Cognitive Behavioral Therapy and Real-Time Pain Management Intervention for Sickle Cell Via Mobile Applications (CaRISMA)

NCT04419168

6/15/2020

F1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Cognitive Behavioral Therapy and Real-Time Pain Management Intervention for Sickle Cell via Mobile Applications (CaRISMA)
Grant Number:	
Study Description:	We are conducting a comparative effectiveness trial among adult patients with sickle cell disease (SCD) who report chronic pain (N = 350), randomized to receive either mobile phone-delivered computerized cognitive behavioral therapy (cCBT; n = 175) or digital education (m-Education; n = 175). Both intervention groups will receive weekly (more frequent if requested or needed) follow-up with a health coach for at least 3 months to reinforce learned materials. Both groups will also use their mobile device to track daily pain, mood, and medication used. They will also be given access to a study-associated online support group page where they can discuss with other patients, issues they faced and what skills were or could be used to address them. Participants will continue all routine care including opioid pain management and novel therapies.
Objectives:	Primary Objective: Determine whether cCBT will confer greater benefit on daily pain intensity and pain interference at 6 months, compared to m-Education Secondary Objectives: Determine whether cCBT will confer greater benefit on depressive symptoms, health care utilization, and opioid misuse behaviors compared to m-Education
Endpoints:	Primary Endpoint: Daily pain intensity, pain interference Secondary Endpoints: Depressive symptoms, health care utilization (opioid prescriptions, acute care visits) and opioid misuse behaviors (Current Opioid Misuse Measure – COMM)
Study Population:	Male and female patients that are 18-65 years of age, have a diagnosis of SCD (any genotype), report chronic pain (i.e., pain ≥ 4 days/week and/or are prescribed long-acting or daily opioid pain medication for past 3 months or longer) and are able to access the study intervention
Phase or Stage:	Phase 2/Phase 3
Description of Sites/Facilities Enrolling Participants:	• **Clinical sites:** University of Pittsburgh Medical Center (UPMC), Johns Hopkins University (JHU), University of Illinois at Chicago (UIC), Ohio State University (OSU), and Duke University (Duke) comprehensive sickle cell centers. All sites serve adults with sickle cell disease. Sites will advertise and identify patients who may be eligible. In addition, Vanderbilt University will advertise the study. **Community-based organizations:** Sickle Cell Warriors, Sickle Cell Community Consortium, and Sickle Cell 101 will promote the study and recruit participants from their online communities.

Description of Study Intervention/Experimental Manipulation: The study interventions are both Internet-delivered, evidence-based tools that have been tailored specifically for the target population through a user-centered approach that has engaged stakeholders at each stage of the process.

1. Computerized cognitive behavioral therapy (cCBT) for pain. The cCBT program will teach users how to recognize negative thoughts and emotions, use cognitive skills and problem-solving, and apply coping behaviors such as distraction, activity scheduling, and relaxation. The cCBT arm emphasizes skills acquisition and learning through practice; this intervention is consistent with the tailored behavioral services patients would receive individually or as a group when working with a psychologist or behavioral pain specialist.

2. Mobile-delivered pain and sickle cell disease education (m-Education). The m-Education program will teach users about chronic pain, healthy lifestyle tips (e.g., nutrition and exercise), and facts about SCD. This program is consistent with the education patients and families would receive with a patient educator.

Study Duration: 3.5 Years

Participant Duration: 12 Months

1.2 SCHEMA

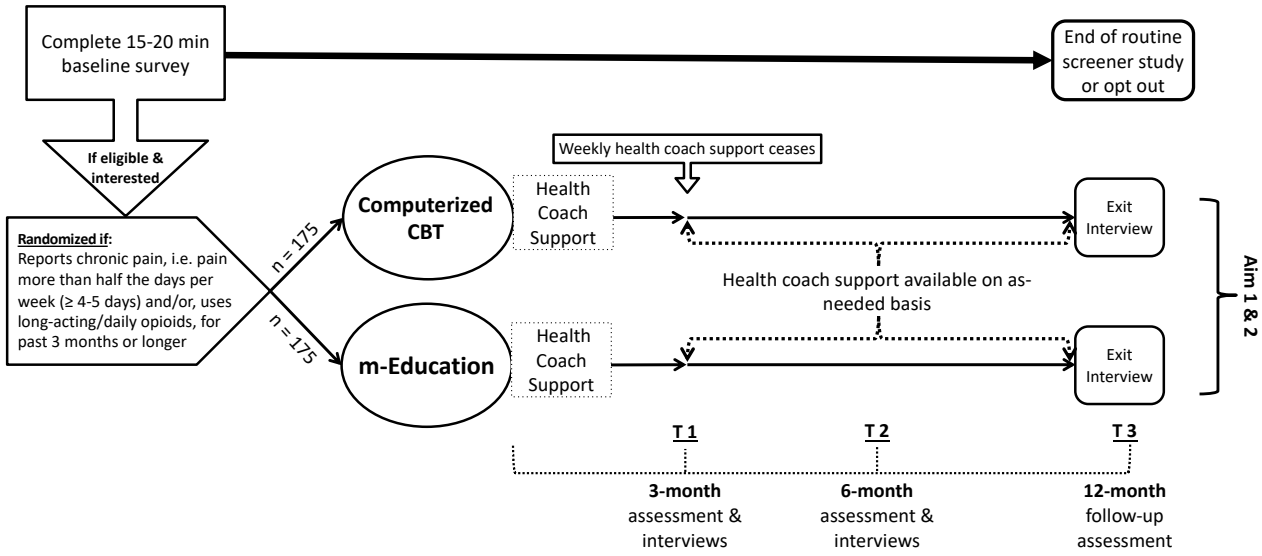


Figure 1 *- CaRISMA study design with two interventions arms and 12 months of follow-up for all participants.*

The structure of the CaRISMA trial. A total of 350 sickle cell patients will be randomized into one of two study arms (cCBT or m-Education). In the first 3 months participants will complete an Internet-delivered

SCD pain intervention on their smartphones, input daily pain logs and have weekly check-ins with a health coach. At baseline, 3-, 6-, and 12-month time points all 350 participants will complete Painimation and self-report outcomes assessments. Selected participants will participate in an additional qualitative interview. Between T1 and T3 participants will communicate with health coaches on an as-needed basis, but will continue to input daily pain logs.

1.3 SCHEDULE OF ACTIVITIES

Table 1 *- Schedule of activities for the CaRISMA Trial over 3.5 years of the project*

Project Milestones and Timeline														
Research Activities	Year 1				Year 2				Year 3				Year 4	
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Develop Manual of Operating Procedures	X	X												
Prepare manuscript of study protocol for publication	X	X												
e-consent, database and intervention setup and planned adaptions	X	X												
Train health coaches, research coordinators and research assistants	X	X												
Obtain central IRB approval		X	X											
Active recruitment, screening and baseline examinations			X	X	X	X	X	X	X					
Recruitment target completions 1=25%, 2=50%, 3=75%, 4=100%				1		2		3		4				
Treatment/support of participants, follow-up and data acquisition			X	X	X	X	X	X	X	X	X	X	X	
DSMB meetings with minutes		X		X		X		X		X		X		X
National meeting abstract submissions								X				X		
SCCC Patient/Family symposium (PF), National SCD CBO Conference (C)	C	PF			C	PF			C	PF			C	PF
Data analysis/interpretation, manuscript preparation/submission											X	X	X	X
Interim (I) and Final (F) Progress Reports		I		I		I		I		I		I		F
Disseminate results/recommendations to stakeholders													X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Cognitive Behavioral Therapy and Real-Time Pain Management Intervention for Sickle Cell via Mobile Application (CaRISMA) is a pragmatic comparative effectiveness trial designed to evaluate the effectiveness of two evidence-based, mobile-technology–delivered behavioral pain interventions for adults with sickle cell disease (SCD) in real-time, routine practice conditions.

Sickle cell disease affects millions of people worldwide and over 100,000 people in the United States. Pain is the most common symptom among adults with sickle cell disease (SCD),[1] yet many of these patients continue to report that their pain is inadequately managed. The effectiveness of pharmacological treatments for pain has been, overall, unsatisfactory. Opioid therapy is the most relied-upon approach to pain management in SCD, despite evidence that it provides inadequate long-term relief and instead leads to negative physical and psychological consequences, including drug dependence.[2,3] There is an urgent need for effective, non-pharmacological pain interventions in SCD.[4-6]

The gap in evidence this study aims to address. There is a need for an adequately powered pragmatic study to show that behavioral pain treatment can be implemented into routine SCD care, in the real world, at scale. Although evidence-based, non-pharmacological interventions for pain are widely used in other pain populations, there are currently no large-scale, adequately powered trials to demonstrate the effectiveness and dissemination potential of any behavioral pain management approach for adults with SCD.[4-7] Medical providers treating adults with sickle cell are unclear what non-pharmacological pain treatment they can offer that will be acceptable and effective for their patients. In the past, cognitive behavioral therapy (CBT) has not routinely been part of pain management in SCD care because of multiple barriers to providing quality CBT pain services, including lack of local availability or access, cost, and even the stigma associated with seeing a mental health specialist. This study aims to demonstrate that behavioral interventions can be an effective component of adult SCD care, and to identify which of the programs tested (cCBT or m-Education) work for which patients and when. If successful this study will determine whether the study interventions have a significant impact on daily pain and pain interference. We will also evaluate spillover effect on depression and anxiety. Providers will have the necessary information to improve pain management in SCD care.

Significance of Problem

Behavioral approaches to managing chronic pain are effective and used routinely in other pain populations. Cognitive behavioral therapy (CBT), in particular, is the gold standard of behavioral approaches to managing pain in the general population. However, despite decades of evidence showing it to be effective in SCD for pain management, CBT is not used routinely as a treatment for pain in SCD and is rarely offered to SCD patients.

There are two primary reasons why CBT is not part of routine SCD care. First, there is a lack of access to CBT due to the expense of providing face-to-face therapy in low-resource clinical settings and a shortage of available CBT-trained therapists, especially those with a sickle cell focus. Even if a CBT therapist were available, therapy is time-consuming and requires travel to a clinic, which is already challenging for patients with limited resources. Second, there are no large-scale studies testing whether CBT is more effective or preferred by adult patients, families, and clinicians over other non-pharmacological strategies like pain education, which is already widely available to the

SCD population through community-based organizations (CBOs) via the Internet and social media and may provide similar health benefits.[8,9]

This study proposes to overcome barriers to routine use of behavioral treatments for pain in adult SCD care. Through the use of mobile technology, we are now able to provide high-quality, evidence-based behavioral pain treatment that can be scaled to reach patients in under-resourced settings. Computerized (Web- or mobile-based) cognitive behavioral therapy (cCBT) is an effective alternative to traditional face-to-face CBT.[10,11] In fact, cCBT is now offered as part of routine care in the UK[12,13] and is offered by several health plans here in the US. We know cCBT is effective for pain[14-17] but we don't know what works best for whom and when. For example, cCBT has not been compared to pain education, which is readily available and accessible to the SCD community via our CBO partners. Thus, in a multisite pragmatic trial, we will compare the effectiveness and patient preference of cCBT versus pain education in adults with SCD.

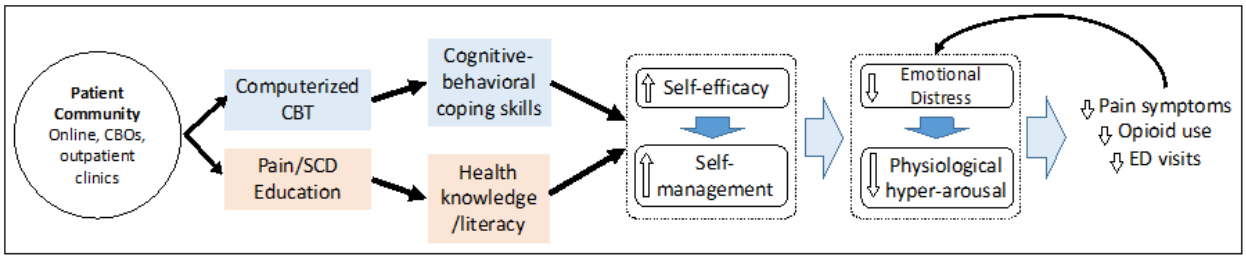


Figure 2 *- Conceptual model for the impact of cognitive behavorial therapy (CBT) and education in sickle cell disease. Interventions implemented through internet forums, community-based organizations (CBOs), and outpatient clinics.*

AIM 1: Compare the effectiveness of two mobile-phone–delivered programs—cCBT versus pain and SCD education (m-Education)—for reducing SCD pain symptoms. In a multisite comparative effectiveness trial conducted at five comprehensive sickle cell centers and three CBOs, we will recruit 350 adults with SCD who report chronic pain and randomize them to one of two groups. For at least 12 weeks, one group will be asked to engage in a mobile cCBT program tailored for adults with SCD (cCBT). The second group will receive pain and SCD education on their mobile phones (m-Education). Both programs use identical mobile-technology platforms; only the content differs. All participants will have weekly check-ins with a health coach during the first 12 weeks and will track pain symptoms daily on the study mobile phone app.

Our study hypotheses are:

H1: cCBT will confer greater benefit on pain outcomes at 6 months, compared to m-Education. Outcomes of this trial will include change in average weekly pain intensity (primary) and pain interference (secondary) at 6 months. As a secondary investigation, we will look at sustainability of the intervention effects out to 12 months.

H2: cCBT will confer greater benefit on depressive symptoms at 6 months, compared to m-Education.

H3: cCBT will confer greater decreases in health care utilization (opioid prescriptions, acute care visits) over 12 months, compared to m-Education.

AIM 2: Assess whether baseline depression symptoms moderate the effect of interventions on pain outcomes. Evidence suggests CBT may be particularly helpful for patients with mental health comorbidities.[18] Therefore, we will evaluate heterogeneity of treatment effect (HTE) by mental health status. Subgroup analysis will be conducted by comparing intervention effects between participants with low and high depression. To further understand

which intervention works best for whom and when, the lived experience of patients in the trial, and differences in perceptions between depression subgroups, we will do a series of qualitative interviews.

Expected Outcomes.

