other team members.

Acupuncture. Dr. Schlaeger will train the licensed acupuncturists, who will be given the acupuncture protocol with written instructions and diagrams. Dr. Schlaeger has also developed a proficiency checklist for the acupuncture protocol that will be used to determine if the acupuncturists are adhering to the protocol.

Additional checklists will be used to determine if research staff assisting with and monitoring the intervention are demonstrating protocol proficiency of greater than 90%, both before they begin and as they continue to approach patients and collect data. There will be a refresher training for research staff every 6 months during the data collection and intervention period. Role-playing will be used to ensure that team members understand the protocols for interacting with participants. All contact with participants by research specialists will be scripted and will be randomly taped and regularly reviewed by Dr. Doorenbos.

Sickle cell clinic physicians and staff will be oriented at one of their respective monthly meetings by Dr. Schlaeger via Zoom. The orientation will include a short introduction to the philosophy of Traditional Chinese Medicine and acupuncture, our sickle cell feasibility study results, a brief overview of the GRACE study acupuncture protocol, and logistics of how and where to refer potential participants for acupuncture. Reorientations to the study will be administered by Dr. Schlaeger as needed.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Team Member	Role	Blinding Status
Dr. Ezenwa and Dr. Schlaeger	Directly managing elements of intervention	Unblinded
All other PI's and Co-Is	Management of higher level study activities at recruitment sites and meeting overall research goals	Blinded
Statistician	Statistical analysis of primary and secondary aims	Blinded
Data Collection Staff	Remote follow-up	Blinded
Site Researcher Managers	Recruitment, randomization, coordinating intervention	Unblinded

Acupuncturists	acupuncture	Unblinded
Data Manager	Manage collected data, run reports	Unblinded

Intervention assignments will not be masked to participants or research managers because of (1) impracticability, and (2) an interest in implementing the interventions as they would be implemented outside of a trial setting. The trial includes a control group that does receive an educational intervention beyond usual clinical care; however, as the educational intervention is written material, it will not be fully possible to determine whether changes observed in the active treatment groups are the result of the interventions or the result of either the increased attention that accompanies trial participation or the natural history of the condition. Bias will be minimized by performing randomization after collection of baseline data, concealing the allocation order, and ascertaining the patient-reported outcomes, including the primary outcome, using standardized, centrally administered questionnaires. PI's and Co-I's will be blinded unless responsible for directly implementing components of the interventions (for clarification, see table above). Staff assisting with data collection, such as following up with participants who do not complete emailed surveys, will be blinded to treatment arm assignment. An unblinded data manager will address issues with randomization and any unblinded reports or other data needs. After the REDCap randomization module is set up with the allocation schedule an independent staff will assign a label to the group assignment number (e.g., 1= control, 2= guided relaxation, etc.). For each randomization, the research staff will enter stratification information and push a button to reveal group assignment. We will restrict access to treatment arm assignment for all blinded personnel, including the statistician, by user right settings within the REDCap system. After the data freeze, the point at which no further data are collected, the statistician will be aware of group numbers (e.g., 1, 2, or 3) but blinded to the meaning of the assignment labels during analyses. An independent statistician will be enlisted to help with DSMB unblinded reports, if requested.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Treatment delivery will be monitored by tracking length, frequency, and intensity of all interventions (e.g., guided relaxation and acupuncture sessions tracked for length and intensity). Should any technical difficulties present (e.g., issues with downloads of guided relaxation recordings), the participant will be contacted by phone or email; all technical problems will be resolved.

Receipt of treatment for the guided relaxation intervention will be assessed by the research team tracking participants' use and duration of the guided relaxation recordings. Adherence will be based on the number of guided relaxation sessions completed (out of 42 prescribed sessions) and categorized as minimal (<14 sessions), some (14–28 sessions), and most (over 28 sessions). For the acupuncture intervention, the treatment dose will be assessed by monitoring participants' acupuncture appointments. Regular interactions between the acupuncturists and Dr. Schlaeger will occur, during which any issues will be reviewed.

