PROTOCOL TITLE:

Self-Management for Families and Youth Living with Sickle Cell Disease - SMYLS

PRINICIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

Specific Aims: Few family-centered self-management interventions exist to assist children with sickle cell disease (SCD) and their families, which deprive this population of skills that may improve symptom management and quality of life. SCD is an inherited complex chronic condition (CCC) that leads to adverse health outcomes such as pain and organ damage affecting approximately 100,000 people in the US. In addition to living with pain and negative health outcomes, children and adults with SCD also face disparities in access to care. Infants and young children with more complicated CCCs, such as SCD, and those who have fewer resources are at greater risk for adverse outcomes such as increased hospital and emergency department (ED) utilization and physical and psychosocial morbidity. Children with SCD and their families, particularly those who are underserved, would benefit from interventions designed to bolster self-management skills and enhance preventive management of the disease to reduce negative complications. Importantly, caregivers of young children with SCD are often new to the disease process and have unique needs and challenges.

Interventions designed to address the unique needs of and barriers encountered by this population could improve effective management of the disease in the home setting. In addition, technology-based resources such as mobile health applications for symptom tracking, may allow intervention delivery to typically difficult-to-reach populations, thereby reducing access barriers to care, including lack of transportation and obtaining childcare. Further, incorporating theory-based family-centered self-management strategies is crucial to support families in developing sustainable, improved self-management behaviors (e.g. monitoring symptoms, and attending clinic appointments) which will ultimately improve symptom management (e.g. pain, fatigue) and quality of life, and decrease costly emergency department (ED) visits and hospitalizations.

The interprofessional team of investigators for this study includes a mentee (Phillips) with a clinical background as a pediatric acute care nurse and research experience with exploring barriers in access to care among children with CCC. Mentors include an R01 funded nurse scientist who is an expert in intervention development and the conduct of clinical trials (Kelechi: primary mentor), an R01 funded clinical psychologist with extensive expertise in technology, user-based design, and intervention adaptation (Ruggiero: co-mentor), a pediatric hematologist/oncologist specializing in clinical care and research with populations with SCD (Kanter: co-mentor), and a biostatistician with extensive research experience (Mueller: co-mentor). This complementary interdisciplinary team has the knowledge, skills, and access to the population to successfully conduct this study, but will also provide the mentee with mentorship and training experiences in theory-based, technology-enhanced intervention research among a population of children with a CCC and their caregivers.

The purpose of this second phase of this study is to conduct feasibility testing of an innovative, technology-based intervention to improve self-management behavior, quality of life, and symptom management (SMYLS) in a sample of children with SCD and their families. Three components are included in the intervention: previously tested educational materials for adults with SCD and their families, a publicly available mHealth application for tracking pain in SCD, and a model of patient-provider communication delivered via mHealth that has been tested with older children with SCD. The goal of the proposed research is to use the theory-based Pediatric Self-Management Model to tailor and pilot test the effect of an integrated intervention on psychosocial and physical symptom management and quality of life for children with SCD ages 8-17 years and their caregivers.

During this second phase of this study, we seek to achieve the following aims:

Primary aim of the study is to: *Assess feasibility of implementation processes including reach, enrollment, fidelity, adoption, acceptability, and satisfaction using the RE-AIM framework with process measures, surveys, and key informant interviews.*

Secondary Aim: Investigate the presence of signals of efficacy on measures of self-management, and physical and psychological symptoms and quality of life.

2.0 Background

Importance of the problem. The significance of this project lies in the fact that it is the first step (adaptation and feasibility testing) in a research continuum that will lead to validation of a technology-based intervention for improving self-management, symptom management, health care utilization and ultimately quality of life among populations of children with complex chronic conditions (CCC) and their caregivers.

Sickle cell disease (SCD) is a highly complex and challenging chronic disorder that negatively influences quality of life in children and families of those with the disorder.[1] SCD is a hereditary CCC that almost exclusively affects African Americans. Nationwide, an estimated 72,000 to 98,000 individuals have SCD; >90% of these are African American.[2] Symptoms of SCD often occur within the first year of life and require lifelong preventive management. SCD is a hemoglobinopathy characterized by an altering in the shape of red blood cells in response to hypoxia, stress, or acidosis.[3,4] These abnormally shaped cells occlude small vessels and cause inflammation, pain, infarction, and ultimately, organ damage.[3,4] The physiological sequelae of SCD lead to high health care needs and utilization, and often, to comorbidities and early death.[5,6] Many children with CCC, particularly SCD, and their families have high health care needs that are frequently unmet or inadequately met. SCD is one of several CCCs affecting children that could benefit from improved self and family management care, such as epilepsy, cerebral palsy, and chronic respiratory disease.[7,8]

SCD as a CCC based in health disparity. Because children with SCD and their families have high health care and "other" needs that endure throughout their lifetime, preventive actions are necessary in early childhood to avoid or mitigate adverse effects of the disease process. For optimal management and minimal adverse effects, persons with SCD and/or caregivers must coordinate appointments with various providers, continuously monitor symptoms, and obtain preventive home therapies. Often, challenges are pronounced early in the disease process as caregivers learn about the disease and treatments. Typically, a multidisciplinary team is established and caregivers learn to coordinate and maintain care. However, SCD primarily affects an underserved population (i.e., African Americans) who disproportionately face barriers such as transportation, obtaining childcare, and taking time from work. In fact, low-income children with SCD have significantly higher hospitalizations and ED visits than other children in general.[9]

Methods to enhance self-care of SCD by affected individual and the family are needed. Self-care interventions to prevent adverse effects of the disease process have not been well implemented for children with SCD. Fortunately, assistance with providing reliable sources of disease and treatment related information, decision-making, and communication with the care team via technology improve family-centered self-management behaviors in older children (ages 10-17 years) with SCD.[10] Assisting families caring for an infant or young child with SCD via a similar technology-based model may lead to improved self-management and quality of life outcomes. Providing resources via this mechanism may reduce burden and maximize outreach to this difficult to reach, underserved, high needs population. Traditional barriers to care such as transportation, childcare, and work conflicts can be overcome. Long-term management of SCD and prevention of adverse outcomes also requires support for self-management skill development. Through technological resources and collaborative relationships with providers, caregivers can receive support to develop self-management skills.