This study will (1) demonstrate the effectiveness of a low-cost, scalable, evidence-based behavioral approach for pain management that meets the needs of patients and providers, and (2) show that behavioral approaches can be readily implemented into routine SCD care. This study will help define best practices for non-opioid approaches to chronic pain management in low-income, racial minority populations, and low-resource care settings.

2.2 BACKGROUND

Sickle cell disease (SCD) is a genetic disorder that affects 100,000 people in the US and millions worldwide.[19] A vast majority of the people affected by sickle cell are of African descent;[20] this is a racial minority group that has been traditionally underserved and suffers from health care disparities.[21] Compared to other rare chronic conditions such as cystic fibrosis that affect primarily people of European descent, SCD receives less funding and has more limited clinical resources.[21] Thus, this is a population in need of more resources and access to high-quality, evidence-based care.

The hallmark of SCD is pain, the most frequently reported symptom and the primary reason patients seek acute care. The recurrent and unpredictable nature of pain in SCD has a significant impact on patients' daily functioning and quality of life.[22,23] Both acute and chronic pain have been associated with more hospitalizations/emergency room visits and with premature death.[24-26] Our stakeholders consistently report pain treatment as the most important area of sickle cell care that needs to be addressed.

Current standards for pain management in SCD are, overall, unsatisfactory.[27,28] There is an overreliance on opioids for pain treatment on the part of both the providers and patients, despite knowledge of the physical and psychological consequences.[2,3,29,30] Up to 87% of adults and up to 44% of children age < 6yrs old with SCD are prescribed opioids[31] even though there are no data on their long-term efficacy. It is likely that side effects and hyper-analgesia contribute to increased pain[32] and a lower overall quality of life.[33] There is a pressing need for effective, non-pharmacologic interventions for chronic pain in patients with SCD.[4]

Providing at least one non-pharmacological treatment is required by the Joint Commission as standard care for pain management.[34] Cognitive behavioral therapy (CBT) is considered the gold standard of non-pharmacological treatment for chronic pain.[35] Although CBT is offered in many pain management clinics, there are several barriers to the widespread implementation of CBT, including availability, accessibility, and cost.[36] Offering CBT via the Internet not only overcomes these barriers but can be as effective as face-to-face CBT.[10,11] A recent meta-analysis found that using computerized CBT (cCBT) can help decrease pain intensity, interference/disability, and catastrophizing, and can have significant spillover effects on depression.[15] cCBT can be particularly effective when accompanied by support of a health coach, an individual who can be available remotely by messaging service or phone to provide guidance on the CBT skills, and well as encouragement and support.[37] Given the effectiveness of cCBT, the UK's National Institute for Health and Care Excellence (NICE) made cCBT standard of care and available to all patients in the UK.[12,13] cCBT is becoming well established as a low-cost add-on to routine care, and is now being offered by several health plans in the US.

SIGNIFICANCE The proposed study addresses the stress-pain cycle **(Figure 3)** and has the potential to demonstrate how the adoption of cCBT or m-Education into clinical practice can improve pain management and decrease opioid use in SCD.

Figure 3 *- Diagram presents the biopsychosocial model adapted to show the hypothesized mechanisms linking behavioral and social factors to physiological pain in SCD. The model suggests that external stressors can initiate negative thoughts and a cycle of stress and pain.*

Understanding pain in SCD using the biopsychosocial model.[38-41] To determine the causes of pain in SCD, we interviewed stakeholders, conducted focus groups, reviewed the literature, analyzed discussions about SCD on social media forums, and consulted with experts in hematology, psychology, and pain. This work led to an adapted version of the biopsychosocial model that we use here as a framework to understand the pain cycle in SCD and guide our research question. As described in **Figure 3**, the experience of unpredictable acute pain and daily, unrelenting chronic pain can lead to deleterious negative thoughts and low self-efficacy; self-efficacy is the degree to which one believes they can succeed in managing their disease. "There is nothing I can do about this pain," said one young adult with SCD as he described the unpredictable and unrelenting nature of his pain and the limited control he had over his health.

This conceptual model shows how a pain event or external stressor such as losing a job can put patients into a vicious cycle of stress, negative emotions, hyper-arousal, and pain (**Figure 3)**. This model aided us in: (1) defining the problem, (2) selecting behavior(s) to target, and (3) describing what needs to change in order to achieve less pain and disability.

This research is focused on outcomes of interest to patients and their caregivers. Negative thoughts and lack of perceived self-efficacy contribute to adults with SCD feeling overwhelmed and helpless. Perceived stress leads to depression and anxiety, as well as increased physiological arousal, and can trigger a vaso-occlusive crisis. In addition to highlighting the negative impact stress has on pain, our stakeholders also provided examples of behavioral strategies they use to cope with emotional distress and pain, such as distraction, relaxation, and positive thinking. Strengthening, expanding, promoting, and connecting these behavioral strategies with self-efficacy will improve SCD care, and potentially reduce reliance on opioid treatments for chronic pain.

T**he primary outcome for this study is change in daily pain intensity**. The University of Pittsburgh (Pitt) Sickle Cell Advocacy Team, a group of patient and caregiver partners, identified pain as the primary aspect of SCD that needs more awareness and attention. We also analyzed posts and comments made between Oct. 2012 and Jun. 2016 on the two most popular SCD Facebook groups, Sickle Cell Warriors and Sickle Cell Unite.[42] Of 32,977 messages, 22.5% (7,446) included the word "pain" or "crisis." Sentiment analyses showed that messages with mentions of pain were associated with less social connection and more negative emotions such as anxiety. This study, therefore, seeks to address pain and the socio-emotional needs expressed by the SCD community.

Mental health symptoms are a major issue that goes unaddressed. Mental health is rarely assessed or treated in SCD,[43] although 22% to 57% of patients with SCD have clinically significant symptoms of depression, and potentially even more patients suffer from anxiety symptoms. The Sickle Cell Community Consortium (SCCC), led by co-I Lakiea Bailey, has identified mental health as a top priority and advocates for educating the community, and for routinely screening for mental health symptoms and providing treatment. This study aims to identify how we can fill this gap in SCD care.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The anticipated risk to the research participants is minimal. The participants will perform routine psychological assessments and self-report questionnaires. There may be some emotional discomfort with engaging in the behavioral intervention and disclosing personal information, but this is expected to be minimal.

Due to the depressive symptoms associated with SCD, this behavioral intervention study may reveal pre-existing suicidal thoughts/behaviors. To safeguard against potential suicide attempts, the PHQ-9 administered at baseline, 3-, 6-, and 12-month time points will be used to screen participants for possible suicide risk factors. A positive response will initiate the Suicide Risk Management Protocol described in **Section 2.3.3, Assessment of Potential Risks and Benefits.**

The social network component of the study also presents some risk. Upon consenting to the study, participants will be linked to a study-associated online support group page (Facebook group) that will be monitored by study staff and one of our community partners, SC101. Though SC101 will monitor the page regularly, there is still a risk for negative or offensive comments to be posted and read by participants before the study team is able to remove them. User participation on the online support group and frequency of access will not be recorded. The identity of participants will not be masked. Information shared by an individual may unintentionally disclose they are participating in the trial or their disease status.

This study also involves the collection of data over the Internet using mobile devices. Although every reasonable effort will be taken, confidentiality during Internet communication procedures cannot be guaranteed and it is possible that additional information beyond that collected for research purposes may be captured and used by others not associated with this study.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no direct benefit to the participants in this study. However, participation in this study will provide access to a vibrant, active online community with frequent interactions from other adults and families affected by SCD. If this intervention is shown to be effective, this research will ultimately benefit patients with chronic pain.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

To minimize the discomfort participants may feel completing psychological assessments and questionnaires, each participant will be assigned a health coach trained in how to manage sensitive information and interactions with participants. Additionally, health coaches will be trained on the Suicide Risk Management Protocol outlined below.

Interactions on the study-associated Facebook page will not be monitored by study staff for data acquisition. However, our SC101 and study staff will monitor page content at least every 24-48 hours. When participants enroll in the study, study staff will explain the recommended etiquette to be followed while using the study-associated Facebook page. In the event that a participant feels offended by content posted on the page, they will have the ability to contact the Facebook page administrator or directly contact study staff or the health coach, who will address the situation.

Informed consent will be obtained electronically from all participants. All staff will be trained in informed consent procedures and will be available to read the consent forms to individuals with low literacy levels. For participants enrolling remotely, a staff person will be available by phone to read the consent. In addition, we will have a consent video that explains the study in detail, as well as risks and benefits. The consent form and video will be available in English only.

All participant information, including contact information, questionnaires, and clinical information, will be monitored by study staff and available only to them. Case report forms and other study-sensitive documents will be stored electronically in password-protected files on our data management system. Only authorized study staff will have access to study data. Study reports will not contain any identifiable information and will present findings in aggregate (or by treatment group). De-identified data may be shared with other researchers in the future.

Suicide Risk Management Protocol (SRMP)

The Suicide Risk Management Protocol (**Figure 4**) will be embedded within the online survey tool, which is administered at baseline screening, and the 3-, 6-, and 12-month follow-up time points. It will be triggered on the participant's screen when he/she enters a positive response to the PHQ-9 question, "Over the last 2 weeks, have you had thoughts that you would be better off dead or of hurting yourself in some way?" A positive response also alerts the patient's designated health coach.

Upon SRMP initiation, the Scale for Suicide Ideation (SSI) will be activated on the participant's screen via our online survey tool in order to gauge severity of suicide risk. There are skip patterns programmed throughout the SSI so that participants need only complete subsequent parts if they score high enough. Each item is scored on a 3-point scale ranging from 0 to 3 and SSI results are dependent upon the answers submitted.

Parts A and B assess the risk for self-harm. If scores for Part A and B are ≥2, the health coach asks about eight established risk factors (Part C). If participants report ≥2 risk factors, the health coach assesses duration and acuteness of self-harm ideation (Part D and E).

Following completion of the SSI assessment, the health coach will be notified about the participant's automatically assigned risk level for self-harm, which ranges from None to Imminent. Specific actions to be executed by the health coach are outlined depending on the participant's risk level.

If the SSI risk determination is **Moderate** or **High** Suicide Risk, the health coach will enter in a "contract of safety" with the participant where they will agree upon a follow-up call within two hours. Immediately after hanging up

with the participant, the health coach will contact the coordinating site clinical psychologist or designated physician to receive directives on what actions to take. At the agreed upon time, the health coach will call the participant and execute those directives. Alerts will be sent to the designited clinical and research staff contacts at the participant's local site. The health coach will record all events in the SRMP Log.

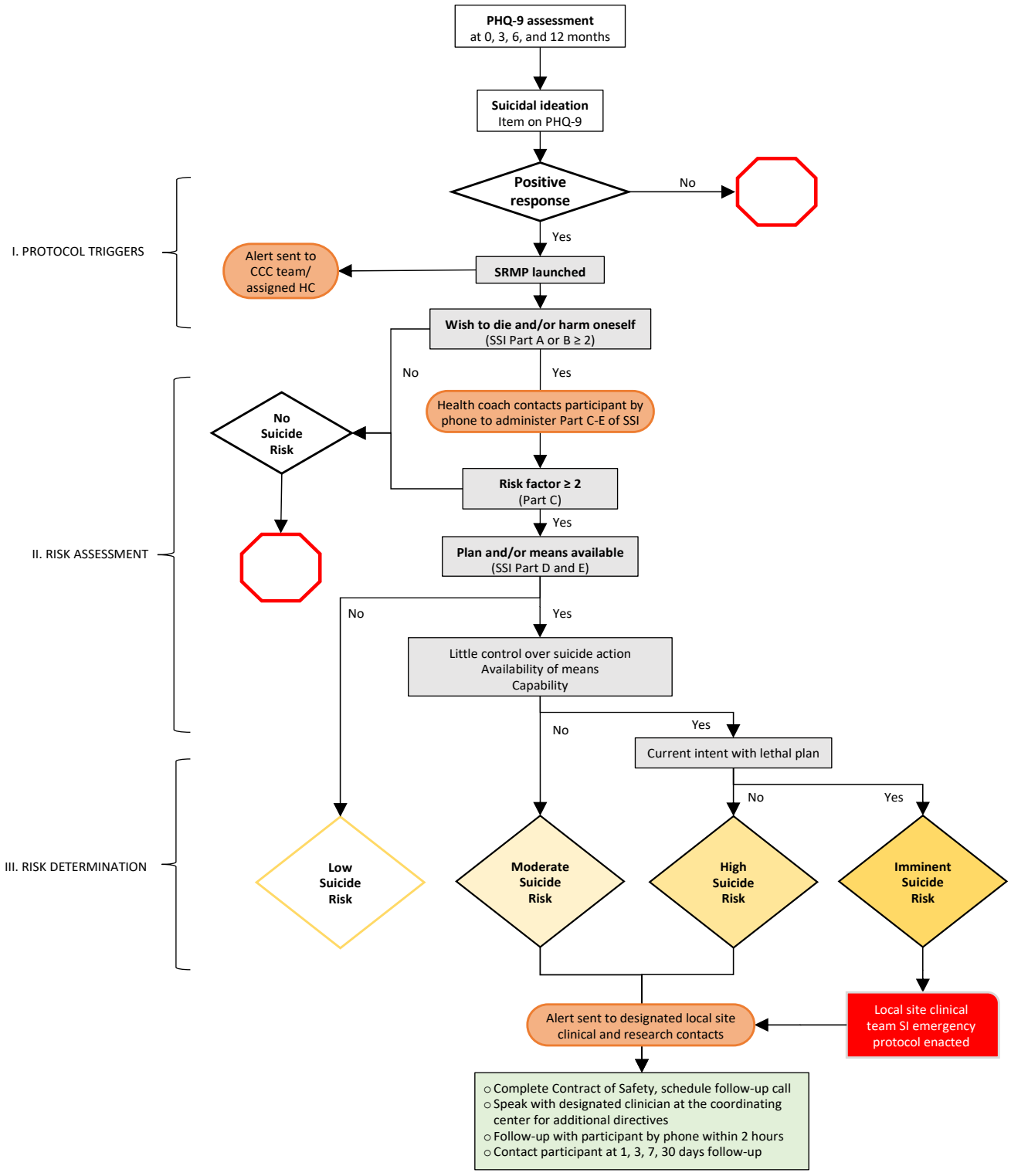


Figure 4 *- Suicide Risk Management Protocol (SRMP) illustrating risk triggers, assessments, and determinations.*

If the SSI risk determination is **Imminent**, the health coach will keep the participant on the phone line and follow the local site suicide prevention plan or dial 9-1-1 on a second phone line. After, the health coach will follow the procedures for Moderate and High Suicide Risk when appropriate. Alerts will be sent to the designited clinical and research staff contacts at the participant's local site.