6.5 CONCOMITANT THERAPY

The following approach will be taken regarding concomitant therapies:

1) Doses and frequency of use of non-opioid analgesics, antidepressants, and anxiolytic and sedative/hypnotic medications will be recorded at baseline, Week 6, Week 12, and Week 24.

2) Use of non-study behavioral therapy or any other non-pharmacological therapy for pain (e.g., physical therapy) will be recorded at baseline, Week 6, Week 12, and Week 24.

3) For the duration of the study, the study team members will encourage patients to seek treatment of co-existing depression and/or anxiety if indicated. They will inform the primary care providers and other relevant clinicians about any mental health symptoms, such as depression and/or anxiety, discovered during study assessments and will develop a collaborative plan, maximizing safety and efficacy of any prescribed medications. Details of such study recommendations and resulting medication orders will be recorded during the 24-week study period.

4) Opioid dose reduction or discontinuation will not be protocolized. The study team will provide information and general recommendations to the participants opioid prescriber, but decisions to prescribe or change opioids will be up to the treating clinician and participant. If a participant develops a new indication for pain medication (e.g., new fracture, dental procedure) during the study intervention period, there may be a need to initiate or increase the dose of an opioid medication. Opioid use during this period will be considered as rescue medication and recommendations for opioid tapering may be put on hold. Once the acute event subsides (based on clinical judgment), the recommendations for opioid tapering will be resumed, as deemed appropriate. The duration of rescue periods will be recorded.

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from acupuncture or guided relaxation but not from the study, remaining assessments will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue.
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. If a participant indicates a desire to withdraw, the study team will discuss the request with the participant and determine whether the participant is willing to allow ongoing data collection for outcomes or adverse event monitoring.

An investigator may discontinue a participant from the study for the following reasons:

- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she cannot be contacted and fails to respond to complete consecutive assessments (6 week, 12 week and 24 week time point) through the end of the study.

The following actions must be taken if a participant fails to return to the clinic for an acupuncture appointment:

- The site will attempt to contact the participant, offer to resend the link to complete the assessment online or over the phone, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 5 telephone calls (including 3 voicemail messages left) and, if necessary, a certified letter to the participant's last known mailing address. These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

The amount of missing data will first be quantified, using the approach recommended by Glick

et al. where possible.[61] We propose to use mixed effects regression models which allow all observed data to be included in the analysis under the assumption that data are missing at random (MAR), essentially providing a full information maximum likelihood solution to missing outcome data.[62] We will incorporate covariates that have predicted missingness in our previous studies to support the validity of the MAR assumption. If substantial missing data occurs, multiple imputation will be used with subsequent sensitivity analyses to explore the impact of imputation on results.[63] Sensitivity analyses such as pattern mixture models will be employed if data are suspected to be missing not at random.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Participants will be identified through a diagnosis of SCD in their medical record, making sure to exclude those with chronic transfusion/exchange program and other exclusionary conditions determined by the PIs.

Those identified through the medical record will be approached in clinic settings. We will also be posting flyers for recruitment in clinic spaces. Interested people will then be asked our screening questions, which include:

- In the past 3 months, how often have you had pain? Never, Some days, Most days, or Every day?
- Chronic pain defined as a response of “Most days”, “Every day”, or “Some days”
- PEG pain interference on general activity (0-10 scale) of ≥3

Participants will be enrolled within one week of answering screening questions. Once enrolled and consented, participants will complete the Baseline Assessment, which consists of questionnaires, including the following:

- Demographic
- PROMIS Pain Interference
- PROMIS Physical Function
- PEG
- Opioid use (will also be confirmed via EHR)
- GAD-7
- PHQ-9
- PROMIS Sleep Disturbance 8a and sleep disturbance question
- Pain Catastrophizing Scale
- PGIC
- TAPS1
- PROMIS GI Constipation 9a
- Clinical data regarding hospitalizations (will also be confirmed via EHR)
- Use of non-study behavioral or other non-pharmacologic treatment for pain

Once participants complete the Baseline Assessment, they will be randomized into one of the three study arms (acupuncture, guided relaxation or standard care).

No physical assessments are conducted as part of this study.

