Home-Based Intervention for Chronic Pain in Adults with Sickle Cell Disease (HIPAS)

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PROTOCOL TITLE: Home-Based Intervention for Chronic Pain in Adults with Sickle Cell Disease (HIPAS)

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	12/15/2020	Revision of the informed consent process to address how participants can access an electronic copy of the consent form in cases of verbal informed consent
2	9/9/2021	Revision of the recruitment methods to include the use of social media and an opt-in/opt-out letter as recruitment strategies, if necessary
3	3/2/2022	Revision of the inclusion criteria to broaden the age range and revision of compensation to participants to provide an increase in the incentives
4 and 5	6/22/2022 7/13/2022	Revision of the recruitment methods to include an additional recruitment site.
6	10/28/2022	Decrease in sample size, from 72 to 50, due to recruitment challenges. Due to the exploratory nature of the intervention (EaseVRx), prior estimates of treatment effect sizes for the individual outcomes (pain, pain coping, sleep, functional activities of daily living, disability, healthcare utilization, and quality of life) were not readily available; thus, the original study was not powered for these

		individual outcomes. Instead, we focused on identifying the minimum detectable effect size at 80% power and 5% significance level. Given that this is a pilot study, our primary objective is to analyze data with the specific intent of establishing population parameters and estimating effect sizes. Modified power calculations indicate that with a sample size of 40, we will have the ability to detect a minimum standardized difference (Cohen's d) of 0.9 with adequate power (80%) at a 5% significance level. The reduced sample size will still allow us to make meaningful conclusions regarding feasibility and estimation of effect sizes. To obtain a final sample size of n = 40, we are looking to enroll n = 50 participants to account for a potential 20% dropout or non-completion rate.
8	5/3/2023	Revision of the informed consent process to include the option of using e-consent for completion of the informed consent form and electronic signature of consent by study team members obtaining verbal informed consent. Revision of data collection procedures to note that study activities and collection of data points will be completed whenever possible given participants' underlying condition and because this is a pilot study.
9	11/9/2023	Revision of the study protocol to include a projection to enroll n = 70 – 90 participants, instead of n = 50 participants, to obtain a final sample size of n = 40. The previous version of the protocol included a projection to enroll n = 50 participants, accounting for a potential 20% drop-out or non-completion rate, to obtain a final sample size of n = 40. However, the observed rate of drop-out or non-completion was more than double the potential estimate. Therefore, more individuals need to be enrolled to try to achieve a final sample size of n = 40.

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1. Study Summary

Study Title	Home-Based Intervention for Chronic Pain in Adults with Sickle Cell Disease (HIPAS)
Study Design	Multi-site, mixed-methods, exploratory, parallel-group RCT
Primary Objective	To determine the feasibility, acceptability, and preliminary efficacy of using EaseVRx for self-management of chronic pain among adults with sickle cell disease
Secondary Objective(s)	To assess how EaseVRx can be tailored for a target audience that predominantly consists of Black individuals
Research Intervention(s)/Interactions	Pain management program (EaseVRx) versus audio control
Study Population	Black, adult men and women (ages 18–50) with a diagnosis of sickle cell disease who experience chronic non vaso-occlusive pain
Sample Size	40
Study Duration for individual participants	12 weeks
Study Specific Abbreviations/ Definitions	Sickle cell disease (SCD) Virtual reality (VR) EaseVRx: 8-week, skills-based, home, virtual reality pain management program
Funding Source (if any)	Federal Agency/National Institutes of Health

2. Objectives

The purpose of this study is to learn about the chronic pain experience of adults with SCD and evaluate a pain management program for future intervention development. The specific aims are:

Aim 1 – To determine the feasibility of using EaseVRx for self-management of chronic pain among adults with SCD.

Aim 2 – To assess the preliminary efficacy of EaseVRx on pain and pain-related outcomes among adults with SCD.

- Hypothesis 1: The preliminary efficacy of EaseVRx among users will include decreased pain; improved pain coping, sleep, and functional activities of daily living; decreased disability and healthcare utilization, and enhanced QOL.

Aim 3 – To assess how EaseVRx can be tailored for a target audience that predominantly consists of Black individuals.

3. Background

Adults with SCD are an underserved, predominantly Black population[1] with high priority, unmet needs for chronic pain management. Chronic, non vaso-occlusive pain in SCD is a major health problem. This pain is currently defined as ongoing pain that was present, in one or more locations, on most days for more than six months.[2] It is attributed to factors including avascular necrosis of joints, bone infarction, leg ulcers, osteomyelitis, and central and peripheral sensitization.[2-6] Among adults, 54% report having pain 51% of the time and 29% report pain almost daily.[3] This pain is associated with negative coping behaviors,[7,8] functional disability,[9] poor quality of life (QOL),[10] and high healthcare utilization[10,11] Chronic pain also contributes to sleep disturbances[12-14], and anxiety and depression,[13,14] which in turn, exacerbate the pain burden.[12,15] Taken together, these factors contribute to lost productivity, morbidity, and mortality.[9,16-18] Opioids are typically used to manage chronic pain but their access is limited because of the opioid epidemic, they are ineffective, and they are associated with greater pain (due to hyperalgesia or sensitization), poorer functional outcomes, and higher healthcare utilization than non-users.[19-24] Therefore, alternative, non-pharmacological, self-management approaches are urgently needed to manage chronic pain in SCD.

Self-management is important for adults, ages 18–40, with SCD because they experience a high incidence of chronic pain and disability due to chronic pain,[9,25] and they account for the majority of the hospitalizations and readmissions due to pain.[26-28] In our preliminary work, Black adults with SCD reported the need for better pain self-management strategies and new resources to support self-management of pain at home.[9,25] Effective chronic pain self-management interventions often use cognitive behavioral therapy (CBT), the "gold standard" biopsychosocial (BPS) approach.[29,30] In adults with SCD, CBT has contributed to more positive coping skills, greater self-efficacy in managing pain, less use of pain medication, and an alleviation of chronic pain.[31] Currently, behavioral interventions like CBT that can address the pain self-management needs of adults with SCD are not readily accessible and are not included in comprehensive SCD care. Barriers to these types of therapies include socio-economic disparities, lack of available local therapists, stigma associated with mental health services, lengthy travel and treatment times, and low engagement even when delivered online.[32,33] There is a need for alternative delivery methods that are more engaging and can be utilized at home.

Virtual reality (VR) can be a more accessible, scalable, and appealing delivery method. The immersive and engaging virtual environment promotes distraction from pain, provides a sense of control, and can lead to cortical re-patterning and consequent reduction in pain perception.[34-38] In chronic pain conditions, such as complex regional pain syndrome, fibromyalgia, chronic migraines, musculoskeletal pain, and low back pain, VR has successfully resulted in pain reduction.[36,37,39,40] In addition, the ability to use VR at home,[41] combined with the popularity of mobile and gaming technology among young adults with SCD,[42-44] suggests that VR is a promising delivery platform. AppliedVR's EaseVRx is a multi-modal, skills-based, 8-

week, VR, mind-body approach to daily management of chronic pain that is designed for home use. Similar to in-person integrative pain management programs, EaseVRx provides therapeutic information to support participants in learning cognitive and behavior self-management skills, and retraining the pain pathways. The program incorporates pain education, pain psychology, biofeedback training to control breathing, relaxation based on mindfulness-based stress reduction (via 360-degree videos), and distraction via interactive games. Program modules are presented in a Netflix-style format. In a RCT of EaseVRx versus audio control in adults with chronic low back pain or fibromyalgia (≥ age 18, n = 97), 76% of the VR users reported no nausea or motion sickness and 83% reported high satisfaction ratings.[40] VR resulted in significant improvement in average pain intensity (p=0.036), pain-related inference with activity (p=0.005), sleep (p<0.001), mood (p<0.001), and stress (p=0.003). Symptom improvement, over time, was found for each pain variable (p<.001) with stronger results strengthening after two weeks. These findings support the feasibility and efficacy of using EaseVRx for chronic pain.