Follow-up after Incident:

Health coaches will follow up with participants assigned **Moderate, High, and Imminent** Suicide Risk. The health coach will reach out 1, 3, 7, and 30 days after the incident to see whether suicidal ideation has decreased or been resolved, and whether the participant has followed through with the recommendation provided by the site psychologist.

3 OBJECTIVES AND ENDPOINTS

Justification as to why the value of the information to be gained outweighs the risks of participation

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Determine whether cCBT will confer greater benefit on daily pain intensity and pain interference at 6 months, compared to m-Education	Daily pain intensity, pain interference	The University of Pittsburgh (Pitt) Sickle Cell Advocacy Team, a group of patient and caregiver partners, identified pain as the primary aspect of SCD that needs more awareness and attention. We also analyzed posts and comments made between Oct. 2012 and Jun. 2016 on the two most popular SCD Facebook groups, Sickle Cell Warriors and Sickle Cell Unite. Of 32,977 messages, 22.5% (7,446) included the word "pain" or "crisis." Sentiment analyses showed that messages with mentions of pain were associated with less social connection and more negative emotions such as anxiety. This study, therefore, will address pain and the socio-emotional needs expressed by the SCD community.
Determine whether cCBT will confer greater benefit on depressive symptoms, health care utilization, and opioid misuse behaviors compared to m-Education	Depressive symptoms, health care utilization (opioid prescriptions, acute care visits), and opioid misuse behaviors (Current Opioid Misuse Measure – COMM)	Mental health is rarely assessed or treated in SCD although 22% to 57% of patients with SCD have clinically significant symptoms of depression, and potentially even more patients suffer from anxiety symptoms. The Sickle Cell Community Consortium (SCCC), led by co-I Lakiea Bailey, has identified mental health as a top priority and advocates for educating the community, and routinely screening for mental health symptoms and providing treatment. This study aims to identify how we can fill this gap in SCD care.

This research is necessary to understand the feasibility of a mobile-technology–based behavioral intervention for pain that predominantly targets a minority population. In designing this study we queried 123 adults with SCD using a short online survey to determine if the proposed project objectives and outcomes were relevant and meaningful to patients and their family members. Stress was the most frequently reported modifiable trigger for pain and **88% of respondents wanted to learn about alternatives to taking narcotics for pain.** Ultimately, our

research program will lead to the implementation and dissemination of a cost-effective, acceptable, and effective behavioral intervention to address chronic pain among adults with SCD without the use of opioids, and improve our ability to deliver effective pain treatment to this and other underserved populations.

4 STUDY DESIGN

4.1 OVERALL DESIGN

CaRISMA is a randomized comparative effectiveness trial among adult patients with SCD who report chronic pain (N = 350) randomized to receive either cCBT (n = 175) or m-Education (n = 175). For at least 12 weeks, one group will be asked to engage in a mobile cCBT program tailored for adults with SCD. The second group will receive pain and SCD education on their mobile phones (m-Education). Both programs use identical mobile-technology platforms; only the content differs. The cCBT program focuses on teaching behavioral coping skills through participants' "seeing and doing" while the pain education arm focuses on improving self-management through participants' "learning and knowing" more about pain and SCD. All participants will have weekly check-ins with a health coach during the first 12 weeks of the intervention and will track pain symptoms daily on the app.

AIM 1: Compare the effectiveness of two mobile phone-delivered programs—cCBT versus pain and SCD education (m-Education)—for reducing SCD pain symptoms. In a multisite comparative effectiveness trial conducted at five comprehensive sickle cell centers and three CBOs, we will recruit 350 adults with SCD who report chronic pain and randomize them to one of two groups. For at least 12 weeks, one group will be asked to engage in a mobile cCBT program tailored for adults with SCD. The second group will receive pain and SCD education on their mobile phones (m-Education). Both programs use identical mobile-technology platforms; only the content differs. All participants will have weekly check-ins with a health coach during the first 12 weeks and will track pain symptoms daily on the intervention. Our study hypotheses are:

H1: cCBT will confer greater benefit on pain outcomes at 6 months, compared to m-Education. Outcomes of this trial will include change in average weekly pain intensity (primary) and pain interference (secondary) at 6 months. As a secondary investigation, we will look at sustainability of the intervention effects at 12 months.

H2: cCBT will confer greater benefit on depressive symptoms at 6 months, compared to m-Education.

H3: cCBT will confer greater decreases in health care utilization (opioid prescriptions, acute care visits) over 12 months, compared to m-Education.

AIM 2: Assess whether baseline depression symptoms moderate the effect of interventions on pain outcomes. Evidence suggests CBT may be particularly helpful for patients with mental health comorbidities. Therefore, we will evaluate heterogeneity of treatment effect (HTE) by mental health status. Subgroup analysis will be conducted by comparing intervention effects between participants with low and high depression. To further understand which intervention works best for whom and when, the lived experience of patients in the trial, and differences in perceptions between depression subgroups, we will do a series of qualitative interviews.

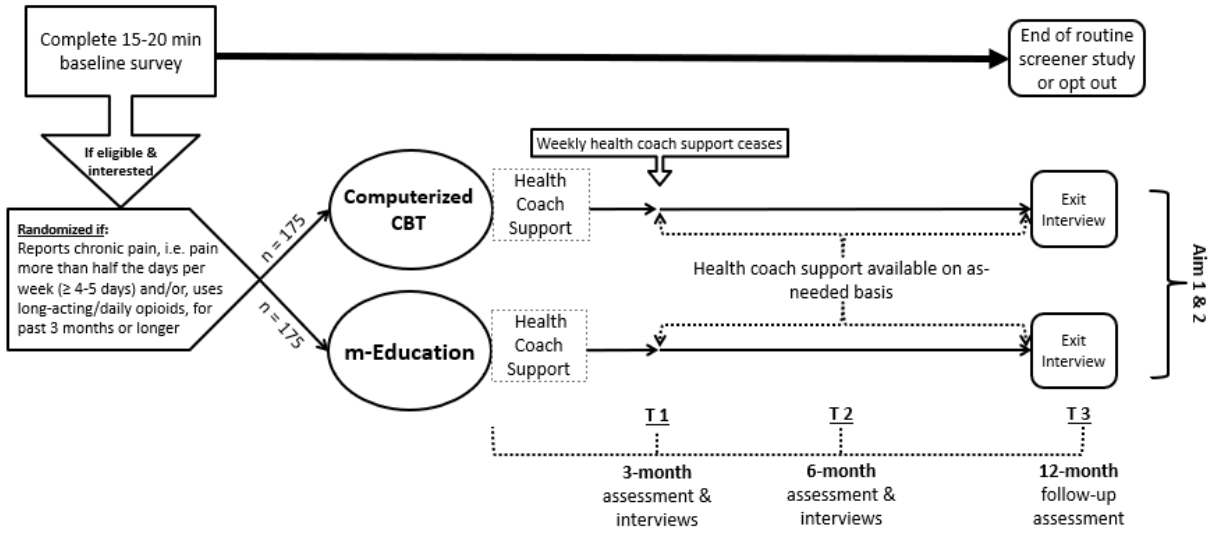


Figure 1 (repeat) *- CaRISMA study design with two interventions arms and 12 months of follow-up for all participants.*

1st Arm in Study Design: Computerized cognitive behavioral therapy (cCBT) for pain. The cCBT program will teach users how to recognize negative thoughts and emotions, use cognitive skills and problem-solving, and apply coping behaviors such as distraction, activity scheduling, and relaxation. The cCBT arm emphasizes skills acquisition and learning through practice; thus, the program involves homework assignments and challenges, as well as continued check-ins with a health coach who helps reinforce the CBT skills and encourages practice and program engagement. The cCBT program also give users access to a study-associated Facebook page where they can discuss with other patients issues they faced and what skills were or could be used to address them. This intervention is consistent with the tailored behavioral services patients would receive individually or as a group when working with a psychologist or behavioral pain specialist.

Table 2 *- Summary of module content for the computerized cognitive behavioral therapy (cCBT) in CaRISMA intervention.*

cCBT Content		
Section Number	**Title**	**Education Content**
1	Introduction	Intro, SMART Goals, 3Ps pain
2	Biology of Stress	How stress can cause pain or make it worse in sickle cell: Fight or Flight response
3	Relaxation	Relaxation: diaphragmatic breathing, muscle relaxation, imagery, mini relaxation
4	Thoughts and Emotions	ABC Model, automatic thoughts, thought restructuring, distress tolerance, schedule pleasant activities
5	Problem-Solving Skills	Bright IDEAS content, framework for solving everyday problems or challenges
6	Healthy lifestyle & Sleep	Nutrition, Activity (Pacing, graded activity), hydration

2nd Arm in Study Design: Mobile-delivered pain and sickle cell disease education (m-Education). The m-Education program will teach users about chronic pain, healthy lifestyle tips (e.g., nutrition and exercise) and facts about SCD.

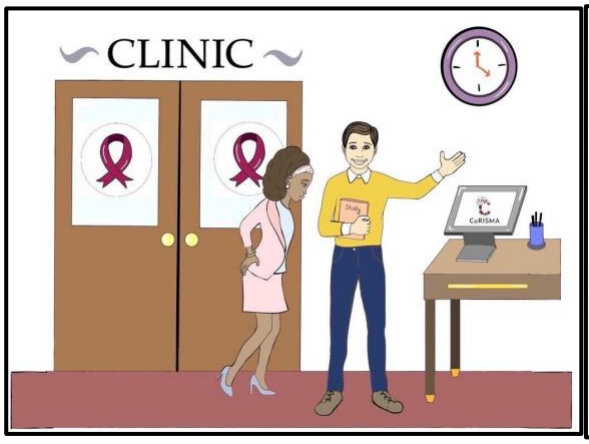
The emphasis will be on knowledge acquisition and will give users an opportunity to apply what they have learned through brief quizzes and discussion with the health coach and the social network. This program is consistent with the education patients and families would receive with a patient educator or what is currently provided through two of our community partners, Sickle Cell Warriors (SCWarriors) and Sickle Cell 101 (SC101), via the Web and social media.

Table 3 *- Summary of module content for m-Education in CaRISMA intervention*

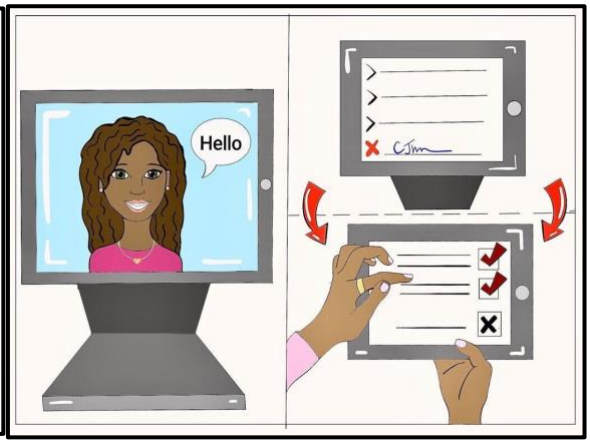
m-Education Content		
Section Number	**Title**	**Education Content**
1	Introduction	Intro to program
2	About sickle cell disease	What is SCD?, terms to know, symptoms and complications to watch out for, heredity
3	Acute and chronic pain	Acute pain, chronic pain, factors that influence pain experience
4	Treatments and medication	About medications, transfusions, pain medications
5	Healthy lifestyle	Diet, exercise, alcohol and drugs, school/work, and hospital stays

General Study Design

This section describes the role of the clinical team in participant recruitment and the consent process. Also described is participant procedures and involvement in the study. Further information on initial procedures and the recruitment process can be found in ***Section 5.5 Strategies for Recruitment and Retention***.

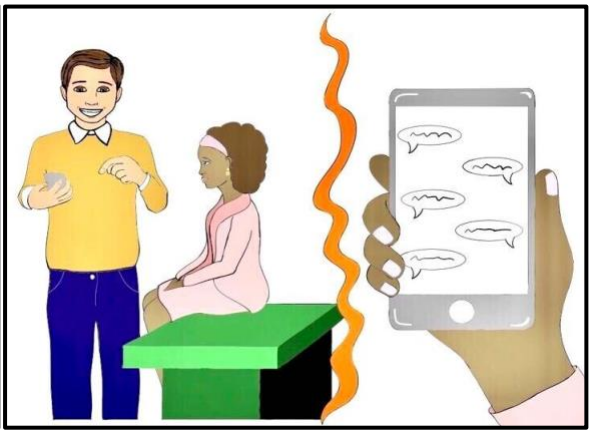


Patient enters Sickle Cell Clinic for routine appointment. During their visit while waiting to be seen, the Research Assistant directs them to the Kiosk where they can learn about CaRISMA.



At the Kiosk, the patient watches the consent video and completes guided prompts to learn about the study. This is followed by a set of study comprehension questions. After informed consent, the patient is asked to complete a set of questionnaires for the baseline measures.

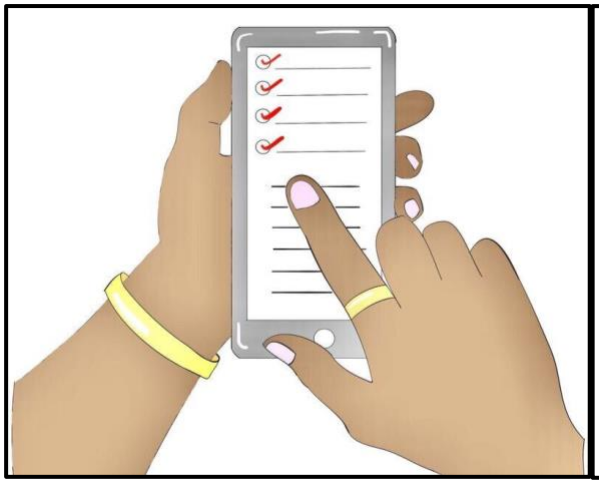
Immediately once a patient submits a signed consent form on the Kiosk or electronic web system, the Research Assistant is alerted on their study cell-phone.

