Clinical Protocol

Digital mental **Well**ness **P**ersonalized for the **L**ifestyles of adolescent and young adult **U**sers with **S**ickle cell disease (RxWell PLUS)

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Designing an Implementation Strategy for Delivering Routine Mental Health Screening and Treatment	
Grant Number:	R34MH125152-01	
Study Description:	This project will develop an implementation strategy for delivering routine mental health screening and treatment to adolescent and young adults with sickle cell disease (SCD). An existing digital cognitive behavioral therapy (CBT) program will be adapted to be engaging and culturally relevant to African Americans. This will be the first study to test a tailored digital CBT for mental health in SCD, and long-term, it will inform the delivery of evidence-based mental health treatment in racial and ethnic minorities living with chronic pain.	
Objectives:	Primary Objective:	Determine whether an adapted digital CBT app will have greater uptake and engagement than standard digital CBT.
	Secondary Objectives:	Determine feasibility of conducting a large scale clinical trial testing digital CBT among adolescents and young adults with SCD.
Endpoints:	Primary Endpoint:	Program Engagement
	Secondary Endpoints:	Pain Interference, Quality of Life
Study Population:	Male and female patients that are between 16 and 35 years of age, have a diagnosis of SCD (any genotype) and report significant depression or anxiety symptoms (i.e., Patient Health Questionnaire [PHQ-9] or Generalized Anxiety Disorder Scale [GAD-7] > 4).	
Phase or Stage:	Phase1	
Description of Sites/Facilities Enrolling Participants:	• **Clinical sites:** University of Pittsburgh Medical Center (UPMC), **Community-based organizations:** Sickle Cell 101, Children's Sickle Cell Foundation	
Description of Study Intervention/Experimental Manipulation:	The study interventions are both cognitive behavioral therapy (CBT) programs delivered through a digital mobile app. The program provides users with brief (5-10 minute) skill building modules and CBT and dialectical behavioral therapy techniques such as relaxation, behavioral activation, distress tolerance, cognitive reframing, and mindfulness meditation, for depression and anxiety.It is for research purposes only. One group will use standard engagement methods while the other group will focus on delivering the CBT in a culturally sensitive manner specific to African Americans.	
Study Duration:	1 Year	
Participant Duration:	1 month	

1.2 SCHEMA

Figure 1. RxWell PLUS study flow diagram for a randomized pilot trial of N=40 adolesdcents and young adults with comorbid sickle cell disease and mental health disorder symptoms

1.3 SCHEDULE OF ACTIVITIES

Schedule of interventions and of monitoring patient outcomes					
Outcome	**Measure**	**Week of Study**			
		1	**2**	**3**	**4**
Primary	Engagement: usage days, technique/sessions completed, log-ins, coach contacts	X			
Process Evaluation	Self-efficacy (SCSES)	X			X
	Mental Health Stigma/ SCD stigma	X			X
	Perceived relevance and relatability	X			
Mental Health	Depression (PHQ-9), Anxiety (GAD-7)	X	X	X	X
Quality of Life	Pain interference (PROMIS)	X			X
	Quality of life (ASCQ-Me)	X			X
Medical	Health care utilization: Opioid prescriptions, ED visits, hospitalizations				X

2 INTRODUCTION

2.1 STUDY RATIONALE

Population- and setting-specific adaptations to interventions can lead to their successful implementation and wider use, yet no studies show how much adaptation is needed to effectively implement digital CBT in different settings. Qualitative data from our group and others show that cultural factors—lack of relatability, representation, and perceived stigma regarding mental health treatment—limit engagement with digital CBT programs. Our proposal will devise changes to advertising, promotion, and health coach communications, that will decrease stigma and make digital CBT more relatable and relevant to young adults with sickle cell disease (SCD). We hypothesize that low-cost adaptations to a digital CBT program will have better engagement than digital CBT with standard implementation strategy. Specific aims are as follows.

AIM 1: Use implementation science (ImS) and human-centered design methods to define the barriers to delivering routine mental health screening and digital CBT to adolescents and young adults with SCD. By leveraging ImS theory, models, and frameworks, we will systematically collect and analyze qualitative data to define and understand stakeholder needs, and cultural

barriers to routine mental health screening and treatment in SCD clinics and the community. Specifically, we will use the Behavior Change Wheel as a validated method for identifying the appropriate behavior change and implementation strategies.

AIM 2: Rapidly iterate, test, and evaluate adaptations to the implementation strategy for a coach-enhanced digital mental health service. Based on findings from Aim 1, we will systematically develop, test, and evaluate changes to how the CBT program is advertised/promoted, and introduced to patients and providers. We will tailor the messages and multimedia content that health coaches send to patients.

AIM 3: Demonstrate that a population-specific implementation strategy improves engagement with a digital CBT-based mental health service. We will recruit 40 adolescents and young adults with SCD (ages 16-35) and comorbid depression and randomize them to either the off-the-shelf digital CBT program and standard implementation strategy that has no content or references to SCD, chronic pain, or the unique challenges facing minority groups, to adapted digital CBT with a SCD-specific implementation approach.

Our hypothesis:
We hypothesize that low-cost adaptations to a digital CBT program will have better engagement than digital CBT with standard implementation strategy. We expect that participants in the adapted digital CBT arm will complete more modules and have more interaction days with the digital CBT program than participants in the standard digital CBT arm.