For adults with SCD, VR therapies may be more efficacious and result in fewer complications than opioid therapy. Thus, they can contribute to cost savings for the healthcare infrastructure. However, EaseVRx has not been tested in SCD. Moreover, the findings of our ongoing systematic review investigating the use and efficacy of VR in chronic pain conditions indicate that, to date, there have been no published studies of VR interventions for chronicpain management for adults with SCD. In addition, currently available VR pain self-management tools are designed for a generic or majority audience. Trials of EaseVRx in SCD are needed to evaluate the feasibility and establish the efficacy of using VR-based therapies to manage chronic pain in Black adults with SCD. In addition, studies are needed to determine how these therapies can be revised to be culturally-tailored for a target audience of predominantly Black individuals. This study will address all of these gaps.

Preliminary data and study models

In conjunction with the literature, the preliminary work conducted by the PI forms the basis for this research.

Role of self-care in young adults with SCD. Using secondary analysis, we evaluated relationships among SCD self-efficacy (perceived ability to function daily and manage SCD symptoms), social support, socio-demographics, self-care, and hospital visits for pain crises in 103 Black, young adults (ages 18-30) with SCD.[21] The majority of participants were female (61.2%), unemployed or disabled (68%), lived with family (73.8%), and had an average of three annual hospital visits for crises. Self-efficacy, social support, and years of education were positively associated with self-management. However, only income was associated with hospital visits for pain crises. These findings illustrate that characteristics important for successful self-management abilities and more proximal outcomes (such as daily pain) may better indicate pain self-management than distal measures (such as hospital visits). Participants also reported doubts about being able to manage their life from day to day. These findings suggest the need for additional support to improve self-management.

Examining the chronic pain experience of young adults with sickle cell. Using a qualitative design, the PI conducted this study to describe the perception of chronic SCD pain, understand self-management strategies used for chronic SCD pain, and complete a needs assessment for self-management of chronic SCD pain among adults.[25] Study participants were recruited from a larger study being conducted to evaluate the effectiveness of a decision aid for therapeutic options in SCD. Eighteen adults, ages 21-46 with SCD, completed an individual, semi-structured interview during which they responded to demographic questions and questions regarding chronic pain in SCD. Of the participants, the majority (n = 10; 55.5%) were 21–30 years of age (mean 33.5, SD 7.6), female (n = 11; 61.1%), employed at least part-time (n = 11; 61.1%), single/never married (n = 13; 72.2%), and had a SCD type of HbSS or sickle cell anemia (n = 10; 55.5%). The majority of the participants reported experiencing chronic pain daily; yet, they were not receiving specific treatment for this pain. Content analysis of the interview transcripts revealed that adults with SCD can differentiate between acute and chronic pain. However, they experience challenges in managing pain and chronic pain negatively affects their quality of life. They utilize a variety of self-management strategies and seek additional interventions for the management of chronic pain that are both beneficial and convenient. Findings were used to revise the semi-structured interview guide that is being used in our ongoing research and will be used in this study.

Chronic pain in adults with sickle cell disease. Our ongoing research (NHLBI Diversity Supplement, 3U01HL128566-02S1) investigates factors that influence chronic pain among Black, young adults (ages 18–40) with SCD[9] and explores the acceptability of potential strategies for future intervention trials. As an aim of this research, we have begun collecting qualitative data regarding patients' perception of and willingness to try a VR pain management program (EaseVRx). In individual interviews, 4 study participants were asked to complete two EaseVRx 15-minute experiences and provide feedback regarding the program. Participants' comments included: 1) *"Because like the way she was speaking to me, it kinda like uplifted me. And then like the music and the birds, and I was lookin at the clouds. It was very relaxing, like umm, my mind was gettin a massage…Very effective."* 2)*"I would use that thing every day…I know I would use it in the morning and I would definitely use it at night."* 3) *"That was cool…I loved it…It's very colorful…Umm, and just the scenery…It was just pretty cool to me."* 4)*"Umm, it has really helpful breathing exercises. It would be effective in calming somebodydown."*

This study will expand upon the findings of this preliminary work. It represents the first essential step in developing a culturally-tailored, non-pharmacological, chronic pain self-management intervention for Black adults with SCD. Study findings will guide possible modification of EaseVRx or development of a novel program to meet the needs and preferences of Black, young adults with SCD. We will then conduct a larger RCT of this program to test its efficacy in reducing the disease burden of SCD and the associated costs to the healthcare system.

Study models. The Technology Acceptance Model (TAM), the Capability, Opportunity, Motivation-Behavior (COM-B) system of the Behavior Change Wheel, and the Integrate, Design,

Assess, and Share (IDEAS) framework will guide this research. The TAM is a framework for understanding user's adoption and use of technology.[45,46] According to the model, an individual's intent to use and actual use of technology are based on perceptions of the technology's usefulness and ease of use. These perceptions are mediated by external variables such as individual differences, system characteristics, social influences, and facilitating conditions. This approach will be used to guide our assessment of feasibility in this study.

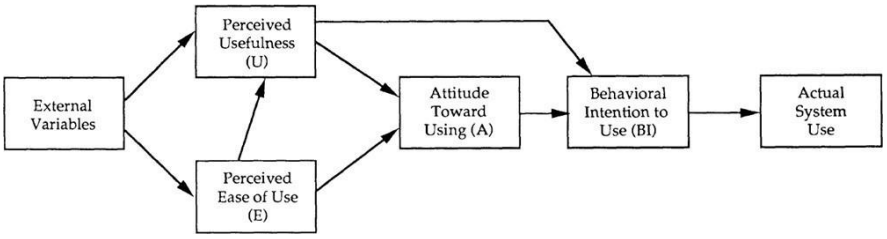


Figure 1. Technology Acceptance Model[45]

The COM-B system of the Behavior Change Wheel suggests that behavior change interventions work by addressing one or more of these significant components: capability (physical and psychological), opportunity (physical and social), and motivation (reflective and automatic processes).[47] These components interact to generate behavior which, in turn, influences these components. EaseVRx addresses all three components in the COM-B system by including elements of education, persuasion, training, modelling, and enablement.

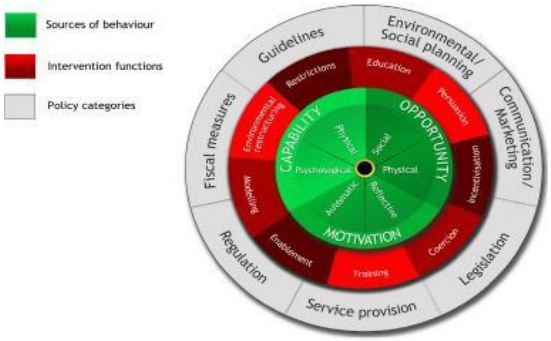


Figure 2. The Behavior Change Wheel[47]

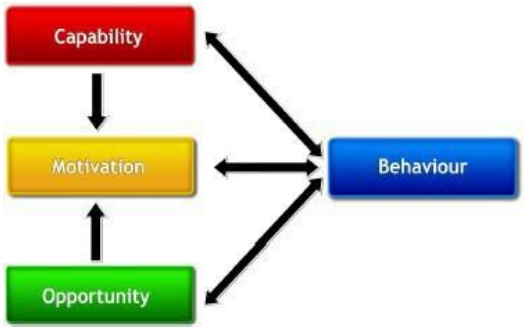


Figure 3. The COM-B system[47]

The IDEAS framework integrates behavioral theory, design thinking, and evaluation and dissemination to better guide the development of digital health interventions for changing behavior.[48] The framework consists of 10 phases that are organized into four overarching categories: integrate insights from users and theory, design iteratively and rapidly with user feedback, assess rigorously, and share intervention and findings. The IDEAS framework, COM-B system, and TAM will be integrated into the methods used for tailoring EaseVRx.