8.2 SAFETY ASSESSMENTS

N/A

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from the IRB at the University of Illinois at Chicago, the reviewing IRB site: An untoward physical or psychological occurrence in a human subject participating in research which occurs during the study having been absent at baseline or, if present at baseline, appears to worsen. The event may be any unfavorable outcome, including abnormal laboratory result, symptom, disease or injury. Adverse events may be expected or unexpected, may not necessarily be caused by the research, and may be serious or not. Adverse events that are unanticipated, related to the research and serious or involve risks to subjects or others qualify as a subset of unanticipated problems.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A *serious adverse event* (SAE*)* is any AE that is:
• fatal or results in death
• life-threatening
• requires or prolongs hospital stay
• results in persistent or significant disability or incapacity
• results in congenital anomalies or birth defects
• an important medical event*
*Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Possibly Related** –Though the AE is not known to occur with the interventions, it cannot be ruled out that it is related.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in sickle cell disease will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The PI will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

We do recognize that participants in this research are individuals living with advanced, progressive chronic disease who have pain. It is possible that during the active intervention period of the study they may have health issues requiring hospitalization unrelated to this research. As eligibility criteria require that participants have advanced, progressive chronic disease, hospitalization during the intervention period is possible but also an expected natural progression of their underlying disease. The MPIs will evaluate all hospitalizations or other reported issues to determine whether there is a relationship between the reported issue and the procedures involved in the research. All events determined as not related will be noted and reported to the IRB in the annual report, and research activities will continue as scheduled.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The PI will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 7 calendar days after the investigator first learns of the event. SAE forms can be completed by research coordinators but must be signed by a health care system MPI.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor/funding agency within 7 days of the investigator becoming aware of the event.
- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer and the DSMB within 3 days of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within 14 days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 14 days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint and Secondary Outcomes at 6 weeks:

  Primary: At 6 weeks, SCD patients randomized to either CIH intervention will have a greater decrease in pain impact compared to SCD randomized to usual care arm.

  Secondary: At 6 weeks, SCD patients randomized to either CIH intervention (acupuncture, guided relaxation) will have greater decrease in opioid use, PEG, sleep, anxiety, depression, pain catastrophizing, global impression of change, substance use and constipation compared to SCD patients randomized to usual care.

Aim 2: Identify the best adaptive intervention for improved outcomes by documenting outcomes among adaptive intervention sequences: (1) initiate guided relaxation and switch to acupuncture for non-responders at midpoint; (2) initiate guided relaxation and continue with guided relaxation for non-responders at midpoint; (3) initiate acupuncture and switch to guided relaxation for non-responders at midpoint or (4) initiate acupuncture and continue with acupuncture for non-responders at midpoint.

From our model we will estimate the adjusted mean outcome for each embedded sequence and control condition at 12 weeks and compare using contrast statements to select the sequence with the greatest improvement.

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

We will explore moderating variables such as, age, sex, and response to Stage 1 treatment using a Q-learning approach. Although our SMART results will provide evidence for a best sequence, Q-learning can be used to develop decision rules for more extensive tailoring if the response differs by sex or age, for example. This approach uses regression models and will involve 2 stages for the proposed study design. Working backward from the final outcome, we can explore variables that predict the best response to the Stage 2 interventions among the non-responders to Stage 1. The goal is to determine explicit decision rules for assigning the 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. The next step examines moderators of response for the Stage 1 intervention, controlling for the optimal Stage 2 intervention for non-responders. 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 impact outcome at Week 12 (end-of-intervention)

and Week 24 follow-up in order to recommend additional tailoring for the combinations of guided relaxation and acupuncture tested by this SMART design. These analyses will be implemented in SAS PROC QLEARN, developed by Murphy and colleagues.