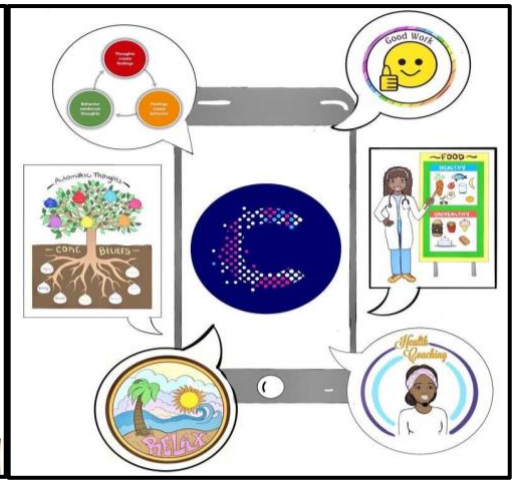


In the same clinic visit, the Research Assistant approaches the now-consented patient. Using her own cell-phone or a study provided mobile device, he guides her through downloading the app, interacting with the chatbot, and links her to the CaRISMA Facebook page. In the first use of the chatbot, the patient is randomized based on their study ID into one of two study arms (CBT or Education).

The patient leaves the clinic and interacts with the virtual intervention at her own pace.

Within 24 hours of consenting, one of the health coaches contacts the patient. The health coach informs the patient that they will have weekly one-on-one check-ins throughout the duration of the intervention.





Through text message or email, the patient receives a link to our online survey tool to complete the follow-up questionnaires at 3, 6, and 12-month time points.

The patient continues completing modules with the intervention, which includes interactive video lessons.

Intervention arm is automatically assigned based on the study ID via the mobile app. When the CaRISMA program is opened for the first time, it will automatically randomize each participant to either study arm: cCBT or m-Education. It will be 1:1 permuted block randomization to prevent imbalance. Because this is an "open-label" randomized controlled trial (RCT), we will monitor randomization over time to make sure group allocation is similar. The participant will not know which arm they have been assigned to, and they will only have access to the materials included in their respective study arm. Participants will receive a link to our online survey tool where they will be asked to respond to six questionnaires and the Painimation app in order to provide their baseline measures. The six questionnaires are as follows: Sickle Cell Self-Efficacy Scale (SCSES), Patient-Reported Outcomes Measurement information System (PROMIS) Pain Interference, Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-ME), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder Scale (GAD-7), and the Current Opioid Misuse Measure (COMM). Painimation is an electronic pain assessment tool developed by our team at the University of Pittsburgh that allows users to better communicate their pain symptoms **(Figure 5).**

In addition, our partners at the Qualitative, Evaluation And Stakeholder Engagement (Qual EASE) Research Services will conduct a set of qualitative interviews to further understand which intervention works best for whom and when, the lived experience of patients in the trial, and differences in perceptions between depression subgroups. Qual EASE will randomly select **48 participants** (of the 350) to be interviewed. Attending the qualitative interviews is completely voluntary and participants may opt out at any time. However, if one of the 48 selected participants does opt out, Qual EASE will invite another participant, of those not previously selected, as a replacement.

Baseline.
Participants will receive a link to our online survey tool where they will be asked to respond to a set of questionnaires and Painimation, a novel pain assessment tool. The questionnaires are as follows: Sickle Cell Self-Efficacy Scale (SCSS), Patient-Reported Outcomes Measurement information System (PROMIS) Pain Interference, Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-ME), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorders Scale (GAD-7), and the Current Opioid Misuse Measure (COMM). For participants who are eligible to be randomized, in addition to baseline questionnaires, items from the Coping Strategies Questionnaire (CSQ) will be asked through the messaging app as participants progress through their respective program.

The Painimation tool is an electronic pain assessment tool developed by our team at the University of Pittsburgh that allows users to better communicate their pain symptoms. Patients are provided with a selection of animations that they use to describe the quality of their pain. The animations can be increased or decreased in speed, color saturation, focus and size, to reflect the intensity of their pain.

For intervention participants, in addition to the quantitative assessments, our partners at the Qualitative, Evaluation And Stakeholder Engagement (Qual EASE) Research Services will conduct a set of qualitative interviews to further understand which intervention works best for whom and when, the lived experience of patients in the trial, and differences in perceptions between depression subgroups. Qual-EASE will randomly select 48 participants (of the 350) to be interviewed. Attending the qualitative interviews is completely voluntary and participants may opt out at any time. However, if one of the 48 selected participants does opt out, Qual-EASE will invite another participant, of those not previously selected, as a replacement.

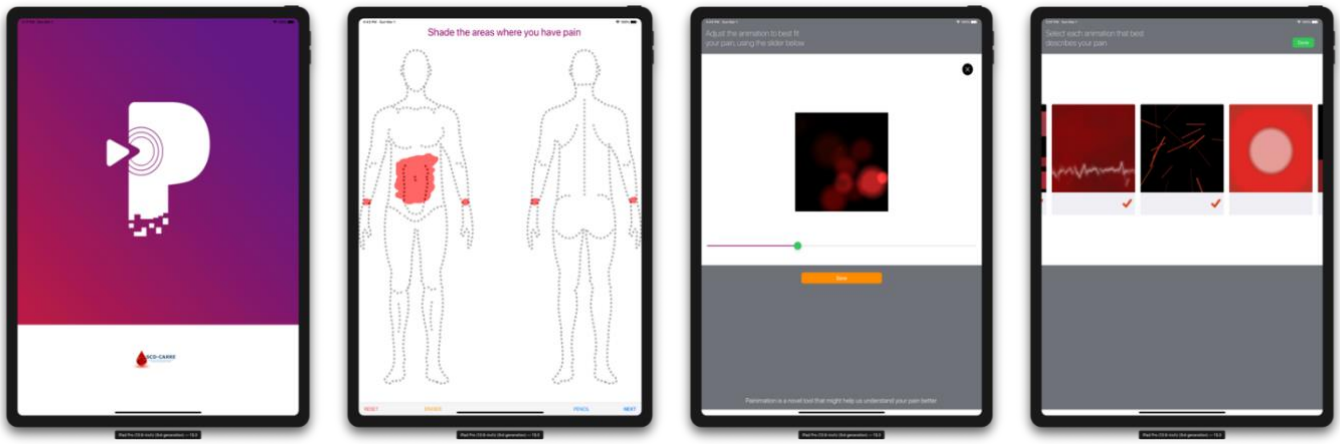


Figure 5 *- Screenshot of the Painimation app showing the splash screen, paintable body image, and selection of painimations to indicate quality and intensity of pain.*

In the first three months of the study, intervention participants will complete all modules of their assigned study arm (cCBT or m-Education) at their own pace. The recommended progression is one module per week; this will give participants time to practice the techniques taught in each module. Participants will be asked to complete a daily electronic diary to track their pain symptoms.

Only intervention arm participants will receive follow up assessment. The convenience comparison group will not be followed with scheduled assessments.

1st Follow-Up (T1). At the end of month 3 (i.e., three months after enrollment, on the same date the participant began the study) participants will again receive a link to our online survey tool to complete the second iteration of Painimation, the SCSS, PROMIS, ASCQ-ME, PHQ-9, and GAD-7. If participants have questions while completing these questionnaires, they may contact their health coach for guidance. Participants will also be asked to complete daily pain intensity entries in the electronic diary. If participants do not complete the questionnaires or the pain intensity entries, health coaches will contact them and remind them to do so. The 48 patients selected for qualitative interviews will have their second interview with Qual-EASE at this time.
Between months 4-6, participants will continue to log their daily pain diary in the CaRISMA intervention but will no longer be expected to have weekly check-ins with their health coach.

2nd Follow-Up (T2). At the end of month 6, participants will receive a link to our online survey tool to complete Painimation, SCSES, PROMIS, ASCQ-ME, PHQ-9, and GAD-7 for the third time. Note: participants will not complete the COMM at T2. Though scheduled weekly check-ins with health coaches will have ceased, participants will still have the opportunity to contact their health coach as needed. Participants will continue to complete daily pain intensity entries through the electronic diary.

Between months 6-12, participants will continue daily pain diary submissions and communication with health coaches as needed. Additionally, Qual EASE will conduct the final set of qualitative interviews with the 48 randomly selected participants.

3rd and final Follow-Up (T3). In the final month of the study (T3), participants will receive a link to our online survey tool to complete Painimation, SCSES, PROMIS, ASCQ-ME, PHQ-9, GAD-7, and COMM for the final time.

Primary Outcome.

Aim 1 of this study is to compare the effectiveness of two mobile phone-delivered programs—cCBT versus pain and SCD education (m-Education)—for reducing SCD pain symptoms (i.e. pain interference). The secondary outcome we expect to change in this study is daily pain intensity. As mentioned above, patients will track pain symptoms using an electronic diary where they will be prompted to complete a symptoms survey once a day. Participants will be encouraged to enter their pain symptoms daily. They will receive reminders to keep entering daily data at each time point (T0, T1, T2, T3). Participants will have the option to snooze the prompt until a more convenient time. For the electronic diary, some format of the following will be administered:

<u>Daily</u>

- Using any number from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable, what is your pain level today?
- Did you take opioid medications today?
- Which one of the following emojis best represents your mood today?

<u>Weekly</u>

- Using any number from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable, what is your pain level today?
- Did you take opiate medications today?
- Compared to what you used yesterday, is the amount of opiate meds you took today less than yesterday, the same as yesterday, or more than yesterday?
- Did you take non-opiate medications today?
- This past week, how often have you been bothered by little interest or pleasure in doing things?
- This past week, how often have you been bothered by feeling down, depressed, or irritable?
- This past week, how often have you been bothered by feeling nervous, anxious, or on edge?
- This past week, how often have you been bothered by not being able to stop or control worry?

Secondary Outcome Measures. Aim 2 of this study is to assess whether baseline depression symptoms moderate the effect of intervention on pain outcomes. To achieve this, patients will be asked to complete the PROMIS Pain Interference Scale[44] at baseline, 3 months, 6 months, and 12 months; PROMIS is a validated questionnaire asking a patient how most day-to-day function is altered by pain. In addition, to assess changes in quality of life and emotional distress, participants will complete the following tests at baseline, 3 months, 6 months, and 12 months: Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-ME); Emotional Functioning and Social Impact scales;[45,46] the Patient Health Questionnaire (PHQ9),[47,48] a 9-item measure of depressive symptoms; and the Generalized Anxiety Disorder Scale (GAD-7). Lastly, to assess changes in use of prescribed opioids, participants will complete the Current Opioid Misuse Measure (COMM)[49] at baseline and 12 month follow-up. See **Table 4**.

Medical Outcomes (PCORnet).

For patients recruited at one of the five clinical sites, we will evaluate objectively measured opioid medication refills and emergency department visits or hospitalizations for pain crisis. We will be working in collaboration with PCORnet to collect data retrospectively (from the past 12 months) and prospectively (12 months from date of enrollment) from patient medical records. These data will allow us to track medications including opioid pain medication prescriptions and refills, and health care utilization (i.e., emergency department visits and

hospitalizations), as well as lab values (e.g., hemoglobin level) and clinical outcomes (e.g., end-organ damage score). For the patients recruited from our community partner organizations or online who are not affiliated with a participating clinical center, we will only acquire or evaluate their medical records for the purpose of confirming their sickle cell diagnosis.

Process evaluation measures. For the intervention to be effective, patients must use the program and acquire coping skills or knowledge about pain and SCD that will help them manage their physical health (e.g., nutrition/exercise), emotional distress, and physiological response to stressors, all factors contributing to pain. As they progress through the intervention, participants will complete elements of the Coping Strategies Questionnaire for sickle cell disease (CSQ)[50] and the Sickle Cell Self-Efficacy Scale (SCSES) shown in **Figure 6**.

1) How sure are you that you can do something to cut down on most of the pain you have when having a pain episode?	Not at all sure	Not sure	Neither	Sure	Very Sure
2) How sure are you that you can keep doing most of the things you do day-to-day?	Not at all sure	Not sure	Neither	Sure	Very Sure
3) How sure are you that you can keep sickle cell disease pain from interfering with your sleep?	Not at all sure	Not sure	Neither	Sure	Very Sure
4) How sure are you that you can reduce your sickle cell disease pain by using methods other than taking extra medication?	Not at all sure	Not sure	Neither	Sure	Very Sure
5) How sure are you that you can control how often or when you get tired?	Not at all sure	Not sure	Neither	Sure	Very Sure
6) How sure are you that you can do something to help yourself feel better if you are feeling sad or blue?	Not at all sure	Not sure	Neither	Sure	Very Sure
7) As compared with other people with sickle cell disease, how sure are you that you can manage your life from day-to-day?	Not at all sure	Not sure	Neither	Sure	Very Sure
8) How sure are you that you can manage your sickle cell disease symptoms so that you can do the things you enjoy doing?	Not at all sure	Not sure	Neither	Sure	Very Sure
9) How sure are you that you can deal with the frustration of having sickle cell disease?	Not at all sure	Not sure	Neither	Sure	Very Sure

Figure 6 *- The nine-question Sickle Cell Self-Efficacy Scale (SCSES)*

Qualitative Interviews. Lastly, to further understand which intervention works best for whom and when, the lived experience of patients in the trial, and differences in perceptions between depression subgroups, we will do a series of qualitative interviews with patients enrolled in both arms of the study, at three time points in the study—at baseline, in order to assess prior patient experience with SCD and treatment for SCD, and their attitudes toward the intervention at the outset; at 3 months when the initial intervention concludes in order to assess their experience with and opinions on the intervention; and at 6-12 months to assess long-term impact of the intervention. At each time point, Qual EASE will select and interview 24 patients in each treatment group, stratified by high or low depression scores, for a total of 48 interviews (i.e., 12 cCBT patients with PHQ ≤10, 12 cCBT patients with PHQ >10, 12 m-Education patients with PHQ ≤10, 12 m-Education patients with PHQ >10). This will allow us to qualitatively compare the experiences of patients with differing depression levels, and to explore quantitative findings with regards to intervention efficacy in patients with differing levels of depression severity. Patient sample size has been selected to allow for high likelihood of our reaching thematic saturation regarding patient experience.[51]

Table 4. Schedule of interventions and of monitoring patient outcomes.