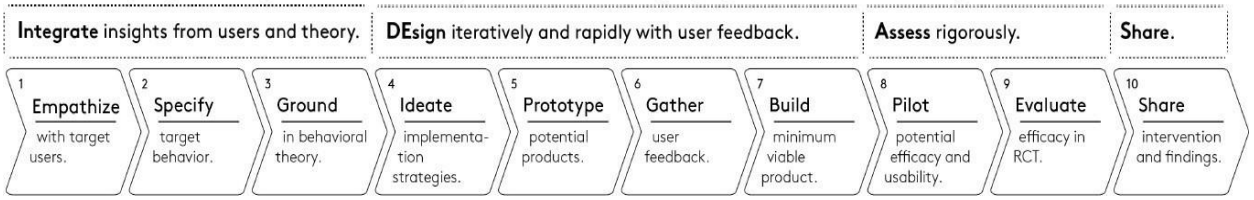


Figure 4. The IDEAS Framework[48]

Significance, Innovation, and Contribution to Science

This study is the first RCT that investigates a VR, biopsychosocial (BPS) intervention for self-management of chronic pain in Black adults with SCD. While most VR studies have primarily focused on distraction or physical rehabilitation, this investigation will also focus on VR's immersive effects, pain management education, and the acquisition of behavioral, pain self-management skills that can be used to cope with pain. We offer a non-pharmacological approach to chronic pain self-management that is scalable, associated with a lower risk of side effects than opioids, and can be implemented into routine SCD care to reduce pharmacological treatment and healthcare utilization. This work will advance current research by helping to address barriers to the success of behavioral therapies such as availability, accessibility, acceptability, and adherence. The proposed research also involves the development of a mobile, culturally-tailored, pain self-management approach for adults with SCD; thus, it addresses unmet needs. Overall, this work has potential to be high impact given the high pain burden associated with SCD, the existing health disparities in comprehensive pain management, and the lack of behavioral interventions that are accessible athome.

This study has the potential to: 1) offer an evidence-based, patient-centered, and outcome-driven self-management strategy that can be used long-term; and 2) advance scientific knowledge by influencing the broader fields of SCD, pain, and technology. Specifically, the proposed study will address gaps in the prior SCD research including: 1) the feasibility and efficacy of utilizing a VR, BPS approach for home self-management of chronic pain; 2) patients' goals, needs, and preferences for chronic pain self-management interventions; 3) culturally-tailored and disease-specific approaches for self-management of chronic pain; and 4) critical elements necessary for developing technology-assisted home-based interventions. Study findings will inform the development of a SCD-specific, non-pharmacological, home self-management intervention for chronic pain that can be used as an adjunct to standard SCDcare. Therefore, the proposed project aligns with the priorities of the National Institute of Nursing Research,[49] National Heart, Lung, and Blood Institute,[50] and the national pain strategy goal[51] to provide effective approaches for self-management of pain in order to decrease the pain burden. Knowledge gained from this work can be applied to other chronic pain conditions and to other applications of VR in the homeenvironment.

4. Study Endpoints

Aim 1 – To determine the feasibility of using EaseVRx for self-management of chronic pain among adults with SCD.

Primary feasibility measures will include enrollment and randomization, engagement, study retention, satisfaction, and safety. Secondary feasibility measures related to participants' satisfaction will include program fit with daily activities, barriers to use, and areas of program confusion or misuse. We will estimate the following parameters to determine whether the intervention shows promise for further investigations to determine its efficacy: 1) enrollment and randomization; 2) dropout or non-completion rate; 3) completion rate of baseline, mid-treatment, and post-treatment assessments; 4) completion rate of weekly VR modules and daily self-report assessments; 5) participant engagement and satisfaction; 6) rate of adverse effects (primary safety endpoint); and 7) participants' perceptions of the content, delivery, and tailoring required. Data collection methods will include program usage statistics (automatically recorded by the VR program), completion of study assessments, and qualitative sessions to collect subjective data. EaseVRx usage data will be surveyed monthly for the duration of the intervention.

Aim 2 – To assess the preliminary efficacy of EaseVRx on pain and pain-related outcomes among adults with SCD.

Outcomes of preliminary efficacy are pain, pain coping, sleep, functional activities of daily living, disability, healthcare utilization, and QOL. Pain coping outcomes are pain catastrophizing, chronic pain acceptance, chronic pain self-efficacy, health literacy, executive function, anxiety, depression, and social support. The pre-specified primary outcome is pain coping, and the primary measure of pain coping is pain catastrophizing. Data collection methods will include (also see the Schedule of Activities):

Demographics questionnaire
Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me^{SM}) SCD Medical History Checklist[52-54]
Medical record data collection form
Pain diary
Chronic Pain Grade Questionnaire[55]
Pain Catastrophizing Scale[56,57]
Chronic Pain Acceptance Questionnaire[58]
Chronic Pain Self-Efficacy Scale[59]
BRIEF Health Literacy ScreeningTool[60,61]
Behavior Rating Inventory of Executive Function ®–Adult Version (BRIEF-A)[62,63]
PROMIS® Emotional Distress – Anxiety[64]
PROMIS® Emotional Distress – Depression[64]
Social Support Questionnaire[65]

ASCQ-Me[SM] Short Forms: Sleep Impact, Pain, Pain Episodes, Emotional Distress, Social Functioning, and Stiffness[52-54]
Questionnaire to Screen for Cybersickness or Digital Motion Sickness
Virtual Reality Sickness Questionnaire[66,67]

- Hypothesis 1: The preliminary efficacy of EaseVRx among users will include decreased pain; improved pain coping, sleep, and functional activities of daily living; decreased disability and healthcare utilization, and enhancedQOL.

Aim 3 – To assess how EaseVRx can be tailored for a target audience that predominantly consists of Black individuals.

We will use a semi-structured interview guide to conduct qualitative sessions that will be audio-recorded. Questions will be developed to: 1) assess participants' technology usage and attitudes; 2) assess participants' satisfaction with the program (usefulness and ease of use, favorable and unfavorable elements), program fit with daily activities, barriers to use, and areas of program confusion or misuse; 3) explore participants' goals, needs, and preferences for chronic pain self-management interventions; 4) understand participants' perceptions of the cultural appropriateness of the program content; 5) identify how participants would revise the program to increase its acceptability and usefulness for Black adults with SCD; and 6) assess self-management strategies currently used for chronic pain and how these strategies can be integrated into a pain program.

Potential strategies for tailoring the program to improve its cultural sensitivity and effectiveness include: 1) working with stakeholders (Black adults with SCD and their families and/or caregivers, SCD providers, and SCD community based organizations) to develop program content; 2) facilitating coping strategies often used among Black individuals by incorporating family and preferred music, addressing spiritual/religious needs, and offering the opportunity for social support; 3) replacing the generic guided relaxation modules with our own tailored versions, and replacing images of individuals and scenery with those selected by stakeholders as being more relevant to the population; 4) including SCD-specific content (such as the education on types of pain, personal stories and testimonials, and strategies for improving the quality of patient-provider relationships; and 5) addressing culturally sensitive concerns such as an emphasis on empowerment, recognition of stress related to ethnic minority status and socio-economic status, awareness of stigma attached to psychological therapy, and possible mistrust of research.