2.2 BACKGROUND

African Americans living with chronic health conditions are more likely to experience depression and other mental health disorders than their healthy counterparts.[1, 2] Compared to whites, African Americans are more likely to experience severe depression but less likely to be diagnosed or receive treatment.[3, 4] Left untreated, depression can increase disease severity and risk for mortality, particularly for groups already at high risk.[5-12]

A model population for health disparities research. One remarkably vulnerable population are adolescents and adults living with sickle cell disease (SCD), a condition that affects millions of people worldwide and over 100,000 people in the United States.[13] A vast majority of the people affected by sickle cell are of African descent;[14] this is a racial minority group that has been traditionally underserved and receives lower quality health care.[15] Compared to other rare chronic conditions that affect primarily people of European descent, such as cystic fibrosis, SCD receives less funding and has more limited clinical resources.[15] Thus, this is a population in need of more mental health resources and access to high-quality, evidence-based care.

Addressing comorbid pain and mental health. As adolescents and young adults navigate the change from pediatric to adult care, they are simultaneously managing several developmental and life transitions. It is not surprising that the adolescent/young adult age group (16-35) experiences the highest incidence of SCD-related pain crises and health care encounters compared to SCD patients from other age groups.[16-19] The severe and unpredictable nature of pain in SCD, combined with exposure to disadvantaged environments and chronic psychosocial stressors characteristic of disadvantaged lifestyles, makes managing mental health in this group challenging.[20] Indeed, adolescents and young adults living with a chronic

disease such as SCD are at high risk for mental health disorders[18, 21-23] and suicide.[24]

Comorbid depression in SCD is associated with increased risk of severe pain, pain-related hospitalizations, opioid dependence, increased medical costs, and mortality.[25] Yet SCD clinics are often under-resourced, and mental health is not assessed during routine SCD care visits. In studies where depression is assessed, 26-65% of patients with SCD meet criteria for a major depressive disorder.[26] Given that physicians are less likely to detect mental health problems in African Americans and in younger patients,[27] many SCD patients suffering from depression may never have their mental health assessed, let alone treated.

Unmet need and barriers to treatment. There is an urgent need for mental health screening and effective, evidence-based treatment of psychological disorders in routine SCD.[28-33] Cognitive behavioral therapy (CBT), in particular, is the gold standard of behavioral approaches to treating depression. Considering the well-established gap in mental health care for SCD patients, however, CBT is not part of comprehensive SCD care.

Many suggest that CBT can be an effective and cost-efficient component of SCD treatment.42-46 However, there are four critical barriers to providing face-to-face CBT services in routine care: 1) availability, 2) accessibility, 3) acceptability, and 4) adherence. 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 who are culturally competent to work with hard-to-reach, minority populations. Even when CBT is available, therapy is time consuming and requires travel to a clinic, which is challenging for adult patients with significant social and economic challenges,[34-36] and for the parents of adolescent patients. [37]

Over the past two decades, face-to-face CBT has been adapted so it can be delivered over the phone, over the internet via desktop computer, and more recently, via mobile devices, first tablet computers (e.g., iPads) and then mobile phones. Although the delivery method has drastically changed, the core components of CBT have remained stable through each adaptation, and now CBT via the Internet and mobile technology not only improves access and availability to evidence-based treatment but can be as effective alternative to traditional face-to-face CBT for depression, other mental health disorders,[38, 39] and even pain and pain-related disability.[40] Given the consistent evidence from several meta-analyses showing the effectiveness of digital CBT (in prior literature referred to as computerized CBT), the UK's National Institute for Health and Care Excellence (NICE) made digital CBT standard of care and available to all patients in the UK.[41, 42] Digital CBT is becoming well-established as a low-cost add-on to routine care, and is now being offered by several health plans in the U.S. including our partner, the University of Pittsburgh Medical Center (UPMC) Health Plan.

Bridging disparities in mental health care with technology. Using digital CBT, we can now deliver high-quality, evidence-based behavioral mental health treatment that can be scaled to reach patients in under-resourced settings. Digital CBT has long been shown to be effective in white populations. More recently, we have shown digital CBT is effective for minorities. We found that digital CBT led to significant decrease in depressive symptoms among African American primary care[43, 44] and SCD patients.[45] Our group has also implemented digital CBT for pain with African American children and adolescents with SCD.[46] Thus, there is ample evidence that digital CBT is ready for implementation in SCD clinics and potentially, through community-based organizations (CBOs) via social media and the Web, creating widespread access to mental health care.

Gap in evidence. No studies have demonstrated the successful implementation and sustainable

delivery of a digital CBT service in SCD or any other underserved population in under-resourced settings. This is in part because, despite promising evidence supporting the use of digital CBT for mental health, attrition and poor adherence with this mode of intervention are common.[47] Moreover, engagement with digital interventions may be especially problematic for minority users. Our work shows that African Americans are even less likely than whites to stick with digital CBT programs. African American primary care patients enrolled in our digital CBT trial were less likely than whites to start the program (75% vs. 87%) and to complete all 8 modules (29% vs. 43%). In our pilot study with SCD adults, although patients reported benefits from digital CBT, the average user completed only 3 of 8 possible sessions. Post-study interviews and a focus group revealed that while SCD patients did indeed feel the CBT skills were useful, the content was often not relevant or relatable and did not represent their real-world cultural and health experience. In addition, interventions with this population have to address cultural stigma, a well-known barrier to recruitment and retention of racial/ethnic minorities in mental health programs. To advance the field, we need innovative approaches to remediating these barriers to the provision, receipt, and benefit of digital CBT-based mental health services in low-resource settings.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Pregnant Women

This is a minimal risk behavioral intervention study. None of the procedures or activities involved in this study will put the mother or fetus at risk. There is no known risk to a fetus for this behavioral intervention. No inducements, monetary or otherwise, will be offered to terminate the pregnancy. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

Due to the depressive symptoms associated with SCD, this behavioral intervention study may reveal pre-existing suicidal thoughts/behaviors. Participants may experience discomfort or embarrassment when sharing or reviewing personal information. In addition, data entered via the internet and text message can be intercepted by a 3rd party.