Outcome	Measure	Month of Study			
		0	3	6	12
Primary	Pain interference (PROMIS)	X	X	X	X
Secondary	Daily pain intensity (mobile app)	X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X			
	Quality of life (ASCQ-Me), depression (PHQ-9), anxiety (GAD-7), Painimation	X	X	X	X
	Opioid Use (COMM)	X			X
Medical	Health care utilization (PCORnet): Opioid prescriptions, ED visits, hospitalizations				X
Process Evaluation	Coping (CSQ), Self-efficacy (SCSES)	X	X	X	X
	Program engagement (treatment dose)	X			

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Preliminary data support the use of both cCBT and pain education delivered via smartphone**.** Co-I Dr. Palermo developed and tested an Internet-delivered cCBT pain intervention called Web-MAP in an RCT involving 48 youth (ages 11-17 years) with a variety of pain conditions (e.g., headache, stomachache, musculoskeletal pain). Significant reductions in pain and disability were found for youth receiving Web-MAP compared to a wait-list control group.[52] Following up on this initial trial, Palermo conducted a large RCT of the Web-MAP cCBT program versus Web-ED, an Internet-delivered pain education program, among 273 youth (ages 10-17 years) with chronic pain (and their parents) recruited from pain centers around the US and Canada.[53] This study found Web-MAP, compared to Web-ED, was associated with greater improvements in pain-related disability ($p = .03$), sleep quality ($p = .02$), pain-related anxiety ($p < .05$), and parent behavior ($p < .001$) and distress ($p = .002$) at 6 months. Dr. Palermo then piloted Web-MAP with 25 youth with SCD (median age = 14.2) and their parents. Treatment engagement was high; youth logged into Web-MAP an average of 15.2 times (SD = 9.4) with over 70% of users completing ≥6 of 8 modules.[54]

cCBT with SCD adults. Dr. Jonassaint (Co-PI) piloted a mobile device-delivered cCBT called *Beating the Blues* and found that 18 adults randomized to cCBT reported improved daily pain and depression compared to 12 adults in usual care.[55]

iCanCope SCD. The iCanCope program is a trial-tested cCBT for pain that has now been tailored specifically for SCD. Currently iCanCope SCD is being tested with adolescents age 12-18 yrs (PI: Palermo). We have expanded the use of

iCanCope to our adult population in pilot testing. iCanCope SCD serves as the core curriculum and functionality for the CBT and education programs being tested here, although we will rebrand and adapt it based on early stakeholder input. Some adaptations that have already been implemented and improved intervention delivery are described below.

How our implementation of cCBT has already changed based on stakeholder input. From our work testing cCBT programs with pediatric and adult patients with SCD we have learned through trial data and interviews that patients find cCBT programs helpful; however, there were several aspects of the cCBT programs that could be improved. We have continued to work with our community partners to update the technology and ensure the content is effective.

Components stakeholders said were essential in a technology-delivered behavioral intervention:

•**Relatability and representativeness.** It was important to patients that they could relate with the content and that they saw other people living with sickle cell throughout the program. Our CBT and education videos are scripted and delivered by our patient partners and highlight interviews with patients discussing their experiences with SCD.

•**Interactive content.** The users did not want static content but an interactive experience that was dynamic and personalized for their specific situation. "I thought Web-MAP was too simple or basic to help me. I want something more interactive that is a more real-world experience." We have added an interactive, artificial intelligence-based chatbot that provides live, 24/7 responses, and evaluates and delivers what the user wants and needs to see next.

•**Social support group.** Having some connection with other patients or users of the program was a consistent theme across all our groups. It was also mentioned frequently as a method patients use to help cope with the stress of living with sickle cell. "We communicate almost every day [on Facebook SCD group], and it really helps." Interventions are directly linked to Facebook groups managed by two of our community partners (SC101 and SCWarriors).

•**Health coach**. The presence of a coach has been expressed by patients as an important and necessary aspect of cCBT. The coaches provide support to patients and maintain engagement. Our stakeholders like the idea of having a real person to contact. Health coaches will be available via text message and phone. We have an adult with SCD serving in this role when possible.

•**Status badges or awards.** Participants wanted some indicator of progress through the program. A review of mobile health apps showed that patients enjoyed receiving achievement awards and status for completion of goals.[56] Programs incorporate unique awards and indicators of status to highlight success and keep users engaged.

4.3 JUSTIFICATION FOR INTERVENTION

The comparators are both evidence-based tools that have been tailored specifically for the target population through a user-centered approach that has engaged stakeholders at each stage of the process.[57]

Both interventions will be implemented using mobile phone-delivered programs for reducing SCD pain symptoms—cCBT versus pain and SCD education (m-Education).

These comparators were selected because:

- Both CBT and pain education have shown some effectiveness for improving pain outcomes in SCD.[7,58]
- CBT and pain education are the most likely non-pharmacological interventions to be effective in this population given the barriers to pain management identified by patients, family members, and clinicians.

- Our team has extensive experience with delivering these interventions, and we have leveraged the active online health-education programs from our community partners.
- Both interventions can be delivered with the exact same mobile app platforms and associated health coach support.
- Digital health interventions are efficacious and there is much interest among SCD patients to utilize these tools.[59-64]

How sites were selected: Study clinical sites are comprehensive care centers that have a history of working with the study PIs, see 200+ adults with SCD a year, and are PCORnet sites. Our community partners have experience working with the research team and are the most visible educational programs or community advocates in the SCD community.

4.4 END-OF-STUDY DEFINITION

Patients NOT participating in qualitative interviews are considered to have completed the study once they have participated in weekly check-ins with a health coach during the first 12 weeks, completed the assessments (Painimation, SCSES, PROMIS, ASCQ-ME, PHQ-9, GAD-7, and COMM) at the scheduled time points *(see schedule breakdown in **Section 4.1 Overall Design**)* and logged a daily pain diary through the end of the first year.

The patients participating in qualitative interviews are considered to have completed the study once they have fulfilled the above, and participated in a qualitative interview at baseline, 3-month, and 6-12 month time points with Qual EASE staff.

5 STUDY POPULATION

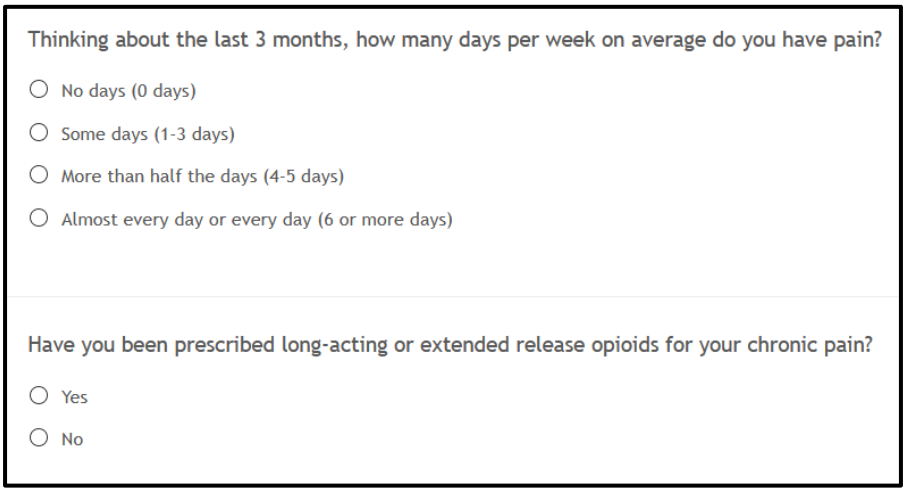
5.1 INCLUSION CRITERIA

Patients are eligible to be included in the study, all of the following criteria must apply:

1. People with any type of SCD (but excluding sickle trait).
2. Male or female, age 18-65 years.
3. Speak English

To be randomized to one of the treatment arms, eligible patients must also:

4. report chronic pain (i.e., pain at least 4 days/week over the past 3 months or longer)
5. and/or being prescribed long-acting or daily opioid pain medication



Pre-screen Chronic Pain Questions

Patients who do not meet criteria 4 and 5 will only complete the battery of questionnaires at baseline and each time they return to clinic for a medical visit. This is a convenience comparison sample of non-chronic pain patients and there will not be scheduled follow-up with this group.

5.2 EXCLUSION CRITERIA

Individuals who have cognitive dysfunction will not be referred to the study by clinical staff. An individual who meets the following criteria will be excluded from participation in this study:

1. Any potential participants who fail the consent comprehension assessment

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Participants who enroll in the study but do not meet eligibility to enter into one of the intervention arms of the study will complete a baseline questionnaire only. We are collecting medical record data from this group consistent with the protocol for eligible participants.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The target sample size for this study is 350 participants and they will be recruited both in-person from five clinical sites (Pitt, Duke, Hopkins, OSU, UIC) and online through our community partners (SC101, SCCC and Sickle Cell Warriors). Vanderbilt University will also advertise the study. This strategy helps ensure that we recruit a representative spectrum of the population and that all patients, regardless of geography, can participate. The study clinical sites are comprehensive care centers that have a history of working with the study PIs, see 200+ adults with SCD a year, and are PCORnet sites. Our community partners have experience working with the research team and are the most visible educational programs or community advocates in the SCD community. See **Table 5** for information about recruitment. The anticipated racial/ethnic and gender distribution of participants is outlined below in **Table 6**. The intervention content and presentation is specifically designed for adults, thus, the age has been restricted to 18-65 years.

<u>In-person recruitment at clinical sites:</u>
At Pitt, Duke, Hopkins, OSU, and UIC, a tablet-administered screening tool and best practice alerts will be used to identify patients with SCD who have chronic pain as indicated by self-report. Best practice alerts will flag patients with a chronic pain diagnosis or who have been prescribed chronic opioid therapy for pain. Each clinical site will screen ~90-100 patients. We expect to approach and screen a sum total of 450 potential participants across all five clinical sites.

<u>Online recruitment through community partners:</u>
Our CBO partners have created an active community that reaches 10000+ patients with SCD. For this study SC101, SCWarriors, and SCCC will seek out potential participants via message blasts on their CBO websites, social media groups, email listservs, and at patient/family meetings. SCWarriors has a unique database of over 550 people who have signed up specifically to participate in clinical research. Interested patients will access a short online screener on a mobile device to confirm eligibility. To be eligible, potential participants must be able to read the study consent and correctly answer comprehension questions (our group is currently using and has published data using this electronic consent process in a clinical study[65] and a large multisite trial of cCBT[53]). Cassandra Trimnell (co-I) will lead online recruitment efforts through SC101. Tosin Ola, RN, will promote the study through SCWarriors, and Lakiea Bailey, PhD, will promote the study through the SCCC network of CBOs.

Once participants finish the initial screener and are approved to be enrolled, they will be complete consent procedures as outlined in the **Consent Procedures and Documentation.** After consenting, they will be assigned a health coach, linked to the study-associated Facebook page, and will receive instructions on how to access the CaRISMA intervention to begin their intervention arm.

5.6 RECRUITMENT PLAN FOR PROSPECTIVE STUDIES

Table 5 *– Recruitment plan including estimated number of eligible patients, total number of participants expected to be approached or screened via the study kiosk and online data capture tool.*

Recruitment Plan	
Estimated number of potentially eligible study participants, from prior research and examining medical records: ~400 eligible patients at OSU, UIC and Duke, Hopkins ~200 eligible at Pitt	1600 at clinical sites
Our community-based organizations reach 10000+ patients. Conservative estimate is that 50% of those are eligible adults with chronic pain	5000 through CBO networks
Total number of study participants expected to be approached in clinic (n = 450) or complete online screener (n = 100)	550
Of those screened, total number of study participants expected to be eligible	450
Of those eligible, total number participants enrolled via clinics (n = 300) and CBOs online (n = 50)	350
Target sample size	350
Total number of clinical sites that will enroll participants	5
Projected rate of enrollment	Month 7 start of enrollment
Estimated percentage of participant dropout	10-15% complete no follow-up assessments 30-40% stop using intervention before reaching Module 4

Table 6. *Estimated final racial/ethnic and gender enrollment table (N = 350)*

Race	**Male (N)**	**Female (N)**	**Total (N)**
American Indian/ Alaska Native			
Asian			
Black/African American	170	170	340
Hawaiian/Pacific Islander			
White			
Multirace	5	5	10
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)			
Non-Hispanic	175	175	350

Participant Incentives

Participants who enroll in the intervention but do not receive a study phone will instead receive payment to cover the cost of cell phone data/usage while on the study, a total of about $250. This will be paid in increments throughout the participant's 12 month participation in the study. At baseline, they will receive $75 after completion of baseline questionnaires, accessing and beginning the intervention program, and making one phone contact with their health coach. At each follow-up: 3-month, 6-month, and 12-month time points, participants will receive $50 after completion of questionnaires for that follow-up assessment. An extra $25 will be given to those who complete all four follow-ups throughout the year-long study.

Participants that are given a cell phone will not receive any monetary compensation. However, they do not have to return the cell phone at the end of the study. The study will cover the costs of the cell phone data plan while the participant is enrolled in the data collection phase of the study.

Participants in the non-intervention comparison group will not receive payment.

How barriers to recruitment and retention will be overcome

It is well known that recruiting and retaining racial minority and low-income participants in clinical trials is challenging.[66] SCD has historically been a particularly challenging population for conducting clinical trials, with 25% of SCD trials being terminated, most due to low enrollment.[67]

Before beginning enrollment, our community partners will help with our study branding, to create a positive public perception and a relationship with the community, both critical to recruitment success.[66] We will monitor the progress and problems with recruitment during weekly conference calls. Sites will exchange recruitment techniques and we will work with our patient partners and stakeholder groups to develop strategies for increasing recruitment and community engagement.

We will have monthly study retention meetings led by Dr. Jonassaint and Ms. Trimnell to discuss recruitment, retention, and engagement at all sites. The health coaches will report to Ms. Trimnell and the study PIs if they are having difficulty contacting any participant on the study. Ms. Trimnell will also visit the health coaches at the University of Pittsburgh and the study staff at each clinical site to teach them how to work effectively with this patient population. She will occasionally visit with the health coaches at the University of Pittsburgh for booster sessions.