5. Study Intervention/Investigational Agent

This study will involve an evaluation of EaseVRx (AppliedVR; Los Angeles, CA) – a commercially available pain management program/wellness application. EaseVRx is a multi-modal, skills-based, 8-week, VR, mind-body approach to daily management of chronic pain that is designed for home use to be worn over the eyes. Similar to in-person integrative

pain management programs, EaseVRx provides therapeutic information to support participants in learning cognitive and behavior self-management skills, and retraining the pain pathways. The program incorporates pain education, pain psychology, biofeedback training to control breathing, relaxation based on mindfulness-based stress reduction (via 360-degree videos), and distraction via interactive games. Program modules are presented in a Netflix-style format. The EaseVRx program focuses on acquisition of self-management skills, such as relaxation, mindfulness, and meditation techniques, that are intended to be used by patients after the end of the program to cope with pain. All program content is mapped to a therapeutically designed curriculum with weekly themes. The content is ordered to support the clinical and engagement goals of the program. However, participants can return to experiences as desired, and we will track the usage data. The core themes that are infused into the curriculum are: acceptance, attention shifting, awareness, rehabilitation, self-compassion, healthy movement, deep relaxation, visualization, knowledge of pain, distraction, and immersive enjoyment.

Participants will be randomized 1:1 to receive either EaseVRx or control. Participants will receive study materials and instructions for home use before being followed prospectively for 8-weeks with follow-up at 12 weeks. Each week, participants in the VR group will be asked to complete 7 assigned modules, averaging 5 minutes in duration and ranging from 2 to 16 minutes in duration, for a total of 56 modules across the program. The order of the modules is fixed but participants can repeat modules as desired. Participants in the control group will be asked to use the audio only version of EaseVRx, which excludes references to visual content, to complete 7 sessions weekly. They will receive an electronic link to the recordings on SoundCloud (a music streaming platform) where they can choose to stream or download the audio recordings on their smartphone, laptop, or desktop computer.

In this study, we will utilize an all-in-one, non-tethered VR headset (see Figure 5) that is pre-loaded with EaseVRx and isdesigned for home use. The goal is to obtain a total of approximately 20 headsets for use by approximately 25 participants so headsets may be used twice. These headsets will be stored at the locked PI's office and managed only by authorized investigators until provided to participants for use.

Figure 5. Pico G24K Headset with AppliedVR Breathing Amplifier

Participants in the VR group will receive a headset in person or via shipment. They will receive education, via AppliedVR onboarding materials such as detailed instructional manuals, to ensure safe and comfortable device use at home. Access to technical support (telephone and email) will also be provided. After the 8-week home use period, the headset will be retrieved from the participants (in person or via shipment) and cleaned according to manufacturer and department sanitary protocols before being provided to subsequent participants for use.

6. Procedures Involved

Study Design

We will conduct a multi-site, mixed-methods, exploratory, parallel-group RCT of EaseVRx versus audio control, engaging a total of 40 Black men and women (ages 18–50) with SCD to: 1) determine the feasibility of using EaseVRx for self-management of chronic pain; 2) assess the preliminary efficacy of EaseVRx on pain and pain-related outcomes; and 3) assess how EaseVRx can be tailored for a target audience that predominantly consists of Black individuals. To obtain a final sample size of n = 40, we will enroll n = 70–90 to account for dropout or non-completion. Using quantitative and qualitative sources, data collection will occur at baseline, mid-treatment (week 4), and post-treatment (week 8) and follow-up (week 12).

Procedures for Participants

After screening patients for eligibility using the inclusion and exclusion criteria, the project coordinator will describe the study to and seek participation from eligible individuals. Participants will be informed that the purpose of the study is to test a pain management intervention that will be delivered in two different ways, but their group allocation will not be revealed. The study conditions will be presented as adjuncts to standard care and there will be no restriction on using other pain management methods. After patients provide written, informed consent or verbal informed consent, they will complete baseline study questionnaires. Once enrolled, participants may self-withdraw at any time, or they may be withdrawn if they fail to or are unable to comply with study procedures. In that case, recruitment will resume and continue until the target number of participants is reached.

After completing baseline questionnaires, participants will be randomized 1:1 to receive either EaseVRx or control. Only individuals meeting the eligibility criteria for VR will be assigned to the VR group. Participants will receive study materials and instructions for home use before being followed prospectively for 8-weeks with follow-up at 12 weeks. Participants in the VR group will receive an all-in-one, non-tethered VR headset (Pico G24K headset with AppliedVR breathing amplifier) that is pre-loaded with EaseVRx. They will receive education and hands-on experience with the VR headset to ensure safe and comfortable device use at home. Access to technical support will also be provided. Each week, participants will be asked to complete 7 assigned modules, averaging 5 minutes in duration and ranging from 2 to 16 minutes in

duration, for a total of 56 modules across the program. The order of the modules is fixed but participants can repeat modules as desired. Participants in the control group will be asked to use the audio only version of EaseVRx, which excludes references to visual content, to complete 7 sessions weekly. They will receive an electronic link to the recordings on SoundCloud (a music streaming platform) where they can choose to stream or download the audio recordings on their smartphone, laptop, or desktop computer.

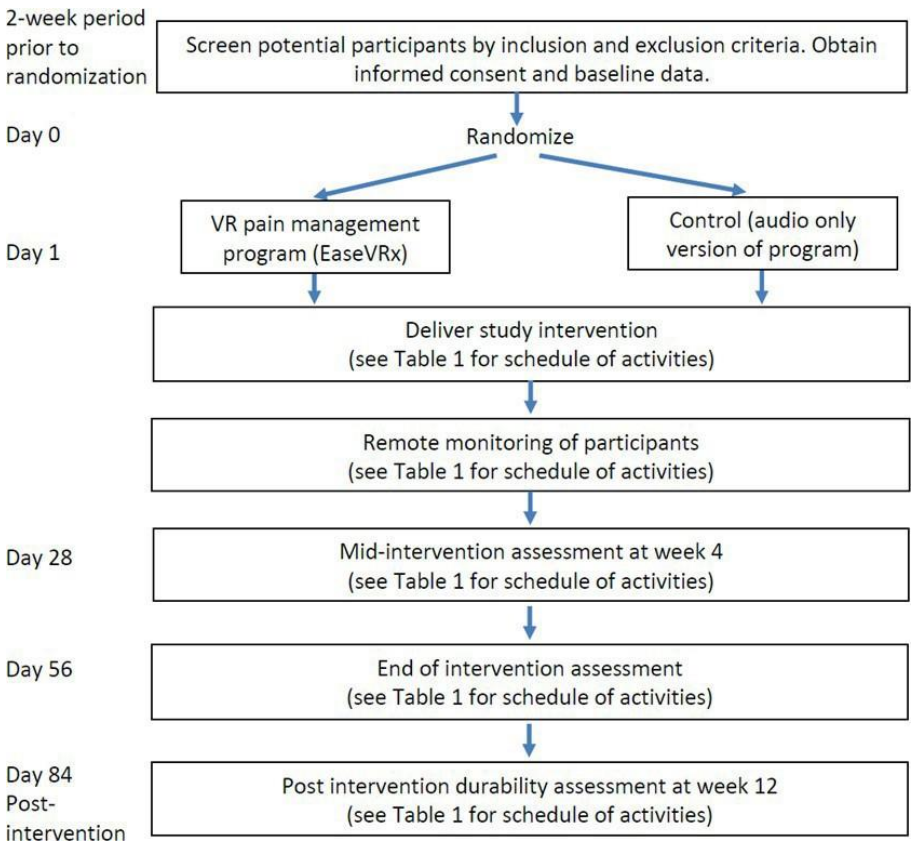
After the treatment period, we will retrieve study materials and conduct the qualitative sessions. Of the participants, we will randomly select approximately 50% (n = 10) from the VR group and approximately 50% (n = 10) from the control group for the qualitative sessions to learn about participants experiences with the treatment program and preferences for pain coping strategies. We may conduct individual interviews in participants' homes or focus groups sessions in a private area of the sickle cell clinic or research office, or may utilize remote options if necessary or if requested by participants.

Data Collection Procedures

Using quantitative and qualitative sources, data collection will occur at baseline, daily, mid-treatment (week 4), and post-treatment (week 8 and follow-up at week 12). Quantitative sources will include survey instruments, a daily pain diary, and electronic medical record review. Qualitative sources will include individual, semi-structured interviews or focus group sessions. Participants' electronic medical records will be reviewed, concurrently with data collection, for demographics, medical history, clinical data, analgesic and non-analgesic medications, and healthcare utilization. After group allocation at baseline, research activities will be conducted remotely in an effort to conceal treatment allocation.