2.3.2 KNOWN POTENTIAL BENEFITS

The possible benefits to participation in this study include the opportunity to allow researchers to evaluate the impact of on-line and mobile technology-based treatment strategies that may improve the care of future sickle cell patients. There is no guarantee that patients participating in this study will receive any benefit.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

While enrolled in the study participants will be given access to a health coach. Health coaches are trained personnel in dealing with individuals at risk, and are skilled at working with individuals at riskof feeling anxious or depressed. They will frequently assess participant risk and act accordingly.

Patients are able to stop the digital CBT program at any time, and we will frequently remind patients that they do not have to answer questions if it makes them uncomfortable.

Data Security

Coded data will be stored electronically and saved onto a separate secure database. Once the participant consents, the encrypted data is sent to a RedCap (or similar) secure server. There are two parts to the encrypted data that is transferred from the mobile device to the server: identifiable information upon enrollment and the non-identifiable study data. These two components are stored separately and linked by a unique identifier. The key linking these two are only accessible by the study staff.

This study 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

Patients will be encouraged to lock their device when not in use and to keep the latest security OS update. Patients will also be encouraged to avoid accessing untrusted sites.

This research is necessary to understand the feasibility of a mobile-technology–based behavioral intervention for mental health that predominantly targets a minority population.

Study endpoints

Primary Outcome Measures
Program engagement. Engagement will be measured by frequency and time on the app, number of lessons completed, and number of interactions (app messages) with health coaches over a 4-week period.

Secondary Outcome Measures
Pain Interference. The PROMIS Pain Interference Scale[86] is a validated questionnaire asking a patient how much day-to-day function is altered by pain. SCD impairs health-related quality of life (HR-QOL) more than most other chronic diseases. PROMIS is designed to allow streamlined, computer-aided administration, and has been tested in multiple populations and conditions including SCD.

Quality of life and mental health. To assess changes in QOL and emotional distress, participants will complete the following tests at baseline and 1 month: Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-ME); Emotional Functioning and Social Impact scales;[87, 88] and the Patient Health Questionnaire (PHQ-9),[89, 90] a 9-item measure of depressive symptoms.

Medical Outcomes
In preparation for a large-scale trial, we will pilot the collection of medical outcomes: opioid medication refills, and emergency department visits or hospitalizations for pain crisis. We will collect data retrospectively (from the past 12 months) and prospectively (12 months from date of enrollment) from patient medical records (Table 3). These data will allow us to track health care utilization, as well as lab values (e.g., hemoglobin level) and clinical outcomes (e.g., end-organ damage score).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a study to assess whether or not a culturally sensitive, population-specific implementation of an intervention increases engagement and effectiveness of a cCBT-based mental health service.

Population- and setting-specific adaptations to interventions can lead to their successful implementation and wider use, yet no studies show how much adaptation is needed to effectively implement digital CBT in different settings. Qualitative data from our group and others show that cultural factors—lack of relatability, representation, and perceived stigma regarding mental health treatment—limit engagement with digital CBT programs. Our proposal will devise changes to advertising, promotion, and health coach communications, that will decrease stigma and make digital CBT more relatable and relevant to young adults with sickle cell disease (SCD). We hypothesize that low-cost adaptations to a digital CBT program will have better engagement than digital CBT with standard implementation strategy.
Specific aims are as follows.

Aim 1: Use implementation science (ImS) and human-centered design methods to define the barriers to delivering routine mental health screening and digital CBT to adolescents and young adults with SCD. By leveraging ImS theory, models, and frameworks, we will systematically collect and analyze qualitative data to define and understand stakeholder needs, and cultural barriers to routine mental health screening and treatment in SCD clinics and the community. Specifically, we will use the Behavior Change Wheel as a validated method for identifying the appropriate behavior change and implementation strategies.

Aim 2: Rapidly iterate, test, and evaluate adaptations to the implementation strategy for a coach-enhanced digital mental health service. Based on findings from Aim 1, we will systematically develop, test, and evaluate changes to how the CBT program is advertised/promoted, and introduced to patients and providers. We will tailor the messages and multimedia content that health coaches send to patients.

Aim 3: Demonstrate that a population-specific implementation strategy improves engagement with a digital CBT-based mental health service. We will recruit 40 adolescents and young adults with SCD (ages 16-35) and comorbid depression and randomize them to either the off-the-shelf digital CBT program and standard implementation strategy that has no content or references to SCD, chronic pain, or the unique challenges facing minority groups, to adapted digital CBT with a SCDspecific implementation approach.

H1: We hypothesize that participants in the adapted digital CBT arm will complete more modules and have more interaction days with the digital CBT program than participants in the standard digital CBT arm.

General Study Design

There are two intervention groups. Both intervention groups will receive cognitive behavioral therapy (CBT) through a digital mobile app.The program provides users with brief (5-10 minute) skill building modules and CBT and dialectical behavioral therapy techniques such as relaxation,

behavioral activation, distress tolerance, cognitive reframing, and mindfulness meditation, for depression and anxiety.It is for research purposes only.

One group will use standard engagement methods while the other group will focus on delivering the CBT in a culturally sensitive manner specific to African Americans.

Both intervention groups will receive weekly (more frequent if requested or needed) follow-up with a health coach who will reinforce CBT content and encourage session completion for at least 4 weeks. In the adapted digital CBT arm, the health coach will use tailored text messages and multimedia communications.

The program provides users with brief (5-10 minute) skill building modules and CBT and dialectical behavioral therapy techniques such as relaxation, behavioral activation, distress tolerance, cognitive reframing, and mindfulness meditation, for depression and anxiety. It is for research purposes only.