We have involved our stakeholders in all aspects of study design and implementation to tailor CaRISMA to their needs and to help achieve optimal intervention engagement. Below is a description of stakeholder involvement:

1. Patients and family members have helped us design the intervention content.
    - Real patients, not actors, are featured in the photos and videos presented in the interventions.
    - Our primary stakeholder partners are co-investigators on this project. Dr. Bailey will consult with Dr. Jonassaint on planning the patient engagement strategy. Ms. Trimnell is leading the patient education arm of the study, has led the design of the content, and will ensure the effectiveness of the intervention education materials throughout the course of the study.
    - Our intervention content is co-developed and contributed by patients, with Ms. Mitchell-Moore, a patient-advocate, serving as a partner on the creative process and on camera talent during the

intervention development. The interventions are heavily reliant on video interviews and statements by patients. We are making it possible for patients to enroll in this study online so patients from any geographic region can participate. This is in response to patients at a patient-led meeting and on social media stating their frustration about not having access to clinical trials being held outside of their geographic location.

2. Dr. Jonassaint will work closely with the CBO partners on patient engagement and recruitment strategy.
    - Ms. Trimnell will lead the patient education arm of the study with consultation from the study team and community partners, and guide what content participants will see on the intervention. This will involve assessing the educational needs of the respective populations and updating the educational materials in the first 6 months of the funding period before the trial begins.
    - Ms. Trimnell will also help with selecting and training health coaches. We will target patients or family members who are qualified, to serve as the research assistants and health coaches. (Our patient stakeholders preferred being mentored or coached by someone who has sickle cell and has experience living with the disease.) Ms. Trimnell will aid in the selection and training of qualified research assistants and coaches. During the study health coaches will communicate regularly with participants and encourage engagement in the CaRISMA intervention.
3. Local and State Policy Makers
    - Each year we will update our local Pennsylvania representatives Ed Gainey and Jake Wheatley, who have been advocates for SCD, and approach policy makers in Harrisburg, PA, regarding this project and the opportunities to disseminate treatment.
4. The Sickle Cell Advocacy Team (SCAT) in Pittsburgh is a patient-led group that was started to provide support, education, and advocacy for the SCD community.
    - The team is composed of patients and their family members, and health providers participate but are not in leadership positions. Leadership positions are all held by patients. SCAT was initiated almost 10 years ago. The size of the group ranges from 15 to 30 people.
    - We will continue to meet with the SCAT group monthly to provide updates and receive feedback on the study.
5. The SCD care team is composed of three nurses, two physician assistants, three attending physicians, and a social worker.
    - The team meets monthly and will help plan, implement, and receive updates on the study progress.
6. Patient Advisory Board
    - Those patients who enrolled in and benefited from our pilot study testing a cCBT program for mental health in SCD were invited to partner with us to provide additional feedback on their experience with cCBT, helping in the development and initial testing of the cCBT program for SCD.
    - The past-participant group is committed to continuing their partnership with us and will serve as advisors over the course of the study.

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

We followed the social-cognitive theory[68] to inform our intervention selection and implementation strategy[69] (**Table 7**)**.** Based on patient interviews (see **Table 8** for interview questions) and feedback from our pilot work, we identified important barriers and facilitators to implementation that we needed to address. Using a social-cognitive theory framework, we categorized the barriers and matched each of them to a corresponding intervention. Elements of the capability, opportunity, motivation, and behavior (COM-B) model[70] were also used to match behavioral targets to specific intervention functions.

***Table** 7 - Barriers to stress/pain management in sickle cell disease based on a social-cognitive theory framework, and the respective intervention functions and behavior change techniques.*

Social-Cognitive Theory Domains	**Barriers**	***Intervention Functions***	***iCanCope Study* Behavior Change Techniques**
Cognitive Influences (Self-efficacy and capability)	Physical – cognitive demands (stressors) and time constraints Psychological – low self-efficacy and knowledge of appropriate coping skills	Social modeling Verbal persuasion Training/ education	Peer-peer support group/virtual social network Video vignettes showing patients managing their pain effectively Teaching skills through online sessions they can complete on their phone 24/7 Provide care coach support to help build skills and apply them Text message prompts and interactions
Environmental Influences (Normative beliefs and social supports)	Physical – lack of access to behavioral interventions Social – perceived lack of support, social disorder (e.g. crime), lack of positive role models, psych therapy is a "white thing"	Enablement Social modeling	Mobile phone accessible training and support Provide online support groups with other patients using skills Video vignettes with real patients Provide pill box and instructions on use
Supporting Factors (Motivations)	Reflective - fear of pain, not wanting to change current opioid habits for something that won't work Lack of intention or motivation to implement skills Autonomic – behavioral pain management not offered in routine care; patients accustomed to treating pain with opioids only	Environmental restructuring Restriction (e.g. limiting # of opioid med refills) Incentivization Education	Provide clinician EMR alert (BPA) to introduce behavioral pain management to patients, refer to behavioral team Outline plans to decrease opioid medication prescribing long-term App that provides goal setting and routine follow-up on progress toward goals Status badges and rewards for completing sessions and practicing skills; praise via text and phone calls

Table 8 *- Theoretical framework used to guide stakeholder interviews and engagement. We engaged stakeholders throughout our study design process to better understand stakeholder needs and the barriers to improved pain management among adults with SCD. This tables shows how interview guides were developed using the Theoretical domains framework (TDF). An online survey sent to Ms. Ola Tosin's Sickle Cell Warriors group included six of these questions.*

Domains	Constructs	Interview Questions
Knowledge	Knowledge about stress and its impact on pain Cognitive-behavioral coping skills and how to apply them Knowledge of disease and self-management	How does stress impact your life? How much stress do you experience on a daily basis? What connection do you see between stress and your pain? Do you know of any methods for reducing stress? How do your thoughts and beliefs, and behaviors impact your level of stress and pain?
Skills	Coping skills Self-management skills	What can you do to manage stress? What can you do to manage your pain? What thoughts and beliefs do you have that increase stress and pain? How can you change those?
Social/professional role/identity	Clinicians' perception of non-pharmacological pain management and alternatives to prescribing opioids Patient's role in pain management	If you could not prescribe opioids, what can patients do to manage pain? What can you do as a patient to better manage your pain? What information should you provide your clinician to help in creating a pain management plan?
Beliefs about capabilities	Confidence and self-efficacy in self-management, using effective coping skills, controlling pain symptoms	How confident are you that you can manage your pain on your own? How confident are you that you could manage your pain without opioid medication?
Beliefs about consequences (anticipated outcomes)	Belief that pain can be managed; non-opioid treatments work; reducing stress will improve pain	Do you think that managing your stress will improve pain? How will changing your thoughts and behaviors improve your pain Can you control your pain and how?
Motivation and goals	Intention Goals	Do you want to decrease use of opioids? Would you try CBT as a means of managing pain? Are there incentives to practicing CBT?
Memory, attention and decision processes	Memory Attention Decision making	Is this something that patients usually use to manage stress/pain? Will you remember to practice? What can help you remember? Why might you decide to not practice and use the CBT skills?
Environmental constraints	Resources/material resources Environmental stressors Person by environment interaction	To what extent do resources facilitate or hinder? (time, materials, car) Are there competing tasks and time restraints? Do therapists have the necessary resources?
Social influences (Norms)	Team working Organizational culture Professional boundaries/roles Management commitment Champions	What do other people with SCD do for pain? Do friends and family facilitate or hinder using CBT skills? Who are people that you know that manage their pain well? What do they do? Does your clinician help you self-manage, is it an expectation? How do they facilitate or hinder your self-management of pain?

Each of the 350 patients recruited will be asked to complete all modules in one of two programs within the Internet-delivered CaRISMA pain intervention: cCBT or m-Education. Participants will only have access to the content that is relevant to their assigned program, which they will be randomized into when they open the CaRISMA intervention for the first time. In addition to completing the modules, participants will also be asked to have weekly check-ins (via phone or text) with their assigned health coach during the first 12 weeks of the intervention when modules are being completed. Participants will log a daily pain diary within the intervention throughout the entire year of the study. The pain diary feature will prevent participant recall or memory bias, which will provide the study team with the most accurate data to track each participant's health outcomes while using the CaRISMA intervention.

The two arms of the study are described below:

Computerized cognitive behavioral therapy (cCBT) for pain. The cCBT program in the CaRISMA intervention focuses on teaching behavioral coping skills through "seeing and doing." cCBT modules will teach users how to recognize negative thoughts and emotions, use cognitive skills and problem-solving, and apply coping behaviors such as distraction, activity scheduling, and relaxation. The cCBT arm emphasizes skills acquisition and learning through practice; thus, the program involves homework assignments and challenges, as well as continued check-ins with a health coach who will help reinforce the CBT skills and encourage practice and program engagement. The cCBT program will also give users access to a study-associated Facebook page where they can discuss with other patients, issues they faced and what skills were or could be used to address them. This program is consistent with the tailored behavioral services patients would receive individually or as a group when working with a psychologist or behavioral pain specialist.

Pain and sickle cell disease education (m-Education). The m-Education program in the CaRISMA intervention focuses on improving self-management through "learning and knowing" more about pain and SCD. The m-Education program will teach users about chronic pain, healthy lifestyle tips (e.g., nutrition and exercise) and facts about SCD. The emphasis will be on knowledge acquisition and will give users an opportunity to apply what they have learned through brief quizzes and discussion with the health coach and the social network. This program is consistent with the education patients and families would receive with a patient educator or what is currently provided through our community partners, Sickle Cell Warriors (SCWarriors) and Sickle Cell 101 (SC101), and SCCC via the Web, social media, and at community events.

6.1.2 ADMINISTRATION AND/OR DOSING

For at least 12 weeks, one group will be asked to engage in a mobile cCBT program tailored for adults with SCD, which mimics the behavioral services SCD patients would receive when working with a psychologist or behavioral pain specialist. The second group will receive pain and SCD education on their mobile phones (m-Education). The CaRISMA intervention, which delivers both cCBT and m-Education programs, is accessed on a smartphone and is made up of **four** primary components:

1) Chatbot and Health Coach Messaging. Using artificial intelligence (AI) similar to Alexa or Siri, we provide 24/7 chat style interactions to assess needs and deliver personalized content to the user. The chatbot goes beyond text messages, using graphical interfaces, widgets, and videos to provide lessons, quizzes,

quick coping tools, and occasional entertainment. Periodically and upon request, our health coaches will send personalized messages via text message or through the chatbot platform.

2) Toolbox and Badges. As users go through the lessons via the chatbot, they can view their progress and gain access to all the lessons and tools they have unlocked. This is where they can also view status badges they received for specific accomplishments.
3) Pain Diary. Users will record their pain, mood, and medications used daily on the CaRISMA intervention. They can also view trends in their pain/mood data.
4) Social. The intervention encourages users to visit CBO social media groups and live meetups run by our CBO partners. Access to outside social support will not be monitored or recorded.

Through interacting with the chatbot, study participants will view video lessons and answer quiz questions to verify understanding of the material. If a quiz question is answered incorrectly, the chatbot will provide the correct answer to clear up any misunderstanding of the material. The chatbot has been programmed by study staff to allow content to be tailored for each participant's needs. Participants are asked personalized questions in between video lessons to aid in transferring the learned techniques to real-world application. Participants interested in learning more are also given the option to view extra, topic-specific content.

In addition to completion of the cCBT or m-Education modules, all participants will track pain symptoms daily on the CaRISMA intervention, and will have weekly check-ins with a health coach by text or phone during the first 12 weeks. At each follow-up assessment, they will complete a battery of questionnaires which can include Painimation, the PROMIS Pain Interference Scale, as well as Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-ME); Emotional Functioning and Social Impact scales; the Patient Health Questionnaire (PHQ9), the Generalized Anxiety Disorder Scale (GAD-7), the Sickle Cell Self-Efficacy Scale (SCSES), and the Current Opioid Misuse Measure (COMM).

The recommended progression is one module per week; however, participants will be allowed to complete the modules at their own pace. In the study design, patients have been allotted 12 weeks to complete all modules in an attempt to increase adherence and prevent participants from feeling overburdened by the lessons. During weekly check-ins, health coaches will encourage participants to continue engaging in the lessons and inputting their daily pain diary, even after completion of the modules.
Engagement will be measured by frequency and time on the intervention, number of lessons completed, and number of interactions (text/phone) with health coaches over the first 12 weeks. Use of the CaRISMA Facebook page is not part of the intervention administration; it is simply a tool supported by the study team to engage the SCD community.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

To maintain intervention continuity and fidelity, before any new content is uploaded to the platform it will undergo a review. The Content Review Group is composed of Drs. Palermo, Stinson, and Lalloo, study Co-Investigators, and will evaluate each added lesson to judge whether it is consistent with the core intervention functions, either cognitive behavioral therapy or pain and sickle cell disease education. No new content will be implemented without consensus of this group. Effectiveness of all digital content will be evaluated by number of

user views, "likes," and activity subsequent to viewing the content. These metrics are also used in an algorithm to decide what content to push to the user next.

The Data Coordinating Center (DCC) led by Co-PI Dr. Abebe will develop the reporting plan. Reporting will follow the most updated Consolidated Standards of Reporting Trials (CONSORT)[71] guidelines and the study will be registered with clinicaltrials.gov. Within nine months of the end of the project period (Year 4), the DCC will develop and make available a codebook, relevant programming code, and study protocol. This will allow for replication of our findings by investigators conducting research in other populations with applicable study design.

Monthly meetings with the study PIs, community partners, and co-investigators will help uncover study-related issues. These issues will be brought to quarterly trial steering committee (TSC) meetings, which will be responsible for overseeing the trial's progress; receiving the Data Monitoring Committee's recommendations regarding safety and benefit of continuing or stopping the trial; ensuring the trial is operating in accordance with similar trials, information from which will be gathered and reviewed; disseminating status and progress updates from the trial to sponsors, funders, and other groups; and making their own recommendations about how to present the results of the trial on a wider scale to a broader audience.