Given the nature of sickle cell disease and individual disease experiences, we anticipate that participants may not be able to complete all study activities or provide data at all time points throughout the study. Because this is a pilot study, study activities and collection of data points will be completed whenever possible.

Study Schema



Study Measures and Schedule of Activities

The valid and reliable survey instruments that will be used to collect study data are described in Table 1. All data will be collected via direct entry into REDCap or another online data management system that can be accessed using a computer or smartphone. Participants will receive a link to complete the electronic surveys and pain diary after baseline data collection.

Table 1. Study Measures and Schedule of Activities

Study Outcomes	Measures (see attached documents)	Data Collection (*W = Week)				
		Baseline	Daily (Day 1 – 56)	W4 (Day 28)	W8 (Day 56)	W12 (Day 84, Follow-up)
Demographics	Demographics questionnaire	x				
	Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me^{SM}) SCD Medical History Checklist	x				
	Medical record data collection form	x				
Pain and self-management of pain	Pain diary	x	x	x	x	x
Pain and disability	Chronic Pain Grade Questionnaire	x		x	x	x
Pain catastrophizing	Pain Catastrophizing Scale	x		x	x	x
Chronic pain acceptance	Chronic Pain Acceptance Questionnaire	x		x	x	x
Chronic pain self-efficacy	Chronic Pain Self-Efficacy Scale	x		x	x	x
Health literacy	BRIEF Health Literacy Screening Tool	x		x	x	x
Executive function	Behavior Rating Inventory of Executive Function ®–Adult Version (BRIEF-A)	x		x	x	x
Anxiety	PROMIS® Emotional Distress - Anxiety	x		x	x	x
Depression	PROMIS® Emotional Distress - Depression	x		x	x	x
Social support	Social Support Questionnaire	x		x	x	x
Sleep	ASCQ-Me^{SM} Sleep Impact Short Form	x		x	x	x
Functional activities of daily living	ASCQ-Me^{SM} Pain Short Form	x		x	x	x
Quality of life	ASCQ-Me^{SM} Short Forms: Pain Episodes, Emotional Distress, Social Functioning, Stiffness	x		x	x	x
Screening prior to treatment	Questionnaire to Screen for Cybersickness or Digital Motion Sickness	x				
	Virtual Reality Sickness Questionnaire		x	x	x	
Participant engagement and acceptability	Program usage statistics (automatically recorded by the VR program) and completion of study questionnaires		x	x	x	
Study retention	Program usage statistics (automatically recorded by the VR program) and completion of study questionnaires	x	x	x	x	x
Participant satisfaction, and participant needs and preferences for tailoring the program	Semi-structured interview guide for qualitative sessions					x

7. Data and Specimen Banking

Not applicable

8. Sharing of Results with Participants

In general, individual study results will not be shared with participants. If we find something of urgent medical importance to participants, we will inform them, although we expect that this will be a very rare occurrence. There may be side effects from the study program or procedures that are not known at this time. It is possible that we may learn something new during the study about the risks of being in it. If this happens, we will contact participants by telephone to inform them of the finding, provide educational information regarding the finding, and if required, instruct them on following up with a primary care provider or seeking care from another clinician or specialist. After informing participants of any new findings, they can decide whether to continue to be in the study or not. Participants may be asked to sign a new consent form that includes the new information if they decide to remain in the study. In the event of any study changes or the need for remote consent, study staff will contact participants via telephone or Zoom (audio only), and they will be asked to provide verbal informed consent after the consent discussion takes place. If participants request a copy of the revised consent form, then they will be emailed a link to the online consent form in REDCap. The email will not contain any information related to the participant's condition.

The research team is committed to the open and timely dissemination of research findings. We will adhere to policies regarding dissemination of information from the proposed study. The proposed study will be registered at ClinicalTrials.gov after the notice of award is received. As outlined in the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, study results will be submitted to ClinicaTrials.gov no later than 12 months after study completion. In addition, a statement related to posting of clinical trial information at ClinicalTrials.gov will be included in the informed consent document. We will also adhere to Emory University's internal policy to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.

De-identified study data may be placed into public databases where, in addition to having no direct identifiers, researchers will need to sign data use agreements before accessing the data. De-identified findings may also be posted on the project website. This can provide a forum for obtaining feedback from research participants and their family members or caregivers, healthcare providers, and visitors such as professionals and non-professionals. In addition, we will share study findings in accordance with the NIH policy. Electronic copies of publications arising from the proposed study will be deposited in PubMed Central with proper tagging of data to ensure online discoverability and accessibility.

9. Study Timelines

- Enrolled individuals will participate in this study for 8 weeks, with follow-up at 12 weeks.
- We anticipate enrolling all participants within the first six months of the study.
- We estimate a two-year study period for completion of all study activities.

10. Inclusion and Exclusion Criteria

Inclusion Criteria

Black adults, ages 18–50 years; diagnosis of SCD; chronic non vaso-occlusive pain experienced > 3 days per week on average for > 6 months; ability to wear a VR head-mounted display and move head in cervical rotation, extension, and flexion; sufficient fine motor control to operate VR equipment such as a controller; and ability to read, write, and understand English.

Exclusion Criteria

1. Conditions: Co-morbidities that may influence pain perception; diagnosis of epilepsy or susceptibility to seizures, migraines, or other neurological disorders that may prevent VR use, and/or other medical conditions due to which individuals are predisposed to nausea and dizziness; susceptibility to claustrophobia, motion sickness or cybersickness (digital motion sickness); history of blackouts; hypersensitivity to flashing lights or motion; lack of stereoscopic vision; severe visual or hearing impairment; inability to operate VR equipment (such as inability to turn head or use hands to operate external controller); and/or injury to the eyes, face, head, or neck that prevents comfortable VR use.

2. Other exclusions: Medical instability as determined by healthcare providers at the study site; significant motor impairment; surgery within the last three months; planning to start a new pain management strategy (such as medication, physiotherapy, acupuncture, or cognitive behavioral therapy) in the next three months; history of major psychiatric disorder (such as schizophrenia or bipolar disorder) not controlled with medication or behavioral factors that would interfere with study procedures; alcohol or substance dependence, heart conditions, or the presence of implanted medical devices (such as cardiac pacemakers) as noted in the electronic health record; cognitive or developmental disabilities; active suicidal ideation; inability to read, write, or understand English; pregnancy; and/or plans for vacation in the next three months.

This study <u>will not</u> include any of these special populations:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

Community Participation

Adults with SCD are the target community for this study. Our preliminary and ongoing studies have been aimed at evaluating the chronic pain experience among adults with SCD and assessing their needs, goals, and preferences for future intervention studies such as this study. Therefore, the needs, goals, and preferences of adults with SCD have been incorporated in the design of this study of adults with SCD. De-identified study findings may be posted on the project website. This can provide a forum for obtaining feedback from the SCD community, which includes research participants and their family members or caregivers, healthcare providers, and visitors such as professionals and non-professionals. In addition, dissemination of results from this study will occur via publications and presentations to the SCD community at national and international professional conferences. Electronic copies of publications arising from the proposed study will be deposited in PubMed Central with proper tagging of data to ensure online discoverability and accessibility.

11. VulnerablePopulations

Not applicable

12. Local Number of Participants

We anticipate accruing a total of 40 participants locally to achieve a total of 50 participants from both recruitment sites. To obtain a final sample size of n = 40, we will enroll n = 70–90 to account for dropout or non-completion. We expect to screen approximately 144 individuals to achieve a total accrual of 40 participants.