All participants will complete short surveys each week they are in the study. These surveys will be sent to their mobile phone as a web URL link. Each week, participants will complete a depression (PHQ-9) and anxiety (GAD7) symptoms questionnaire. At 1 and 4 weeks only, participants will also complete measures of Self-efficacy (SCSES), stigma, pain interference (PROMIS), and quality of life (ASCQ-ME). In addition, as part of the intervention, participants are asked to interact with their assigned digital CBT program at least once per week if not more.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

African Americans living with chronic health conditions are more likely to experience depression and other mental health disorders than their healthy counterparts.[1, 2] Compared to whites, African Americans are more likely to experience severe depression but less likely to be diagnosed or receive treatment.[3, 4] Left untreated, depression can increase disease severity and risk for mortality, particularly for groups already at high risk.[5-12]

One remarkably vulnerable population are adolescents and adults living with sickle cell disease (SCD), a condition that affects millions of people worldwide and over 100,000 people in the United States.[13] A vast majority of the people affected by sickle cell are of African descent;[14] this is a racial minority group that has been traditionally underserved and receives lower quality health care.[15] Compared to other rare chronic conditions that affect primarily people of European descent, such as cystic fibrosis, SCD receives less funding and has more limited clinical resources.[15] Thus, this is a population in need of more mental health resources and access to high-quality, evidence-based care.

As adolescents and young adults navigate the change from pediatric to adult care, they are simultaneously managing several developmental and life transitions. It is not surprising that the adolescent/young adult age group (16-30) experiences the highest incidence of SCD-related pain crises and health care encounters compared to SCD patients from other age groups.[16-19] The severe and unpredictable nature of pain in SCD, combined with exposure to disadvantaged environments and chronic psychosocial stressors characteristic of disadvantaged lifestyles, makes managing mental health in this group challenging.[20] Indeed, adolescents and young adults living with a chronic disease such as SCD are at high risk for mental health disorders[18, 21-23] and suicide.[24]

Comorbid depression in SCD is associated with increased risk of severe pain, pain-related hospitalizations, opioid dependence, increased medical costs, and mortality. [25] Yet SCD clinics are often under-resourced, and mental health is not assessed during routine SCD care visits. In studies where depression is assessed, 26-65% of patients with SCD meet criteria for a major depressive disorder.[26] Given that physicians are less likely to detect mental health problems in African Americans and in younger patients,[27] many SCD patients suffering from depression may never have their mental health assessed, let alone treated.

There is an urgent need for mental health screening and effective, evidence-based treatment of psychological disorders in routine SCD.[28-33] Cognitive behavioral therapy (CBT), in particular, is the gold standard of behavioral approaches to treating depression. Considering the well-established gap in mental health care for SCD patients, however, CBT is not part of comprehensive SCD care.

Many suggest that CBT can be an effective and cost-efficient component of SCD treatment.42-46 However, there are four critical barriers to providing face-to-face CBT services in routine care: 1) availability, 2) accessibility, 3) acceptability, and 4) adherence. 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 who are culturally competent to work with hard-to-reach, minority populations. Even when CBT is available, therapy is time consuming and requires travel to a clinic, which is challenging for adult patients with significant social and economic challenges,[34-36] and for the parents of adolescent patients. [37]

Over the past two decades, face-to-face CBT has been adapted so it can be delivered over the phone, over the internet via desktop computer, and more recently, via mobile devices, first tablet computers (e.g., iPads) and then mobile phones. Although the delivery method has drastically changed, the core components of CBT have remained stable through each adaptation, and now CBT via the Internet and mobile technology not only improves access and availability to evidence-based treatment but can be as effective alternative to traditional face-to-face CBT for depression, other mental health disorders,[38, 39] and even pain and pain-related disability.[40] Given the consistent evidence from several meta-analyses showing the effectiveness of digital CBT (in prior literature referred to as computerized CBT), the UK's National Institute for Health and Care Excellence (NICE) made digital CBT standard of care and available to all patients in the UK.[41, 42] Digital CBT is becoming well-established as a low-cost add-on to routine care, and is now being offered by several health plans in the U.S. including our partner, the University of Pittsburgh Medical Center (UPMC) Health Plan.

4.3 JUSTIFICATION FOR INTERVENTION

Bridging disparities in mental health care with technology. Using digital CBT, we can now deliver high-quality, evidence-based behavioral mental health treatment that can be scaled to reach patients in under-resourced settings. Digital CBT has long been shown to be effective in white populations. More recently, we have shown digital CBT is effective for minorities. We found that digital CBT led to significant decrease in depressive symptoms among African American primary care[43, 44] and SCD patients.[45] Our group has also implemented digital CBT for pain with African American children and adolescents with SCD.[46] Thus, there is ample evidence that digital CBT is ready for implementation in SCD clinics and potentially, through community-

based organizations (CBOs) via social media and the Web, creating widespread access to mental health care.