How will decisions be reached? Wherever possible, the TSC will reach a consensus with all members (non-independent and independent) on the preferred plan of action for addressing an issue. If consensus cannot be reached, the issue will be put up for a vote. Where there is a tie vote, Dr. Abebe's vote will be outweighed by that of the non-independent members. In preparation for each quarterly TSC meeting, Dr. Abebe will prepare a report similar to the following template based on Harman et al.:

1. Summary of the data monitoring committee (DMC) recommendations, unless the TSC has decided to serve in the role as the DMC.
2. Actual recruitment rate versus target rate (by month/quarter).
3. Acceptance rate as a proportion of the following: i) those invited to participate, and ii) if known, all eligible participants.
4. Percentage of participants proceeding through each trial stage to allow monitoring of the recruitment and retention, including missing outcome data. Not split by treatment/intervention arms.
5. Quarterly forecasts of recruitment for the planned remainder of the trial.
6. Losses to follow-up as follows: i) as a proportion of those entered, and ii) per quarter.
7. Data management metrics: rate of returns, volume of queries, time to return, enhanced metrics via electronic data capture.
8. Number for whom follow-up has been completed successfully (or still being successfully followed).
9. Overall withdrawal rate and level of withdrawal summarizing those patients who have withdrawn from treatment but are still in follow-up and those who withdraw with no future contact.
10. Summary of adherence to treatment/intervention. Not split by treatment/intervention arms.
11. Summary of adverse events including type, for example, adverse events, serious adverse events, and suspected unexpected serious adverse reactions.
12. Completeness of data collected.

13. Any available results (pooled).
14. Summary of protocol deviations overall and by site.
15. Any organizational problems or other trial issues.
16. Other issues or documents specific to this trial as requested by the TSC.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization: Participants will be randomized in an equal fashion (1:1) to both study arms. Random permuted block randomization will be used to create an allocation list that will integrated within our Web-based data entry system. Stratification will be based on recruitment site (Pitt, Duke, Hopkins, OSU, UIC) or through one of the community partners (SC101, SCCC, and Sickle Cell Warriors).

Reduce the potential for biases. The introduction to both interventions will look identical and participants will not be told what type of training they are receiving. We will make every effort to mask the intervention type; however, as with all behavioral interventions, completely blinding participants to the intervention is challenging. The investigative team will continue to maintain clinical equipoise regarding the comparative therapeutic merits of each treatment. Randomization will avoid selection bias as well as volunteer or referral bias. A dropout analysis will be carried out to determine the contribution of attrition bias. All outcomes measures will be collected electronically, without an interview, to avoid expectation bias. We have also found this mode of data collection to be superior to assessments by phone for timely follow-up. Finally, we will avoid participant recall or memory bias by asking patients to record daily pain, fatigue, and other health outcomes via mobile device.

To limit potential bias from investigators, we are implementing a dual PI plan that separates data collection, monitoring, and analysis from the day-to-day implementation of the study interventions and engagements with community partners who can influence the outcomes of the trial. Broadly put, Dr. Jonassaint will be primarily responsible for stakeholder and community engagement and the scientific/clinical aspects of this trial, while Dr. Abebe will be responsible for the data and statistical analysis of the trial. In addition to limiting bias, we believe that due to the intensive plan we have outlined for stakeholder and community engagement, the overall project benefits from having a PI (Dr. Jonassaint) who is dedicated to this role and who has less responsibility for data oversight.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

The major assumption is that patients will complete the intervention program to which they are randomly assigned. Although we have implemented several methods to promote engagement and limit dropout (e.g., health coaches[72]), digital interventions often experience high attrition over time with few participants completing all assigned modules.[73] We will track the reasons for noncompletion and seek patterns (e.g., moved away, died, started working and became too busy, people with higher cognitive level lost interest) that are amenable to statistical analysis of the missing data.

We will have monthly study retention meetings led by Dr. Jonassaint and Ms. Trimnell to discuss recruitment, retention, and engagement at all sites. The health coaches will report to Ms. Trimnell and the study PIs if they are having difficulty contacting any participant on the study. Ms. Trimnell will also visit the health coaches at the University of Pittsburgh and the study staff at each clinical site to teach them how to work effectively with this patient population. She will occasionally visit with the health coaches at the University of Pittsburgh for booster sessions.

Ms. Trimnell will train health coaches on how to keep track of each participant's progress throughout the intervention. Each participant will be required to complete all modules, as well as weekly health coach check-ins during the first 12 weeks, and daily pain diaries throughout the 12 months of the study. In addition, participants will also be required to complete Painimation, , the SCSES, PROMIS, ASCQ-ME, PHQ-9, and GAD-7 questionnaires at baseline, 3-, 6-, and 12-month time points, as well as the COMM at baseline and 12-month follow-up. Failure to complete any of these will prompt health coaches to reach out via text message or phone to encourage participants to complete missing items. The qualitative interview delivered by Qual EASE is the only optional activity in the intervention. Since only 48 of the 350 participants will be selected for interview, any participant that opts out will be replaced by another participant, of those not previously selected.

The principal investigators or study staff will review all data collection forms on a quarterly basis for data completeness and accuracy as well as protocol compliance. Data on adherence to the treatment protocol will be collected twice weekly by research staff and reviewed quarterly by the study PIs. Adherence of the research participants to the cCBT sessions and education modules will be evaluated by frequency of logins to the intervention and completion of sessions. If adherence falls below the suggested rate of 50%, which might inhibit the ability of the study to test its primary hypotheses, the PIs will suggest a conference call for study investigators to discuss methods for improving adherence. The principal investigators, co-investigators, and the research staff will meet on a monthly interval to re-evaluate study goals, subject recruitment, data coding and retention, documentation and identification of adverse events, complaints, and confidentiality of subjects. Progress of the research study will be evaluated, including assessments of data quality, timelines, participant recruitment, accrual, and retention. If recruitment is below 50% within the first 2 months of the study, the principal investigator will suggest a conference call for the study investigators to discuss methods of improving recruitment, including expanding the age inclusion criteria. The principal investigator will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should be re-evaluated and changed. The PIs will promptly report any unanticipated problems that occur during the conduct of the study according to the reporting criteria and timelines under the current IRB policies.

6.5 CONCOMITANT THERAPY

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

Semi-annually, the DCC and Data Safety Monitoring Board (DSMB) will review of collected data (including adverse events, unanticipated problems, and subject withdrawals), to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may be discontinued from study treatment at any time if the participant or the investigator feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Participant withdrawal of consent (or assent)
- Participant is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the participant to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up

If a participant is withdrawn from treatment due to an adverse event, the participant will be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized.
All participants who discontinue study treatment should come in for an early discontinuation visit as soon as possible and will be encouraged to complete all remaining scheduled assessments (Pain Interference measure will be prioritized).
All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.
Reasonable attempts will be made by the investigator to ascertain a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be specified in the participant's source documents.

7.3 LOST TO FOLLOW-UP

Intervention engagement and health coach contacts. Patients who stop reporting data in the intervention will receive inquiry text messages or a phone call (Health Coach Protocol). Since participation in the study is completely voluntary, patients may choose to discontinue the intervention at any time. During the first 12 weeks, participants are encouraged to have weekly check-ins with health coaches. This can be in the form of a text or email where there is at least one response from the participant, or phone call of any duration. Failure to check in with health coach will not affect enrollment in the study; however, health coaches will reach out three times to solicit a text, email, or phone call response from participants.

Follow-up assessments. The study sites will take preventive measures to avoid a subject's being lost to follow-up (e.g., document different ways of contact such as telephone number, email address, etc.). At baseline, 3-, 6-, and 12-month time points participants will receive links to complete Painimation, the SCSES, PROMIS, ASCQ-ME, PHQ-9, and GAD-7 on our online survey tool; COMM questionnaires will be sent at baseline and 12 months (*See **Section 4.1 Overall Design** for schedule breakdown*). Completion of the questionnaires is a required component of the study. Not completing questionnaires within 4 weeks of due date is considered a missed follow-up. In the event that a follow-up assessment is not completed, every possible effort will be made by study site personnel to contact the subject. For each follow-up, at least three documented contact attempts must be made on different days to the last available telephone number. If the subject is still unreachable after all contact attempts, they will be considered to be lost to follow-up (LTF). The site should document all attempts and LTF information in the trial database (see **Table 9**).

***Table 9** – Lost to follow-up (LTF) procedures based on attempts to contact and follow-up period*

Attempt	3-month follow-up	6-month follow-up	12-month follow-up
1	✗	✗	✗
2	✓	✗	✗
3		✗	✓
Action	Patient has responded; continue intervention and encourage daily pain diary.	Patient unresponsive; mark **lost to follow-up** (LTF)	LTF, but still contact if questionnaires are not completed. Patient has restarted communication; continue intervention and encourage daily pain diary

We will minimize missing data by use of a paperless data collection system and by contacting participants when data are not entered in a timely fashion. We will attempt to characterize the mechanism of missingness (missing completely at random, missing at random, or not missing at random) by comparing rates of missingness/attrition between study arms. Additionally, we will compare baseline characteristics between participants with and without missing outcome data. If we conclude that our missingness is random, then our likelihood-based approach for the primary analyses will address this. Otherwise, if the missingness can be characterized as non-ignorable (not missing at random), we will use approaches such as joint modeling or shared parameter models to produce unbiased estimates of treatment effects. All reasons for dropout or other missing values will be entered by research staff or community groups (if encountering the patient using community activities), tabulated and summarized, and results will be reported using the CONSORT diagram.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

When a potential CaRISMA participant becomes interested in enrolling, they will first be asked to fill out an electronic eligibility screener to confirm inclusion criteria. Immediately after getting accepted into the study, participants will complete separate questionnaires that will serve as their baseline measure. These questionnaires will be completed three more times throughout the course of the study. CaRISMA participants will also complete a daily pain diary throughout the first year of the study.

1. Eligibility Screener: All patients interested in enrolling will be required to complete this online screener to confirm eligibility. It will be accessible at the five clinics for those recruited in-person. A link will be distributed to those recruited online.
2. Coping Strategies Questionnaire (CSQ): Assesses coping in chronic pain patients through item-level factor analysis. Elements of the CSQ will be asked in the chatbot.
3. Sickle Cell Self-Efficacy Scale (SCSES): Assesses the ability of sickle cell patients to function on a day-to-day basis and manage their SCD symptoms.
4. Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Scale: Assesses patient-reported outcomes (physical, mental, and social health) in adults and children
5. Adults Sickle Cell Quality of Life Measurement Information System (ASCQ-ME): Measure patient reported outcomes in adults with sickle cell disease.
6. Patient Health Questionnaire (PHQ-9): Assesses the degree of depression severity.
7. Generalized Anxiety Dieorder Scale (GAD-7): Assess the degree of anxiety.
8. Daily pain diary: Participants will log a daily pain diary in the CaRISMA interventions for the entire year of the study.
9. Current Opioid Misuse Measure (COMM): self-reported; monitors indicators of current aberrant drug-related behaviors in patients with chronic pain on opioid therapy. This measure will only be completed at baseline and 12 months.
10. Painimation: an electronic pain assessment tool developed by our team at the University of Pittsburgh that allows users to better communicate their pain symptoms. Patients are provided with a selection of animations that they use to describe the quality of their pain. The animations can be adjusted to reflect the intensity of their pain.

8.2 SAFETY ASSESSMENTS

The PHQ-9 administered at baseline, 3-, 6-, and 12-month time points will be used to assess suicide risk. A positive answer to a PHQ-9 question “Over the last 2 weeks, have you had thoughts that you would be better off dead or of hurting yourself in some way?” will trigger the Scale for Suicide Ideation questionnaire developed to determine the level of immediate suicide risk. Individuals who are not affiliated with one of the participating clinical sites and are completing the Web questionnaires will only receive the PHQ-8 and will not be assessed for suicidality.
To read more about this risk management protocol, go to ***Section 2.3.3. Assessment of Potential Risks and Benefits.***

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The following definitions are taken directly from Rozental et al 2014, which addresses Internet interventions, and Linden 2013, which discusses the negative effects in face-to-face behavioral treatment.

Deterioration **detail here, only mentioned in passing in 5.13 osiris** Items marked *** below not in osiris
Deterioration is defined as worsening of target symptoms and monitored by a validated outcome measure or behavioral measure, i.e., an increase of symptom severity, or increased frequency of intrusive thoughts. In order to distinguish temporary from enduring deterioration, we will rely on consecutive measures and follow-up. Weekly check-ins by the health coach during treatment, e.g. "Do you feel like your pain or mood is worsening?", administration of the PHQ-9 or the numerical pain scale. The health coaches will be trained to assess for negative/intrusive thoughts. The PHQ and pain scale will be administered post-treatment at 3-month, 6-month, and 12-month follow-up. Post-treatment data will be routinely analyzed each month for unexpected deviations from expected, e.g. greater than a standard deviation increase in pain or depressive symptoms. The exact alert threshold will be determined based on baseline distribution of study data.

Adverse events
Adverse events (AEs) consist of negative events probably emerging from treatment and perceived as adverse by the patient, causing deterioration of target symptoms and/or negative experiences that extend beyond the completion of treatment, e.g., increased anxiety during cognitive behavioral therapy training, or being embarrassed by revealing negative thoughts and insecurities to the health coach. Adverse events could reveal negative effects that are directly attributable to treatment, providing our team and other researchers with information on possible mechanisms underlying negative effects. During treatment, the health coaches will routinely assess for increasing negative affect. Post-treatment, the GAD-7 will be administered at 3, 6, and 12 months to assess for increasing anxiety.

**** In Osiris 5.13 , also unexpected problems (UPs), medical monitor, timing of reporting.****

Severe adverse events
Severe adverse events (SAEs) are negative events that occur during treatment and result in deterioration of target symptoms and/or adverse reactions requiring some form of high-intensity treatment. In this study, we are primarily identifying severe adverse events as deliberate self-harm, and suicidal ideation or attempts. Because of the risks involved, we will closely monitor, document, and report self-harm and suicide related behaviors (ideation or attempts) regardless if they are deemed related to treatment or not.

Next 4 topics not in Osiris
Novel symptoms
Novel symptoms consist of the emergence of new psychological symptoms, unrelated to the symptoms targeted in treatment, which may or may not be associated with treatment, e.g., occurrence of insomnia during treatment of social anxiety, or decreased self-esteem during treatment of panic disorder. Similar to adverse events, novel symptoms could provide valuable information on negative effects that would otherwise go unnoticed, but differs from adverse events as novel symptoms should be unrelated to the symptoms targeted in treatment.