13. Recruitment Methods

After obtaining approvals, active and passive recruitment for this study will take place at the Georgia Comprehensive Sickle Cell Center at Grady Memorial Hospital (Grady) in Atlanta, Georgia and the James R. Clark Sickle Cell Memorial Foundation (SC Memorial Foundation) in Columbia, South Carolina. Active recruitment by the project coordinator will involve the weekly screening for eligibility and enrollment of adults who receive care in the sickle cell clinic at Grady and who are served by the SC Memorial Foundation. Potential participants will be identified and screened for eligibility, using the inclusion and exclusion criteria, by conducting an initial review of medical records or obtaining patient report. Active recruitment may also occur through healthcare providers and community health workers who inform potential participants about the study, either in person or via mailed opt-in/opt-out letters, if necessary (see attached document), and provide them with contact information for the project coordinator or principal investigator (PI). Passive recruitment will occur via the use of flyers placed at the sickle cell clinic and SC Memorial Foundation to inform potential participants about the study. If necessary, these flyers may also be published on social

media including Instagram, Facebook, and Twitter or via a website developed specifically for the study. Interested individuals will be invited to contact the program coordinator or PI, using the contact information provided on the flyers (see attached document), for further information. In the event of any enrollment shortfalls, we will do the following to achieve recruitment goals: consider loosening the exclusion criteria, expand the study to an additional sickle cell clinic, utilize area resources to increase the efficiency of participant enrollment, and/or extend the recruitment period.

The James R. Clark Sickle Cell Memorial Foundation (SC Memorial Foundation) is not engaged in this research. The Foundation will serve as a community-based, recruitment site through which potential participants will be contacted and informed about the study. Emory study staff will coordinate, in person or remotely, recruitment and participant onboarding activities for potential participants identified through the SC Memorial Foundation.

The participant burden is estimated to be 45 minutes at each time point for surveys, 2 hours weekly of intervention for 8 weeks, and 1 hour for qualitative sessions. Participants will receive $50 after baseline, $50 after each 4-week study period ($150 in total), and $50 after the qualitative sessions.

14. Withdrawal of Participants

Data collection will be monitored daily by the study team. Participants will be sent a reminder text or email if they do not submit data after 4 days. If no response is received after 2 days, a team member will conduct a telephone call. We will use a maximum of 3 attempts to contact participants. If 2 weeks have passed since last data submission and contact attempts have been unsuccessful, the participant will be considered lost to follow-up and will be withdrawn from the study. Before making this determination, we will try to regain contact with the participant (via 3 telephone calls and, if necessary, a certified letter mailed to the participant's last known address). These attempts will be documented in the participant's study file.

We may conclude an individual's participation in this study without their consent for any reason, especially if we believe it is in their best interest or if they were to object to any future changes that may be made in the study plan. Expected reasons for conclusion of participation may include:

- Experiencing any symptoms of cybersickness or digital motion sickness (such as dizziness, lightheadedness, issues with balance, nausea, and/or vomiting) during or afterexposureto VR
- Experiencing severe mentaldistress

If participants do not finish any portion of the study, then they will be compensated for the portion(s) they have completed and will no longer have their data collected after they have withdrawn from the study. Data that were already collected may still be used for this study as we try to understand pain in individuals with sickle cell and develop interventions. If participants would like us to discontinue use of their data after they withdraw from the study, then they will contact the principal investigator, at

the mailing address provided, with a written request. Once we receive the written request, their data will be destroyed.

15. Risks to Participants

Potential Risks

This study involves minimal risk, if any. Exposure to VR may result in an infrequent physical risk of cybersickness or digital motion sickness. In addition, we will solicit information regarding participants' pain and disease experiences. Therefore, there is a potential, likely, infrequent psychological risk because discussion of these experiences might result in emotional distress and/or embarrassment to the participants. There may also be rare, social risks in that there may be social harm (i.e., stigmatization) to the participant and larger community of individuals with SCD. A breach of confidentiality may result in social consequences such as being perceived negatively by healthcare providers, family members, or employers. Economic consequences may also arise if individuals need to choose an alternate healthcare provider because of a breach of confidentiality. This alternate healthcare provider may be in another county or state. Accordingly, the participant may incur costs for transportation and/or care.

Procedures to Reduce Risks

Study recruitment and data collection will occur in person, in a private area of the SCD clinic, SC Foundation, or research center, or remotely while participants are at home. All potential participants will be screened for eligibility using the inclusion and exclusion criteria. Eligible participants will receive information about the study, and will be asked to complete an informed consent, or a verbal informed consent, and a Health Insurance Portable and Accountability Act (HIPAA) authorization form. The informed consent document states that participants may choose to not answer any question or may end their participation in the study at any time. During the interviews or focus group sessions, participants will be reminded that their participation is voluntary and that they may stop at any time if they are uncomfortable with any questions.

Prior to treatment, we will ask potential participants screening questions, using the Questionnaire to Screen for Cybersickness or Digital Motion Sickness, to determine whether they have had or may have any of these issues. If so, they will not be considered eligible for participating in the VR group only. If they are considered eligible for the VR group (provided no affirmative responses to the screening questions), then participants will remotely complete the Virtual Reality Sickness Questionnaire before each use of the VR program. Only individuals without severe symptoms, as reflected on the questionnaire, will move forward with VR use. These individuals will also be asked to remotely complete the Virtual Reality Sickness Questionnaire after each use of the VR program. Participants who are randomized to the VR group will be instructed to adhere to the usage recommendations specified by the VR program’s manufacturer. In addition, VR participants will be instructed not to use the VR device while ambulating, and that they should use the headset a maximum of 3 times per 24-hour period (morning, noon, and evening) for not more than 30 minutes consecutively. During the 8-week, home VR

use period, we will use telephone calls or text messages to conduct weekly study assessments of adverse events. Users of the VR program who experience adverse events are free to suspend or halt VR use at any time by removing the headset. This can remedy the VR side effects. In addition, the VR program offers a range of experiences to allow participants to identify lower risk experiences. For participants who experience adverse events, we will discontinue their study participation and refer them to a member of the medical team as needed for any medical follow-up. All participants will have the ability to withdraw from the study at any time.

At this time, the risks of VR during pregnancy (i.e., risks to the pregnant woman, the embryo, or fetus) are not yet known. Therefore, to protect against possible side effects, women who are pregnant or nursing a child will not participate in exposure to VR. Female participants will be asked to immediately notify study staff if they become pregnant during the study. In that case, they will not be exposed to VR but may continue with other remaining study activities.

Active suicidal ideation, as documented in the patient's medical records, is one of the exclusion criteria. Among eligible participants, we will assess depression with the PROMIS® Emotional Distress – Depression (Short Form) at baseline, mid-treatment, and monthly post-treatment via remote data collection. This measure does not include a suicide item. To manage participants who score in the upper range of the depression measure or disclose suicidal ideation, we will utilize the following protocol.

a. At the end of the survey in the questionnaire management system, participants will see this statement: *If you are feeling distressed or you are having thoughts of hurting yourself, please call 911, call the 24-hour Georgia Crisis and Access Line at 1-800-715-4225, call the South Carolina 24-hour Crisis Response Dispatcher at 1-833-364-2274, go to Grady Memorial Hospital or your local hospital, or call your healthcare provider.*

b. The questionnaire management system will be designed to identify scores that indicate risk for serious depression (severe category) based on the scale's psychometrics: mild (T scores of 55–60), moderate (T scores of 60–70), and severe (T scores > 70)[64]. These scores will be regularly monitored. Between data collection time-points, participants can also be assessed via the planned weekly text messages or telephone calls that will be used to promote engagement and retention. The PI will be immediately notified of any severe scores or disclosed suicidal ideation.

c. Once notified, the PI will implement timely and appropriate follow-up to ensure the safety of the participants. We will inform participants that their responses indicate that they may be experiencing meaningful levels of depression and take the following steps to attempt to connect them with appropriate care during remote data collection.