Gap in evidence. No studies have demonstrated the successful implementation and sustainable delivery of a digital CBT service in SCD or any other underserved population in under-resourced settings. This is in part because, despite promising evidence supporting the use of digital CBT for mental health, attrition and poor adherence with this mode of intervention are common.[47] Moreover, engagement with digital interventions may be especially problematic for minority users. Our work shows that African Americans are even less likely than whites to stick with digital CBT programs. African American primary care patients enrolled in our digital CBT trial were less likely than whites to start the program (75% vs. 87%) and to complete all 8 modules (29% vs. 43%). In our pilot study with SCD adults, although patients reported benefits from digital CBT, the average user completed only 3 of 8 possible sessions. Post-study interviews and a focus group revealed that while SCD patients did indeed feel the CBT skills were useful, the content was often not relevant or relatable and did not represent their real-world cultural and health experience. In addition, interventions with this population have to address cultural stigma, a wellknown barrier to recruitment and retention of racial/ethnic minorities in mental health programs. To advance the field, we need innovative approaches to remediating these barriers to the provision, receipt, and benefit of digital CBT-based mental health services in low-resource settings

4.4 END-OF-STUDY DEFINITION

Patients are considered to have completed the study once they have participated in weekly check-ins with a health coach during the 4 weeks and completed the assessments (STIG-9, SCSES, PROMIS, ASCQ-ME, PHQ-9, GAD-7) at the scheduled time points.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible for the study, patients must:

- be between 16 and 35 years of age
- have a diagnosis of SCD (any genotype)
- report significant depression or anxiety symptoms (i.e., Patient Health Questionnaire [PHQ-9] or Generalized Anxiety Disorder Scale [GAD-7] > 4).

5.2 EXCLUSION CRITERIA

Patients are ineligible if they:

- Are unable to read English or understand the consent process
- Are cognitively impaired adults as determined by their treating physician
- Have any condition that in the opinion of the investigator would not allow the patient to continue on the study

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Potential participants will be screened for eligibility prior to enrolling into the study. A de-identified log that includes all screenings, study eligibility and consent will be completed by the research coordinators obtaining consent.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

At each participating clinical site (Pediatric and Adult SCD Clinics), we will use electronically-administered screening tools, medical record screening and if available, best practice alerts, to identify patients with SCD who have high risk for mental health disorders as indicated by self-report. Best practice alerts will flag patients with a history of mental health diagnosis or who have been prescribed psychopharmacological medication for mental health. In addition to recruitment in the local clinics, potential participants may be recruited through community-based organization websites, social media groups, email listservs, and patient/family meetings. The community-based organization websites are: Sickle Cell 101 (https://www.sc101.org/) and Children's Sickle Cell Foundation (http://cscfkids.org/).
We have access to these organizations because Sickle Cell 101 and Children's Sickle Cell Foundation are investigators/consultants on the grant that funds this project.

Electronic Screening and Consent Tool. Interested patients will access a short online screener on any mobile device (a compatible smartphone device is necessary to participate; loaner devices will be provided as needed). 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 on this electronic consent process in a clinical study and a large multisite trial of digital CBT.

Compensation
Due to COVID-19, focus groups will be remote. Remote focus group participants will receive a $30 grub hub gift card in lieu of food provided at in person focus groups.
If randomized to one of the intervention arms, participants will receive compensation in the form of $50 for the baseline assessment and starting the CBT program. Then participants will be compensated $50 for completion of the 1-month follow-up assessment period for a total up to $100. Also, travel and parking reimbursement may be received for the amount of $10 for each study-related visit, if applicable.

5.6 RECRUITMENT PLAN FOR PROSPECTIVE STUDIES

Review of study enrollment accuracy will be collected twice weekly by research staff and evaluated quarterly by the principal investigator.

The principal investigator, collaborators, 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. There will be an evaluation of the progress of the research study, including assessments of data quality, time lines, participant recruitment, accrual, and retention. If recruitment is below 50% of projected within the first 3 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.

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

Each of the 40 participants recruited will be asked to complete one of two CBT programs through a digital mobile app. Participants will only have access to the content within their assigned program.

Both programs will provide users with brief skill building modules and CBT and dialectical behavioral therapy techniques such as relaxation, behavioral activation, distress tolerance, cognitive reframing, and mindfulness meditation, for depression and anxiety. However, one group will use standard engagement methods; the other group will focus on delivering CBT in a culturally sensitive manner specific to African Americans.

6.1.2 ADMINISTRATION AND/OR DOSING

For at least 4 weeks, participants will engage in one of two CBT programs administered through a digital mobile app. Participants will be asked to interact with their assigned program at least once per week, if not more. Both programs will provide participants with brief 5-10 minute skill building modules. In addition to the app-delivered content, participants will also receive weekly (more frequent if requested or needed) follow-up with a health coach. Health coach sessions will reinforce CBT contnet and encourage participant completion of modules for at least 4 weeks.

All participants will complete short surveys each week they are in the study. These surveys will be sent to their mobile phone as a web URL link. Each week, participants will complete a depression (PHQ-9) and anxiety (GAD7) symptoms questionnaire. At 1 and 4 weeks only, participants will also complete measures of Self-efficacy (SCSES), stigma, pain interference (PROMIS), and quality of life (ASCQ-ME).

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. No new content will be implemented without consensus of the core Pitt and UPMC Health Plan investigators. 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.

For Health Coach Training see the Health Coach Protocol in the electronic binder.

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.

Reduce the potential for bias. 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.

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), digital interventions often experience high attrition over time with few participants completing all assigned modules. 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.

Quarterly assessments will be made of data quality and timeliness, participant recruitment, accrual and retention, participant risk/benefit ratio, protection of confidentiality of information, and any other factors that affect the study. The IRB will be informed immediately on a case by case basis, of any adverse outcomes, while requests for modifications of the protocol will be submitted to the IRB on a quarterly basis. Confidentiality of the data and the results of monitoring will be protected.

Parameters to be Monitored. The following progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

- An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data.
- A review of collected data (including adverse events, unanticipated problems, andsubject 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.
- An assessment of external factors or relevant information (e.g., pertinent scientificliterature reports or therapeutic development, results of related studies) that may have an impact on the safety and study participants or the ethics of the research study.
- A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

The principal investigator will 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 investigator 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

Throughout the course of the research the principal investigator will review 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

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 study, participants are encouraged to have weekly check-ins with health coaches. This can be in the form of a message via the health app where there is at least one response from the participant. Failure to check in with health coach will not affect enrollment in the study; however, health coaches will reach out per the health coach protocol to solicit a 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.). Each week, participants will complete a depression (PHQ-9) and anxiety (GAD7) symptoms questionnaire. At 1 and 4 weeks only, participants will also complete measures of Self-efficacy (SCSES), stigma, pain interference (PROMIS), and quality of life (ASCQ-ME).