9.2 SAMPLE SIZE DETERMINATION

Power Considerations. Our goal is to recruit 366 and retain 330 participants accounting for 10% attrition by end of study. At 6 weeks we anticipate 5% attrition based on our previous work yielding a sample size of 116 per treatment arm. The table below shows the most conservative minimal detectable differences in group means (standard deviation units) for the two primary endpoint comparisons using a two-sided test and alpha=0.025 for our proposed sample size of 116 per group, adjusting for clustering effects due to acupuncturists. We adjusted the variance of the treatment arm using a range of plausible intraclass correlations (ICC) and average group sizes per acupuncturist. Pragmatic trials commonly have ICCs ranging from 0.01-0.05. We assumed a range of 6 to 9 acupuncturists across the three sites; more than 9 acupuncturists are possible further increasing study power. Based on a published effect size of 0.5 for acupuncture and 0.57 for our previous work, we estimate 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 (PIS) measured at 6 weeks.

. **Power**	**N per group**	**Participants per Acupuncturist**	**ICC**	**Minimal Detectable Difference**
0.90	116	13-19	0.005	0.47
0.90	116	13-19	0.01-0.02	0.48-0.50
0.85	116	13-19	0.03-0.04	0.48-0.50
0.85	116	13-15	0.05-0.06	0.49-0.51
0.80	116	13-19	0.05-0.06	0.46-0.50

Aim 2 power considerations. Aim 2 proposes to identify the best treatment sequence among the 4 embedded sequences in this trial. We have planned that a sample of 220 will be available to test this aim. Based on the web-based calculator (*http://methodologymedia.psu.edu/smart/samplesize*), we determined the sample size of 205 will yield a probability of .85 for choosing the best strategy from among 4 embedded treatment sequences given an effect size of 0.3 between the strongest two sequences. The table below varies the probability and effect size to show the effect on sample size.

Probability of detecting best treatment sequence π	**Effect size between two strongest sequences δ**	**Sample size needed**
0.8	0.3	161
0.85	0.3	205
0.9	0.3	269
0.85	0.4	117
0.85	0.2	465

Minimum Detectable Differences for Research Questions Based on Target Sample Size			
Assumes 80% power, 5% type I error		Minimum Detectable Difference	
Research Question	Expected N	Cohen's D	Pain Impact
Aim 1 RCT Main effect comparing each CIH control at 6 weeks	330	0.38	2.4
Choose best treatment sequence*	220	0.30	1.9
Main effect of initial treatment on 12 week outcome	220	0.38	2.4
Main effect of secondary treatment for non-responders^	144	0.61	3.8
*85% probability *http://methodologymedia.psu.edu/smart/samplesize* ^Assumes 40% respond to initial treatment, a higher response rate will result in less power (exploratory question)			
Crivello AI, Levy JA, Murphy SA. Statistical Methodology for a SMART Design in the Development of Adaptive Treatment Strategies. (Tech. Rep. No. 07-82). University Park, PA: The Pennsylvania State University, The Methodology Center. 2007.			
Crivello AI, Levy JA, Murphy SA. Evaluation of Sample Size Formulae for Developing Adaptive Treatment Strategies Using a SMART Design. (Tech. Rep. No. 07-81). University Park, PA: The Pennsylvania State University, The Methodology Center. 2007.			

9.3 POPULATIONS FOR ANALYSES

We will conduct Intention to Treat and Per Protocol Analysis for Aim 1. Per protocol will include participants receiving 70% or more of the intended intervention.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Categorical and continuous data will be summarized using frequencies, percentages, means with standard deviations or median and interquartile depending on the distributions. Inferential tests will be two-tailed, presenting actual p-values, and will use alpha=.05 as the type I error rate unless otherwise indicated. Covariates will include stratification variables; others will be defined in a subsequent SAP.

Variables that are do not conform to assumptions for normal distribution of residuals in multivariable models will be transformed to improve the distribution.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Aim 1 analyses of the primary endpoint and secondary outcomes will use the same modeling approach. All are interval level measures that will be measured at baseline and 6 weeks. We will investigate mean differences at 6 weeks controlling for the baseline level of the outcome and stratification variables used for randomization, use of opioids and PROMIS pain interference. Clustering due to common acupuncturists will be addressed by including indicators for each acupuncturist as a repeated factor in a GEE model.. We are unable to determine the number of participants per acupuncturist given the logistical differences at each site but the desired range is 13-19 for the initial randomization We will attempt to balance caseloads of acupuncturists and will seek to add acupuncturists if the maximum (19) is approached, by 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, and predictors of missingness. Models will be estimated using full information maximum likelihood to retain all participants and utilize all available data. Among secondary outcomes, a Benjamini Hochberg approach will be applied using a false discovery rate of 0.05.[64]