- If participants disclose suicidal ideation, we will contact them directly and "warm transfer" them to 911 or a crisis line (such as the 24-hour Georgia Crisis and Access Line, the 24-hour South Carolina Crisis Response

Dispatcher, or Emory Healthcare's 24-hour crisis line). The Georgia Crisis and Access Line and the South Carolina Crisis Response Dispatcher provide a number of services, including screening and assessment of callers for intensity of service response, conducting "warm transfer" of individuals to 911 for emergencies, and crisis assistance (24/7 mobile response to assess the situation, de- escalate the crisis, consult, and refer with post-crisis follow-up to assure linkage with recommended services).[68] "Warm transfer" refers to the process of transferring a call while having the opportunity to share information with the crisis line staff prior to the call transfer. This also allows for all of us (i.e., research personnel, crisis line staff, and participant) to be on the call at the same time if needed.

- If participants experience severe depression scores, we will contact them directly and refer them to Grady Memorial Hospital (Emergency Department or Behavioral Health Outpatient Center) or the emergency department at their local hospital for treatment.
- These participants will be provided with a list of mental health resources. They will also be encouraged to follow up with their primary care practitioner about their symptoms or they can give us permission to contact the practitioner on their behalf.
- A clinician (clinical psychologist) will be able to provide additional assistance if needed.

We will conduct an internal study review and these participants will be given the option to discontinue the study or continue study procedures. The PI will document all of these activities.

If adverse events occur, the date and time of onset and outcome, course, intensity, action taken, and causality to study treatment will be assessed by the PI. The PI will also review the outcome and adverse event data to determine whether a change to the anticipated risk-to-benefit assessment is required, and whether the study should continue as originally designed or should be revised. The IRB will be informed immediately of any adverse events and requests for modifications of the study protocol will be submitted quarterly. Confidentiality of the data and the results of monitoring will be protected.

16. Potential Benefits to Participants

Potential study risks are reasonable in comparison to the benefits and knowledge that will be gained from the study. Benefits of the study may include education regarding pain self-management, enhanced pain self-management skills, improved coping with pain, and decreased use of opioids for pain among adults with SCD. Participants may also receive an indirect benefit by sharing their information as a part of a larger study that will result in future interventions for enhancing the well-being

of individuals with SCD. Knowledge gained from the study can be used by healthcare professionals to provide better care to adults living with SCD and to better equip patients with the resources and skills necessary to effectively participate in theirown pain management. In addition, information obtained from the study will help to decrease stigmatization experienced by members of this population.

17. Compensation to Participants

Participants will receive compensation in the form of gift cards (physical or electronic) throughout the study. They will receive $50 after baseline, $50 after each 4-week study period ($150 in total), and $50 after the qualitative sessions.

18. Data Management andConfidentiality

Data Management

Electronic methods, including REDCap and Microsoft Office, will be used to organize and manage data collected from this study. A data collection log will be used to enable tracking of data collection activities. Data collection logs will specify what data are to be collected for each participant, using which instruments, with expected and actual dates of data collection. Detailed reports of completed instruments listed by participant identification number will be generated for program management purposes; for instance, to plan for conducting focus group sessions or individual interviews.

Data Analysis

Data will be collected and managed by using REDCap. All quantitative data will be verified and periodic quality assurance checks of data entry will be performed. Once finalized, data will be exported from REDCap into the Statistical Package for the Social Sciences (SPSS Version 26) for statistical analysis. We will code the surveys manually and evaluate their psychometric properties in the sample. Initial data analysis will include descriptive statistics (e.g., means, standard deviations, frequencies, and percentages) on sample characteristics and outcomes at each time point. To ensure balance in participants' characteristics by intervention group at baseline, we will compare the sociodemographic and clinical characteristics (e.g., age, gender, disease severity, and comorbidities) of participants using t-tests or chi-square tests as appropriate. Any differences across treatment groups will be accounted for in subsequent analysis. We will also evaluate any attrition according to participants' characteristics. We will assess distributional assumptions of outcomes and perform appropriate transformations to remedy any violations. We will minimize missing data by monitoring data regularly and implementing successful methods for obtaining follow-up data. When data cannot be collected, sensitivity analysis will be performed to evaluate the impact of missing data on results. We also plan to use the restricted maximum likelihood (REML) method for model estimation whenever possible to minimize the impact of missing data. All outcomes will be compared among participants in both arms. All statistical tests will be two-sided and intent-to-treat procedures

will be employed. Additionally, all analyses will include sex (male vs female) as a biological variable to assess differences in outcomes within each group.

Number and percent will be used to summarize the primary feasibility measures while content analysis will be used to summarize the secondary feasibility measures. Optimal treatment will be determined by correlations among the engagement outcomes and measures of preliminary efficacy. We will use mixed-effects models to test whether the outcomes differ across the treatment group over time (from pre- to post intervention). Depending on the type of outcome (continuous or categorical), linear or generalized mixed effects models will be used, respectively. In this approach, each participant is treated as an experimental unit with repeated observations over time. The model will include fixed effects of time, intervention group, and time x intervention group interaction, and assume an unstructured variance–covariance matrix to describe the covariance structure. We will adjust for any baseline group differences in participant characteristics. A significant interaction effect will indicate significant differences in outcomes by treatment groups over time. We will select the most parsimonious model using Akaike information criterion (AIC) and Bayesian information criterion (BIC). Hypotheses tests based on specific contrasts in the mixed model and the interaction term between time and intervention group will be performed to test whether subjects in the intervention group demonstrated improved outcomes compared to the control group. The model-based estimates of the outcome measures for the two treatment groups at each time point will be used to estimate effect sizes for future studies.

Interview data will be transcribed verbatim then checked for accuracy by the PI before being subjected to content analysis.[69,70] A TAM-based codebook will be used to assist with analysis. Codes may include TAM constructs related to user intent, usage behavior, usefulness, and ease of use.[45,46] We will review transcripts to assign codes based on concepts that emerge, select exemplars illustrating these concepts, and sort codes into categories. As analysis progresses, constant comparison will be used to refine existing codes and identify new codes to fit the data.[69,70] As the qualitative sessions progress, information gleaned from earlier sessions may be used to modify later sessions so that findings are confirmed by multiple participants. We will review findings for accuracy of data interpretations, themes generated, and conclusions.

Confidentiality

To protect confidentiality and maintain the privacy of study participants, we will strictly adhere to HIPAA protocol and use a Certificate of Confidentiality. All data will be kept confidential and will only be used for research purposes. The PI will ensure that study records are stored securely. All paper study records will be stored in locked file cabinets in a locked office at Emory University's Nell Hodgson Woodruff School of Nursing, to which only the PI and research staff will have access. A copy of the signed informed consent form and any identifying numbers will be placed in a secure file cabinet that is separate from other study records. A copy of the completed verbal informed consent form will be stored on password protected University computers that contain data encryption software and computer locks to prevent theft. Each participant will be given a unique study identification number that does not reveal

personal identifying information. Relevant medical information will be written on study forms, which will have the participant's study number only. Additionally, during each interaction as a part of the study, we will inform prospective participants that no study data will be entered into their medical records or provided to anyone without their written permission.

Although all study related documents will only be labeled with a unique participant number that does not contain any identifying information, there is a need to link the participant number to personal identifiers in order to contact study participants after baseline data collection. A linkage document will be stored on a password protected, encrypted network drive. Personally identifiable information will be accessible only to study personnel. There will be blinding of the statistician to group assignments. The code for random assignments will be kept in a hidden folder that is not accessible to any study staff with patient contact or data analysis responsibilities. The statistician will receive two groups of datasets marked as group A and B. These groups will be randomly labeled by the project coordinator before the datasets are sent to the statistician. Using this method, the PI, co-I, and statistician will remain blind to group assignments until after data are collected and analyzed.