Completion of the questionnaires is a required component of the study. Not completing questionnaires within 2 weeks of the 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.

8 STATISTICAL CONSIDERATIONS

8.1 SAMPLE SIZE DETERMINATION

We anticipate randomizing, in an equal allocation ratio, a total of 40 participants with follow-up through at least 4 weeks, which will be the main time point for primary analysis.

For the primary test of engagement comparing standard vs. adapted digital CBT, the power calculation is based on the comparison of intervention groups for the main outcome of difference in usage days modules completed. Based on prior data (see preliminary data - Digital CBT in Medical Clinics), we would expect 50% less engagement for African Americans vs whites with our standard digital CBT app. Thus, to detect a 150% improvement in engagement related to adapted vs standard CBT for usage days (e.g 20 vs 10 usage days), with 80% power, a total of N=34 (n=17 per arm) is necessary. We are accounting for 10% attrition at 4 weeks.

8.2 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.

8.3 STATISTICAL ANALYSES

8.3.1 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.

8.3.2 ANALYSIS OF THE PRIMARY AND SECONDARY ENDPOINT(S)

Primary and Secondary Analyses. We will employ linear regression models for the primary outcome of usage days and the secondary outcome of techniques and sessions completed (Hypothesis 1) as a function of study arm (standard CBT vs. adapted CBT). We will account for multiple observations for each participant by including a random effect for subject. Additionally, baseline variables with clinically meaningful between-arm differences will be included as covariates.

Process evaluation. Change scores, baseline to 4 weeks, perceived stigma, relevance, relatability, will be tested as potential mediating variables. Contrasts will be estimated to assess the impact of standard and adapted CBT intervention on 4-week differences in perceived relevance, relatability, and stigma. We will then test whether lower perceived mental health

stigma and higher perceived program representativeness and relevance in the adapted CBT arm, mediates any observed group differences in engagement and program satisfaction.

8.3.4 PLANNED INTERIM ANALYSES

N/A. Analysis will be conducted at the end of week 4 after the study is complete.

8.3.5 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.

8.3.6 SUB-GROUP ANALYSES

Planned sensitivity analyses to determine the impact of key assumptions. 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[94]), digital interventions often experience high attrition over time with few participants completing all assigned modules.[95] We will track the reasons for non-completion 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. Sensitivity to this assumption can be determined by comparing analysis by three levels of participation in the intervention: enrollment and intervention assignment (Intent-to-Treat), participation in at least half the intervention, and zero participation in the intervention. Propensity score methods could also be used to deal with missing data. We will also test for differences in retention by recruitment site (e.g., community vs. clinical).

The comparative effectiveness trial with two active arms might show that both interventions work moderately well, which means there might not be superiority for the entire population. One intervention might be more suitable for certain subgroups of patients, so our Aim 2 analysis of primary and secondary outcomes by mental health subgroup should provide valuable information on suitability of the intervention for different subgroups.

8.3.9 EXPLORATORY ANALYSES

Due to limited power, evaluation of secondary outcomes will only be exploratory. Linear mixed models will account for change in outcomes over time. Depression (PHQ-9) will be modeled as a function of time, study arm, and time-by-study arm interaction. We will account for multiple

observations for participant by including a random effect for subject. As a secondary investigation, we will test group differences in pain intensity using a similar strategy.

Medical record review will be performed at 12 months post participation. Healthcare utilization 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 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 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).

This 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 trial data capture system. Any deviations from the protocol must be explained and documented by the investigator.

The co-principal investigators areresponsible 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.

9.1.1 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 via any mobile device. 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.

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. 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.
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.

9.1.2 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.

9.1.3 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.

University of Pittsburgh

Center for Research on Health Care

Consent to Participate in a Research Study

Title:	**Designing an Implementation Strategy for Delivering Routine Mental Health Screening and Treatment for Adolescents and Adults with Sickle Cell Disease**
Principal Investigator:	Charles Jonassaint, PHD, MHS. Assistant Professor of Medicine University of Pittsburgh, Suite 600, 230 McKee Place Pittsburgh, PA 15213, Tel: (412) 586-6850
Source of Support	National Institute of Mental Health

INTRODUCTION

Why is this research being done?

We want to see how to improve mental health for adolescents and young adults (AYAs) living with sickle cell disease (SCD). As part of this study, we will be adapting an existing, smartphone-based, mental health program, to make it fit the needs of AYAs with SCD. To accomplish this we will have meetings with patients, family members, and SCD providers, to better understand how we can make mental health care, delivered through a smartphone, work for the sickle cell community. What we learn from these meetings will inform how we adapt the smartphone app and mental health program. We will next test whether the new, adapted app and mental health program are more engaging and helpful to AYAs with SCD than the original app and mental health program that were not designed with SCD in mind. To accomplish this comparison test, 40 adolescents and young adults (age 16-35) who have SCD and elevated symptoms of depression and/or anxiety symptoms will be randomly selected to either receive the adapted mental health program or the original, “off the shelf” mental health program.

Who is being asked to take part in this research study?