Dropout

Dropout concerns the number of patients choosing to end treatment prematurely. Early termination can be related to deterioration of target symptoms, nonresponse, and/or experiencing adverse events, presumably related to treatment, e.g., increase in symptom severity, or demoralization. It may also be that dropout was related to a decrease in symptom severity, i.e., some patients might experience relief after a short period of time, perceiving more treatment as redundant. When feasible, we will make every effort to contact participants by phone and/or electronic survey to determine the reason for dropout or discontinuation of the intervention.

Nonresponse

Nonresponse is characterized by the lack of a predicted positive effect on target symptoms, possibly attributable to treatment, resulting in status quo, demoralization, and discouragement to seek help elsewhere, i.e., absence of any treatment effect. Nonresponse in the first 3 months will be assessed by the health coach, e.g. “To what extent do you feel like your symptoms have improved over the past 4 weeks of this program?” In the context of nonresponse, the health coach will work with the participant to explore the reason for and characteristics of the nonresponse, i.e., some patients might have deteriorated without treatment, or external factors might be responsible for the nonresponse, e.g., bereavement, or other psychosocial stressors. Potential factors contributing to nonresponse will be recorded in health coach case report forms. Nonresponse will also be assessed on quantitative measures at the 3-month and 6-month follow-up assessments. If patient is no longer in contact with the health coach at this point, we will not make any effort to assess of the reason for and characteristics of nonresponse.

Unwanted events

Unwanted events are defined as all events experienced as negative by the patient during treatment, which may or may not be related to the interventions being used, and does not necessarily influence treatment outcome, e.g., issues related to the treatment content, increased anxiety during exposure in vivo, and frustration caused by technical issues. Anxiety will be measured at regular follow-up points (3, 6, 12 months). Reported technical difficulties and our response to those technical difficulties will be recorded.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of analysis (e.g., feasibility/acceptability, efficacy, effectiveness, implementation) and time period for which each endpoint will be analyzed. Include this information for each hypothesis being tested, if multiple hypotheses are present. If the study is intended as a feasibility or pilot study, please consider that a formal hypothesis may not be available at the time of protocol writing. If so, include a statement indicating that hypotheses will be generated or that descriptive statistics only will be calculated.

- Primary Efficacy Endpoint(s): Pain interference

  H_0: 6-month change in pain interference will not differ between the two intervention arms
  H_1: 6-month change in pain interference will differ between the two intervention arms

- Secondary Efficacy Endpoint(s): Pain intensity, depressive symptoms, health care utilization (opioid prescriptions, acute care visits) and opioid misuse behaviors (Current Opioid Misuse Measure – COMM)

9.2 SAMPLE SIZE DETERMINATION

We anticipate randomizing, in an equal allocation ratio, a total of 350 participants with follow-up through at least 6 months, which will be the main time point for primary analysis.

Aim 1. For the primary test of comparative effectiveness of cCBT vs. m-Education for the trial, the power calculation is based on the comparison of intervention groups for the main outcome of change in daily pain intensity; the effect size we are powered for also applies to the key secondary outcomes: pain interference and depression (PHQ-9). Specifically, we have 80% power to detect a difference of 0.37 standard deviations between study arms on 6-month changes in the outcome. Additionally, we are accounting for 15% attrition at 6 months.

Aim 2. For the tests of interactions, we will identify baseline depressive symptom subgroups with either low or high depression (PHQ ≤ 10 versus PHQ > 10). In order to detect small-moderated effect sizes (similar to the main effect in Aim 1) for the HTE, we would need approximately four times as many participants as we do for Aim 1 (N=1400). Median trial size in SCD is 142; less than 50% of trials meet >90% of their recruitment target.[67] Thus, achieving the required sample size would not be feasible; however, when combined with our qualitative data, the quantitative data from Aim 2 will be critical for informing future dissemination of the intervention.

9.3 POPULATIONS FOR ANALYSES

Our models will be based on an intent-to-treat principle as we will take measures to ensure limited dropout or non-adherence.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All primary and secondary analyses will be preceded by descriptive analyses of baseline and clinical characteristics. Summary statistics will include means and standard deviations for continuous variables, and sample proportions for categorical variables. Median and inter-quartile range values will accompany continuous variables that are non-normal. Results will be presented for the entire sample and stratified by intervention arm. We will assess between-arm imbalance of baseline covariates by calculating standardized mean differences. For continuous variables, we will assess normality by visually inspecting univariate distribution via a normal probability plot. Transformations will be implemented if required.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

We will employ linear mixed models for the primary outcome of pain intensity and the secondary outcome of pain interference (Hypothesis 1) as a function of time, study arm (cCBT vs. m-Education), time-by-study arm interaction, study site, and baseline depression level (PHQ-9 ≤ 10 vs. PHQ-9 > 10). We will account for multiple observations for each participant by including a random effect for subject. Additionally, baseline variables with large clinically meaningful between-arm differences will be included as covariates. Contrasts will be estimated to assess the impact of cCBT and m-Education intervention on 6month improvements in pain. As a secondary investigation, we will use the same linear mixed models to address whether the 6-month improvements are sustainable to 12 months.

We will answer Hypothesis 2 using a similar analytic strategy. Depression (PHQ-9) will be modeled as a function of time, study arm, time-by-study arm interaction, and study site. We will account for multiple observations for participant by including a random effect for each subject.

Healthcare utilization (Hypothesis 3) will be compared between study arms using generalized linear models to account for count data (i.e., Poisson regression) for each of the following: the number of opioid prescriptions, number of ED visits, and number of hospitalizations over 12 months post study entry. Predictors will include study arm, study site, and baseline depression level. The corresponding health care utilization in 12 months prior to study entry will be entered as a covariate in each model. We will offset each model by participant's time on the study.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

<u>Qualitative Analysis for Aim 2</u>

Interviews will be conducted and analyzed by Dr. Megan Hamm and the Qualitative, Evaluation and Stakeholder Engagement Research Services (Qual EASE) in the Data Center of the Center for Research on Health Care at Pitt. Dr. Hamm will review interview scripts in conjunction with the rest of the study team to ensure that all relevant topics are covered, and Qual EASE staff will conduct pilot interviews with individuals identified by the study team as being sufficiently familiar with the topic to provide feedback on the guides. Experienced Qual EASE interviewers will be trained in the scripts, and will conduct the telephonic interviews with Dr. Hamm's supervision.

Analysis of the interviews will combine thematic analysis and constant comparison method. Codes will be developed via open coding of the transcripts to determine topics and themes that emerged in the interview transcripts, but input on topics or themes that the study team anticipates being relevant will also be solicited,

resulting in simultaneously inductive and deductive development of the codebook. Once the codebook has been finalized, two data analysts from Qual EASE will be trained in the use of the codebook, following which both coders will independently code 25% of transcripts. Coding will then be compared for the purposes of calculating Cohen's Kappa Inter-Coder Reliability scores. Any coding discrepancies identified during this comparison will be adjudicated until full agreement is achieved. After satisfactory intercoder reliability (Cohen's Kappa >0.6) is achieved, the primary coder will code the remaining transcripts. The completed coding will form the basis of a thematic analysis of the data, as well as a constant comparative analysis to compare the experience of patients by depression level. Analyses will be conducted by the primary coder and Dr. Hamm.

9.4.4 PLANNED INTERIM ANALYSES

N/A. Analysis will be conducted at the end of month 12 after the study is complete.

9.4.5 ADDRESSING MISSING DATA

Addressing missing data: We will minimize missing data by use of a paperless data collection system and by contacting participants when data are not entered in a timely fashion. We will attempt to characterize the mechanism of missingness (missing completely at random, missing at random, or not missing at random) by comparing rates of missingness/attrition between study arms. Additionally, we will compare baseline characteristics between participants with and without missing outcome data. If we conclude that our missingness is random, then our likelihood-based approach for the primary analyses will address this. Otherwise, if the missingness can be characterized as non-ignorable (not missing at random), we will use approaches such as joint modeling or shared parameter models to produce unbiased estimates of treatment effects. All reasons for dropout or other missing values will be entered by research staff or community groups (if encountering the patient during community activities), tabulated and summarized, and results will be reported using the Consolidated Standards of Reporting Trials (CONSORT) diagram. Patients who stop reporting data in the app will receive inquiry text messages or a phone call.

9.4.6 SUB-GROUP ANALYSES

The objective of Aim 2, examining heterogeneity of treatment effect (HTE), is to determine whether the intervention works better for some than for others. We again pre-specify our analysis plan and will examine differences in main outcomes for patients with high (PHQ-9 > 10) versus low (PHQ-9 ≤ 10) depression. These subgroups are most relevant so that end results can meaningfully inform patients about what works best for whom, and in turn, better support individuals as they seek treatment for pain. Furthermore, in examining differential impact of the interventions, based on these subgroups, providers, payers, and other decision makers can target resources in a manner that best meets the needs of those in need of services, reduces variations in practice, and improves health outcomes. We will augment the primary analysis models for pain intensity with relevant main effects for baseline depression level, and 2- and 3-way interactions with study arm and time. Of primary interest will be the significance of the 3-way interaction (time-by-study arm-by-baseline depression level). If significant, we will present treatment effect estimates and measures of variability in the form of confidence intervals within each subgroup. Two-sided tests of level 0.05 of the interactions between intervention and HTE subgroup will allow us to test whether depression moderates impact of intervention on pain outcomes. Although

hypotheses are stated with direction, we will conduct two-sided tests to be conservative. For all of the above described models, we will focus on the 6-month outcome.

9.4.9 EXPLORATORY ANALYSES

Change in scores from baseline to 3 months and from baseline to 6 months, for coping skills and self-efficacy, and program engagement/dose measures, will be tested as potential mediating variables. We will use the framework of Kraemer et al. 2008 to calculate effect sizes accounting for the impact of the potential mediator variable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

The CaRISMA trial will rely primarily on the review of the IRB, University of Pittsburgh Human Research Protection Office, while establishing an agreement that all site-specific IRBs will review their informed consent documents to ensure local concerns are adequately addressed.

Documented approval from appropriate independent ethics committees (IEC)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations, and organizations. When necessary, an extension, amendment, or renewal of the IEC/IRB approval must be obtained and also forwarded to the Clinical Coordinating Center (CCC).

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by the CCC. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol change should be submitted to the IEC/IRB, to the CCC and through the CaRISMA data capture system. Any deviations from the protocol must be explained and documented by the investigator.

The co-principal investigators are responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The principal investigator is responsible for personally overseeing the treatment of all study patients. The principal investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all GCP guidelines regarding clinical trials both during and after study completion.

The principal investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

10.1.1 INFORMED CONSENT PROCESS

Prior to performing any of the research study procedures or interventions, participants must provide informed consent. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The consent process will occur over the Internet and is self-guided. Potential participants can access the consent website via their own electronic device or in the clinical setting via a tablet computer station (kiosk). A video presentation will explain the study to the potential participants in a language understandable to participants, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation, etc.). Additionally, the most pertinent consent language will be presented on separate web pages where the user must click a button indicating acknowledgment and

understanding of the content to advance to the next screen. Each segment of the consent is presented in concise, easy to understand and clear language. Finally, the full consent document will be presented in PDF form on screen for the potential participant to read in its entirety. Note that potential participants are not expected to read the full consent document. All of the information contained in the consent document is explained via the video and website click-through process. The consent form and video will be available in English only.

In the clinical setting, staff will be available to potential participants to explain the study verbally, and to answer questions and clarify understanding of the study. For potential participants that are accessing the consent website outside of the clinical setting, a method for contacting study staff remotely will be provided. Upon reviewing all materials, the user will be given adequate opportunity to consider all options. Once the potential participant indicates they are interested in participating in the study, they will be asked a series of question to test comprehension and recall of the information presented. The questions presented will address important facts about study participation to confirm the potential participant's understanding of the study procedures. Only if all questions are answered correctly will the potential participant be permitted to proceed to the consent process. Every effort will be made to ensure that participants have comprehended the study information prior to obtaining participant's voluntary agreement to participate.

In addition, older potential participants whose competency to consent is in question will be tested for sufficient comprehension and recall of the information presented. Prospective participants who do not remember the important facts about participation in the research study after repeated testing will not be included in the study.

The informed consent document and explainer video will include the following General Data Protection Regulation (GDPR)-compliant consent information and language:

- The identity of the Principal Investigator;
- The purpose of data collection;
- The types of data collected;
- The right to withdraw from the research and the mechanism for withdrawal;
- Who will have access to the data;
- Information regarding automated processing of data for decision making about the individual;
- Information regarding data security, including storage and transfer of data;
- How long data will be stored;
- Whether and under what conditions data may be used for future research.

Before a signature is obtained on the informed consent form, the participant will be reminded that participation is completely voluntary and that they may withdraw at ANY time during the study time without any disadvantage and without having to provide any reasons for this decision. Participants will receive a copy of the informed consent form, electronically via email or text message, as a signed PDF document.

Consent records, including time and date of consent, will be maintained for each subject. We will ensure that security measures are in place to protect information from unauthorized access and damage. We will implement technical and organizational security measures to protect personal data, including encryption, redundancy, backup and security testing. There will also be breach notification requirements.

During the course of the study, participants will be provided with any new information that arises (e.g., new study procedure, change in risk/benefit profile) that may affect a participant's decision whether or not to continue participation in the study. Participants who have already signed consent will be presented with a revised consent

form with the new study procedures and/or what has changed since they last provided consent. A copy of the revised consent will be given to the participants for their records.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

If this study is prematurely terminated or temporarily suspended, the PI will promptly inform ongoing study participants, the IRB, and sponsor/funding agency and provide the reason(s) for the termination or temporary suspension. Section 7, Study Intervention/Experimental Manipulation Discontinuation and Participant Discontinuation/Withdrawal, describes handling of consented/enrolled study participants in the event the study is prematurely terminated.

10.1.3 CONFIDENTIALITY AND PRIVACY

All participant information, including contact information, questionnaires, and clinical information, will be monitored by study staff and available only to them. Case report forms will be locked in cabinets and electronic data will be stored in password-protected files. Only authorized study staff will have access to study data. Study reports will not contain any identifiable information and will present findings in aggregate (or by treatment group).

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