In the context of the model, i.e., $y_{i2} = \beta_0 + \beta_1 x_1 + \beta_2 y_{i1} + e_i$, testing for group differences while adjusting for the baseline measure of the outcome:

α=.05

H0: β_{1a}=0

H1: $\beta_{1a}\neq 0$

H0: β_{1b}=0

H1: $\beta_{1b}\neq 0$

Note: β_1 is a vector of 2 parameters for three initial treatment arms.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Aim 2 analyses will be finalized with guidance from the Collaboratory Biostatistics Core and published in the SOP.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Treatment arms will be compared on their baseline demographic and clinical characteristics using descriptive statistics. Categorical and continuous data will be summarized using frequencies,

percentages, means with standard deviations or median and interquartile depending on the distributions. Inferential statistics will not be used.

9.4.6 PLANNED INTERIM ANALYSES

Use of the SMART design provides an interim measure of study outcome. We will summarize the number of participants requiring an additional six weeks of intervention due to non-response. Other planned analyses will include enrollment progress, adherence and protocol deviations, and a summary adverse events.

9.4.7 SUB-GROUP ANALYSES

We will explore moderating variables such as, age, sex, and response to Stage 1 treatment using a Q-learning approach. Although our SMART results will provide evidence for a best sequence, Q-learning can be used to develop decision rules for more extensive tailoring if the response differs by sex or age, for example. This approach uses regression models and will involve 2 stages for the proposed study design. Working backward from the final outcome, we can explore variables that predict the best response to the Stage 2 interventions among the non-responders to Stage 1. The goal is to determine explicit decision rules for assigning the 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. The next step examines moderators of response for the Stage 1 intervention, controlling for the optimal Stage 2 intervention for non-responders. 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 impact outcome at Week 12 (end-of-intervention) and Week 24 follow-up in order to recommend additional tailoring for the combinations of guided relaxation and acupuncture tested by this SMART design. These analyses will be implemented in SAS PROC QLEARN, developed by Murphy and colleagues.

Race will not be investigated with this approach because the participants will be predominantly African American.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

Duration of effect will be examined using Model from Aim 2 using outcomes at 24 weeks. Additional analyses will explore dose response and sensitivity of findings to additional covariate adjustment if we observe imbalance in baseline characteristics despite randomization or attributes associated with attrition.

We will also conduct analyses to examine the treatment sequence effects (Aim 2) among non-responders, however, this will likely be underpowered and shall be presented as exploratory.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention.

The following consent materials are submitted with this protocol:

- Informed consent document for patient participants for Aims 1 through 3
- Informed consent for staff/provider focus groups
- Recruitment flyer
- Recruitment script for patient participants
- Recruitment email for staff/provider focus groups

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The consenting process will be performed by a qualified investigator or study site designee. The study team member will discuss the study goals and procedures with the potential participant and assess understanding of the content in the consent form before obtaining written informed consent from the participant. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will also have the opportunity to discuss the study with family members or surrogates, and to fully consider the decision to participate or not. A signed copy of the informed consent form will be stored in a locked cabinet in a locked office.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding

agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the UIC College of Nursing. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by UIC College of Nursing research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the UIC College of Nursing.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Contact Principal Investigator
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10.1.6 SAFETY OVERSIGHT

The DSMB is an independent group of experts that advises the study investigators. All regular members of the DSMB for the trial will be eligible for service as voting members of the DSMB.

No members of the DSMB may have any conflicts of interest (financial, regulatory, or professional) with the study. At the beginning of every DSMB meeting, the Executive Administrator or the DSMB Chair will

reconfirm that no conflict of interest exists for DSMB members. Members will disclose potential conflicts of interest prior to any discussion. The DSMB will determine how to handle such potential conflicts. The DSMB may require that a member with a potential conflict not vote or it may take other actions or decisions deemed appropriate.