All adolescent and young adult patients (age 16-35) with sickle cell disease receiving treatment at the Pediatric and Adult Sickle Cell Disease Clinics at UPMC are being asked to participate. All participants will complete some short questionnaires that measure emotional and physical health. From this group, we will be asking at least 40 AYA with depression and/or anxiety to enroll in the intervention portion of this study. The interventions programs are both based on cognitive behavioral therapy (CBT), which aims to help individuals better manage stress through changing negative thoughts and emotions. Participants will test either one of the two electronic interventions: adapted CBT for SCD or original CBT. To qualify, patients be between 16 and 35 years of age, have a diagnosis of SCD (any genotype) and report significant depression or anxiety symptoms (i.e., Patient Health Questionnaire [PHQ-9] or Generalized Anxiety Disorder Scale [GAD-7] 5).

How long will I be in the study?

Your total participation in this study will be as long as 4 weeks. You can decide to stop participating in the study at any time regardless of your eligibility for the intervention arm or whichever portion of the study you take part in. The study doctor may take you off the study if any of the following occur:

- You are not able to follow all the study-related instructions
- The study is not in your best interest or is stopped

What procedures will be performed if you participate in this study?

You will complete a short set of questionnaires to assess depression, anxiety, and the influence of SCD on various areas of your life, such as your emotional and physical health. Eligibility to take part in the study is based on the initial visit (screening visit). If you are eligible and decide to participate in the intervention portion of this study, we will randomize you (like pulling names from a hat) to receive either the adapted CBT for SCD or the original program. Whichever group you are in, you will receive your usual medical care while you are in the study. Participating in the intervention portion of the study is completely voluntary.

If you are eligible for the study intervention arm and you choose to participate, you will be randomized into one of the mental health CBT programs. Twenty patients will be enrolled into the CBT program adapted for SCD and twenty patients will be enrolled into the original program. Neither you nor your doctor nor any member of the research team can determine which program you are assigned to, a computer program makes the assignment randomly.

What is the intervention?

In addition to receiving usual care, you will be registered to a digital mental health program and asked to use a smartphone to complete CBT modules through an app. The app will teach you how to better manage stress using cognitive behavioral therapy techniques. This approach involves changing your thoughts and behaviors so you can limit the negative impact of stress on your life. You will have access to these sessions for the 4 weeks that you are participating in the study. You are encouraged to use the CBT program as frequently and as long as needed, within the 4-week timeframe of the study. In addition to the smartphone app, you will also have a "health coach," a person who will help you practice the skills you are learning and apply these skills in your everyday life. At the start of the study, your health coach will reach out via phone to get to know you and ask about your goals. After that, your health coach will message you in the app, as frequently as is needed to help you reach your goals. Each week, you will be sent questions in the app that will be used to track your depression and/or anxiety symptoms as well as your pain. When you finish the study, we will ask you to complete questionnaires to tell us how helpful the CBT program and the health coach were.

Mobile phone app and assessments

You will use your own mobile phone for the study. A member of the study team can be available by phone or in some circumstances, in person, to help you access and navigate the program via your smartphone and get you registered. Over the course of the study, you will use your smartphone to access your assigned CBT program. We will be using information directly from the app to better understand each program. Information includes (but will not be limited to):

- How often the app is accessed
- The number and type of modules completed
- Messages sent between you and your health coach (these messages will be de-identified to protect your privacy)

At the end of the 4 weeks, you will be asked to complete follow-up questionnaires. You will be able to access these on your smartphone. We will send you the link and remind you when it is time to complete these questionnaires.

Intervention Arm Study Diagram

Qualitative Interviews

The investigator, along with a study staff person, will conduct individual and group interviews with patients who have been enrolled in this study. Qualitative interview questions will include (but will not be limited to): What did you like about the intervention program? What did you not like? Tell me about your experience working with the therapists or health coach? How could they improve the quality of care you received? How was the program helpful or not helpful for addressing your distress and pain

symptoms?

The interviews will be conducted in person or over the phone. The results of the interviews will be used to help us understand the attitudes of patients towards the interventions, the health coach support, and how useful the interventions are to patients and families. We will use this information to fine-tune the programs.

The qualitative portion of the study is completely voluntary. You can complete the study without it. If you are asked to participate it is your choice whether you would like to take part.

What are the possible risks, side effects, and discomforts of this research study?
Although this is a low-risk study, you should be aware of the possible risks that may arise in this study. They include the potential for a breach of confidentiality, and the possibility that you may feel uncomfortable, anxious, or embarrassed discussing personal matters.

The discussion of personal problems can occasionally be stressful, uncomfortable, or embarrassing to some people. You are not obligated to answer any questions or perform any tasks that make you uncomfortable. Furthermore, you may choose to stop being part of our study at any time.

No experimental medications, placebos (sugar pills) or medical devices are involved in this study. Any pain medications that you may receive will be prescribed by your physician(s) and taken under your physician's direction, as we will neither prescribe, nor provide you with, any pain medications.

Because your information is being used in this research study, there is a risk that information could be accessed by people other than members of this research team. Breaches in confidentiality involving medical information could impact future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or result in stigmatization. To minimize these risks, all of the information collected and used for this research will be stored in a locked cabinet in a locked office or on a secure, password-protected database, which will not be accessible to anyone other than our research team.

This study uses mobile devices to collect data over the Internet. Although every reasonable effort has been taken, confidentiality during Internet communication activities 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.

Text and email messages sent to you from the research team are not secure and can be read by someone viewing your device. To protect your privacy, messages and emails sent for study purposes will not contain any protected health information, sensitive subject material (e.g. health diagnosis), or personal identifiers. You should not send sensitive information to anyone on the research team over text or email. If there is something sensitive that needs to be shared, you can message your health coach in the mobile app or request a phone call with the study Principal Investigator.

What are possible benefits from taking part in this study?
There is no guarantee you personally will receive any benefit from being in this study. However, by completing this study you will be helping researchers understand the impact of online treatment strategies, and in the future, that may improve the care of sickle cell patients like you.