Electronic data will be collected and stored via secure databases such as REDCap and AppliedVR's software system (for device usage data). All downloaded electronic data will be saved in password protected files. Additionally, all computers on which data will be stored and evaluated are password protected, will have data encryption software, and will have computer locks to prevent theft. All computers have a privacy screen so that information displayed on the monitor is not visible to others unless seated directly in front of the monitor. Data may be shared among the research team in person or via secured university email. Any shared data will not include identifying information and participants will not be identified in any report or publication about this study. All identifiable data will be destroyed after completion of the study and dissemination of findings. Digital files will be kept for 5 years and then will be destroyed.

19. Provisions to Monitor the Data to Ensure the Safety of Participants

The PI will be primarily responsible for study monitoring. All study personnel will complete CITI and HIPAA training prior to initiating any work with study participants. Quality oversight to measure fidelity to study procedures will be conducted by the PI and the research team. Measures for safeguarding the security of study data will include: ensuring that all study personnel will maintain required IRB certification; when in use, keeping paper study documents safe from public view; assigning a non-identifiable study number to each participant; ensuring that all devices used to collect, store, and review study data are password-protected; collecting and storing electronic data via secure databases; storing paper documents in secured, locked areas; restricting access to data to authorized personnel only; and de-identifying participants' data for use in reports or publications.

The PI, co-investigator, and project coordinator will meet weekly at the study outset then monthly to assess study goals, timelines, participant recruitment and retention, data quality, data coding and management, and identification and documentation of unanticipated problems, complaints, or breach of confidentiality. If participant enrollment falls below 50% within two months of initiation of enrollment, or adherence falls below 50%, both of which

might inhibit the ability to test study outcomes, the PI will meet with the study team to discuss alternative methods for improving recruitment and adherence.

Data on adherence to the treatment protocol will be collected twice weekly by research staff and reviewed weekly by the PI. Participants' compliance with treatment will be evaluated by the frequency of program use and actual minutes used. Monthly assessments will made of protocol compliance, participant recruitment, accrual and retention, participant withdrawals, data quality and timeliness, risk-to-benefit evaluation, unanticipated problems (including adverse events), protection of confidentiality of information, and any other factors that may affect the study. In the case of adverse events, the date and time of onset and outcome, course, intensity, action taken, and causality to study treatment will be assessed by the PI. The PI will also review the outcome and adverse event data to determine whether a change to the anticipated risk-to-benefit assessment is required, and whether the study should continue as originally designed or should be revised. The IRB will be informed immediately of any adverse events and requests for modifications of the study protocol will be submitted quarterly. Confidentiality of the data and the results of monitoring will be protected.

A summary of the following assessments will be provided to the IRB annually at the time of study renewal or more frequently as required: list of research personnel who participated in the data and safety monitoring; the frequency of monitoring that took place during the renewal intervals and/or the dates on which data and safety monitoring was conducted; cumulative data related to unanticipated problems, including a determination of causality and a re-evaluation of the risk-to-benefit assessment; if applicable, pertinent scientific literature reports, therapeutic developments, or results of related studies that may influence the safety of study participants or the ethics of conducting the research study; outcome of reviews conducted to ensure participants' privacy and the confidentiality of research data; final conclusions regarding changes to the anticipated risk-to-benefit assessment of study participation; and final recommendations related to continuing, changing, or discontinuing the study.

20. Provisions to Protect the Privacy Interests of Participants

We will strictly adhere to HIPAA regulations to safeguard participants' privacy interests and their protected health information (PHI). We will ask permission to access and utilize any PHI, such as through the electronic medical record. All data will be kept confidential and will only be used for research purposes. The steps that will be taken to protect confidentiality and maintain the privacy of study participants will be outlined on the informed consent. These steps include: using a study number, rather than the participant's name, in data records, presentations, or publications; using a Certificate of Confidentiality; utilizing data use agreements for any future researchers who may want access to de-identified study data; not placing their research data into their electronic medical record; and not sharing any information about them with unauthorized individuals or without their written permission. If desired, participants will be able to revoke their permission for use of their PHI at any time during the study by contacting the study team in writing. We will help participants feel at ease with this study during the informed consent process and throughout the study by providing detailed information regarding the study purpose, research activities, their rights as a study

participant, their ability to choose not to answer any questions at any time, and their ability to discontinue participation at any time.

21. Economic Burden to Participants

There are no anticipated costs to patients for participating in this study. Participants will not be charged for any of the research activities.

22. Consent Process

The consent process will be completed by the project coordinator or principal investigator and will take place in person, in a private area of the SCD clinic, SC Foundation, research center, or remotely. After screening, eligible patients will receive information about the study. At least 15 minutes will be devoted to the consent discussion during which the study will be described to patients, they will be asked to explain what they understand about the study, and they will have an opportunity to ask questions and take any necessary time that is desired prior to making a decision regarding participation. Once an affirmative decision has been made, individuals will be asked to complete the informed consent and HIPAA authorization form. If there is period of more than 60 minutes between the initial consent discussion and an affirmative decision to participate in the study, the project coordinator or principal investigator will review the consent discussion prior to obtaining consent. While study activities are being conducted remotely post-baseline, the project coordinator or principal investigator will remind the participants of their continued rights and assess their understanding of the study to ensure ongoing consent. This assessment of ongoing consent will be completed by the project coordinator or principal investigator during the check-ins that will be conducted via text messages or telephone calls and prior to conducting the post-intervention interviews. To minimize the possibility of coercion or undue influence, participants will be reminded that neither their study participation nor decision not to participate will influence their healthcare in any way.

In the event of any study changes or the need for remote consent, study staff will contact participants via telephone or Zoom (audio only) and they will be asked to provide verbal informed consent after the consent discussion takes place. As an option, e-consent may be utilized for completion of the informed consent form and electronic signature of consent may be used by study team members obtaining verbal informed consent. If participants request a copy of the revised consent form, then they will be emailed a link to the online consent form in REDCap. The email will not contain any information related to the participant's condition.

Non-English-Speaking Participants: Not applicable

The target population for this study consists of Black or African American adults with SCD. Members of this population are proficient with the English language.

Participants who are not yet adults (infants, children, teenagers): Notapplicable

Cognitively Impaired Adults: Not applicable

Adults Unable to Consent: Not applicable

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception): Not applicable

23. Setting

The research team will identify and recruit potential participants at the Georgia Comprehensive Sickle Cell Center at Grady Memorial Hospital (Grady) in Atlanta, Georgia and the James R. Clark Sickle Cell Memorial Foundation (SC Memorial Foundation) in Columbia, South Carolina. After baseline, research procedures will be conducted remotely while participants are at home or may be conducted in a private area of the research center (Nell Hodgson Woodruff School of Nursing at Emory University) or the SC Memorial Foundation if in-person activities are necessary.

24. Resources Available

Of the 1100 adults annually served by the SCD center, over 50% are ages 18–40 and experience chronic pain, and approximately 30 individuals in this age range are seen in the SCD clinic weekly.[71,72] In addition, the SC Memorial Foundation has a client roster of approximately 400 adults. Therefore, it is feasible to recruit the required number of suitable participants (n = 50).

Medical resources (such as Grady or local area hospitals) and psychological resources (such as the Georgia Crisis and Access Line, the South Carolina Crisis Response Dispatcher, or local area hospitals) will be available to participants to address any unanticipated consequences of this research. A clinician (clinical psychologist) will also be available to provide additional assistance if needed to manage participants who score in the upper range of the depression measure or disclose suicidal ideation during the study.

During the two-year study period projected for completion of research activities, the percentage of time that will be allocated to conducting and completing the research is 100% for the project coordinator, 30% for the PI, and 5% for the co-PI. The PI will be primarily responsible for study monitoring. Prior to the start of the study and routinely throughout the study, the PI will meet with all study personnel to ensure that they are adequately informed regarding the study protocol, research procedures, and their roles and responsibilities, and that they complete CITI and HIPAA training prior to initiating any work with study participants.

25. References

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