The primary responsibilities of the DSMB are to 1) perform periodic reviews of accumulated study data and evaluate them for participant safety, study conduct and progress, and efficacy, and 2) make recommendations to the study investigators concerning the continuation, modification, or termination of the trial. The DSMB will consider study-specific data, as well as relevant background knowledge about the diseases, interventions, and/or patient population under study. The DSMB will maintain the confidentiality of its internal discussions and activities, as well as the contents of reports provided to it.

Prior to study implementation the DSMB will review the protocol and define its deliberative processes, including stopping guidelines, unmasking (unblinding), event triggers that would call for an unscheduled review, and voting procedures. The Executive Administrator will take notes and provide administrative support during the meetings.

Following study initiation, the DSMB will review data on safety, study conduct, and scientific validity and integrity of the trial every 12 months. The DSMB will also assess the performance of overall study operations and any other relevant issues at each meeting. The DSMB will likely meet 5 times during the study to review data.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. All sites will follow a common quality management plan.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will occur online through REDCap, a HIPAA-Compliant database. Participants will be able to access their surveys online. Acupuncture visit tracking will be entered into REDCap by each site's research specialist.

Usage tracking of the Guided Relaxation intervention is held on the secure University of Florida servers.

Hardcopies of the signed consent forms will be kept in a locked cabinet in a locked officed designated at each site.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the UIC College of Nursing. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after completion of study activities. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported NIH Program Official and the UIC. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

In addition, this study will follow the HEAL Public Access and Data Sharing Policy, which prioritizes expedient and transparent data sharing to combat the public health crisis of the opioid misuse, addiction, and overdose. To this end, this study will share Underlying Primary Data, which will include self-reported demographics, self-reported questionnaires, and interviews. Underlying Primary Data will be stripped of identifiers according to the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Participants will be notified prior to providing their informed consent that de-identified study data will be shared.

The data and associated documentation will be made available to users only under a data-sharing agreement that provides for (a) a commitment to using the data only for research purposes and not to identify any individual patient; (b) a commitment to securing the data using appropriate computer technology; and (c) a commitment to destroying or returning the data after analyses are completed. Such a data-use agreement will be executed through the PIs and the University of Illinois at Chicago College of Nursing. The database can then be accessed via our secure website, in a format that can be used by a variety of statistical software packages. We will make our data and results publicly available (predominately online), so that they can easily be found.

We will publish our results in open-source manuscripts that will be available to the public. Electronic copies of publications will be deposited in PubMed Central with proper tagging of metadata to ensure online discoverability and accessibility within four weeks of acceptance by a journal. Publications will be published under the Creative Commons Attribution 4.0 Generic License (CC BY 4.0) or an equivalent license, or otherwise dedicated to the public domain (e.g., Creative Commons public domain tool, CC0). To the extent feasible, Underlying Primary Data will be shared simultaneously with the publication and made immediately accessible through release under the Creative Commons Attribution 4.0 Generic

License (CC BY 4.0) or an equivalent license, or otherwise dedicated to the public domain (e.g., Creative Commons public domain tool, CC0). Before submitting Underlying Primary Data, we will work with our Institutional Review Board (IRB) and Data Safety and Monitoring Board to assess the informed consent materials and to determine whether the Underlying Primary Data may be shared as contemplated in this policy.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCCIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIH	Complementary and Integrative Health
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCD	Sickle Cell Disease
SMART	Sequential, Multiple Assignment, Randomized Trials
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SRS	Self-report Survey
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
0.1	2/1/2021	Initial Draft	Not applicable; this is the first version of the protocol.
0.2	4/1/2021	Changes throughout document in response to review	Response to reviewer comments of Initial Draft
0.3	6/10/2021	-NCT number added (registration approved since last protocol version) -study measure and blinding procedure questions clarified -inserted blinding table	Response to NIH review comments
0.4	7/12/2021	Changes in response to NIH review comments regarding blinding and limiting the number of participants per acupuncturist	NIH review comments

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