What treatments or procedures are available to me if I decide not to take part in this research study?
You and your doctor may decide to treat your condition with counseling, medications, and/or referral to a behavioral health specialist, all in accordance with your health care coverage.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
If new information, either good or bad, about this treatment develops during the course of this study which may cause you to change your mind about continuing in this research study, we will notify you promptly.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?
None of the procedures you receive during this research study (study-related psychotherapy, interviews, and psychiatric assessments for either CBT program) will be billed to you or your health insurance. If you get a bill or believe your health insurance has been billed for something that is part of the study, notify a member of the research team. Any evaluations or drug treatments that are not part of this study will be your responsibility. The principle investigator or other members of the research team can give you more information about this.

Who will pay if I am injured as a result of taking part in this study?
If you believe that you are injured as a result of the research procedures performed, we request that you contact the study's Principal Investigator, Dr. Jonassaint, whose contact information is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If you have a research-related injury that requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

Will I be paid if I take part in this research study?
If you participate in a focus group, you will be provided food in the form of a $30 Grub Hub gift card.

If you are randomized to one of the intervention arms you will receive compensation in the form of $50 for the baseline assessment and starting the CBT program. Then you will be compensated $50 for completion of the 1-month follow-up assessment period for a total up to $100. Also, you may receive travel and parking reimbursement for the amount of $10 for each study-related visit, if applicable.

All compensation is taxable income to the participant regardless of the amount. If a participant receives $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 28% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 72% of the expected payment.

Who will know about my participation in this research study?
To protect your privacy and maintain the confidentiality of information we obtain from you and from your medical records, all electronic records will be stored in password-protected files. On these records, we will identify you by a case number rather than by your name, and the code linking your name to the case number will be maintained separately with very limited access to research team members.

Will this research study involve the use or disclosure of my identifiable medical information?
We are also requesting your authorization or permission to review your past, present and/or future medical information from your hospital and/or other (e.g., physician office) records. Specifically, we will review your medical diagnoses, number/type of prescribed pain medications, number of scripts written 12 months before and 12 months after intervention, number of ED visits, hospitalizations and standard care visits and quality of life and care measures. This information will inform us on who benefits the most from the program. No information/data that is collected exclusively as part of this research study will be placed in the medical records. However, if the study staff become concerned for your health, they may contact your referring physician and this information may be recorded in your medical record.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a

summary of the results. You can search this website at any time.

Who will have access to identifiable information related to my participation in this research study?
In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

- Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

- Authorized representatives of the sponsor of this research study will review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.

- This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

- There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

- Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, UPMC and University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor. The investigators involved in the conduct of this research study may receive funding from the sponsor to perform the research procedures and to provide the sponsor with identifiable research and medical information related to your participation in the study.

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?
The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for an indefinite period of time. This authorization is valid for an indefinite period of time.

Additionally, if all information that identifies you is removed from the research data, your remaining research data could then be used for future research studies or distributed to another investigator for future studies without additional informed consent being obtained.

May I have access to my medical information that results from my participation in this research study?
In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

Is my participation in this research study voluntary?
Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. However, if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study. Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will also have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

May I withdraw, at a future date, my consent for participation in this research study?
You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.
To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to Dr. Jonassaint, the Principal Investigator of this research study at the address listed on the first page of this form. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh, or on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

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VOLUNTARY CONSENT (FOR PARTICIPANTS AGE 18 YEARS OR GREATER)
The above information has been explained to me and all of my current questions have been

answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified member of the research team or by Dr. Jonassaint (412.586.6850). I understand that I may always request that my questions, concerns or complaints be addressed to Dr. Jonassaint. At any time I may also contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1.866.212.2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. **By signing this form I agree to participate in this research study, and allow the use and disclosure of my medical record information for the purposes described above.** A copy of this consent form will be given to me.

_____
Print Name of Participant

_____ _____
Participant's Signature Date / Time

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CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date / Time

PARENTAL PERMISSION (For children ages 16-17 or children less than 17 who are developmentally able to sign his/her name when verbal assent is obtained from the child**)**

All the above has been explained to me and all my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research during my participation, and that such future questions will be answered by the researchers listed on the first page of this form. I understand that I may always request that my questions, concerns or complaints be addressed by the listed investigators.

If I have any questions about my rights as a research participant, or if I wish to talk to someone other than the research team, I may call the University of Pittsburgh Human Subjects Protection Advocate toll-free at 866-212-2668. A copy of this form will be provided to me/my child.

_____
Printed Name of Child-Subject

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study and provide my authorization to share his/her medical records with the research team.

_____ _____
Parent's or Guardian's Name (Print) Relationship to Participant (Child)

_____ _____
Parent or Guardian Signature Date

CERTIFICATION of INFORMED CONSENT
I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____
Name of Person Obtaining Consent (Print) Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date

CHILD ASSENT
This research has been explained to me, and I agree to participate.

_____ _____
Signature of Child-Subject Date

VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to (name of child) in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she provided affirmative agreement (i.e., assent) to participate in this research.

_____ _____
Signature of Person Obtaining Assent Date

THE BELOW ONLY NEEDS TO BE SIGNED IF THE SUBJECT IS A CHILD AND TURNS 18.

CONSENT FOR CONTINUED RESEARCH PARTICIPATION

I understand that I am currently participating in a research study. I further understand that consent for my participation in this research study was initially obtained from one of my parents/my authorized representative as a result of my inability to provide direct consent at the time that this initial consent was requested. I have now reached the age of 18 and I am able to provide direct consent for continued participation in this research study.

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given.

I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. By signing this form I agree to continued participation in this research study.

By signing below, I agree to continue my participation in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Name of Person Obtaining Consent (Print) Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date