Technology-based self-management has the potential to address barriers. Use of a technology-based intervention that has been tailored to meet child/adolescent/caregiver-reported needs is expected to increase engagement and reach of self-management strategies. Our technology-based intervention (a **s**elf-**m**anagement program for **y**outh **l**iving with **s**ickle cell disease - SMYLS) consists of three components: previously tested electronic educational materials on the SCD process and management; a publicly available, web-based, mHealth application for SCD pain monitoring and tracking; and a previously-tested model of patient-provider communication delivered via mHealth communication with a provider with expertise in SCD. Innovative delivery of coaching and support

provided by the provider through messaging is also expected to increase self-management behaviors and lead to improved health outcomes. By delivering messages, information can be personalized to aid in learning about pain, symptom management, and preventive care.

Theoretical Framework. The Pediatric Self-Management Framework[7] guides the present study and provides an ideal underpinning to our proposed methods because it outlines multilevel influences that affect self-management and family-centered self-management behaviors through multiple processes, and guides prediction of the outcomes associated with influences, behaviors, and processes. According to this framework, self-management influences, processes, and behaviors exist on the individual, family, community, and health care system domains. Because this study will focus on children ages 8- 17 years and their caregivers, and on the caregiver-provider relationship, we will target the family and health care system domains. Specific influences, processes, and behaviors addressed in this study are outlined in Table 1.

Table 1: Intervention Self-Management Influences, Processes, and Behaviors

Self-management Influences	Self-management Processes	Self-management Behaviors
• Family disease and treatment knowledge • Parental monitoring and supervision • Parental involvement • Patient (parental)-provider communication	• Determining child's health care needs • Communication with medical team • Seeking disease and treatment related information • Determining child's health care needs • Allocation of treatment responsibility • Learning about patient's disease and treatments • Provision of support for treatment regimens • Modification of communication styles • Shared decision making	• Giving medication and treatments such as home physical and respiratory therapy • Attending clinic appointments • Monitoring and tracking symptoms • Introducing and supporting lifestyle modifications • Providing recommended therapies

This is Phase II of the overall study. During Phase I, we refined the development and design of the intervention, by conducting user focus groups and pilot testing the app among a target population of users. Now, in Phase II, we aim to deploy the intervention in a real-world settin3.0 **Intervention to be studied**

The intervention is a multicomponent (3-part) technology-based package. The intervention targets influences and processes informed by the Pediatric Self-Management framework (Table 1). Component 1 (education) consists of continuous access to directed educational resources on the SCD process, treatment, home management strategies, symptom prevention and management strategies. These materials are easily accessible via a mobile device given to caregivers and children (8-17 years) and will include patient-centered PDF files and links to websites developed and tested by authoritative sources. An example includes the patient education materials provided by NIH NHLBI such as the Sickle Cell Disease Infographic: Monitoring Pain (Figure 1). To address potential literacy barriers, an

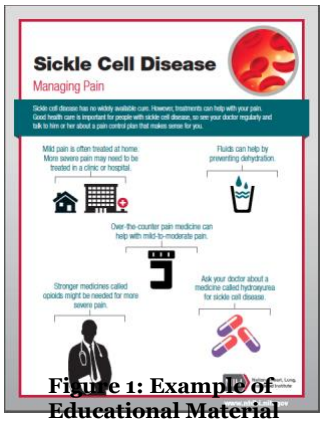

Figure 1: Example of Educational Material

application that reads PDF files aloud (e.g. @Voice Aloud Reader) is downloaded onto devices. Component 2 (symptom monitoring and tracking) consists of a mobile-device based publicly available application for tracking and monitoring pain in SCD that also permits upload of symptom logs and text alerts to a health care provider (Voice Crisis Alert). Component 3 (caregiver-provider communication) is based on Jacob et al. (2013)'s intervention with an mHealth intervention for older children with SCD. This component consists of a technology-based connection with a provider who will: respond to alerts delivered via the mHealth application, monitor pain symptoms delivered via the mHealth application, and respond to messages. A provider at the MUSC Pediatric Sickle Cell Clinic will collaborate with caregivers to coach caregivers on the care of the child and provide support to the caregiver.[10] Caregivers will receive a daily message using a semi-structured protocol to "check in" with participants and promote engagement. All components are integrated into the web-based app. A secure portal is in place for messaging that encrypts all messages and protects confidentiality.

Children (8-17) with SCD and their caregivers will complete self-report and proxy assessments as described in Table 1 below; data will be recorded in REDCap by the PI or project coordinator

Major tasks and domains	**Measures/instruments/ questions and Cronbach's alpha ( )**	**Data sources and time points**
Demographics/clinical characteristics	Age, child age, health history, race/ethnicity, medications, health care utilization, rural/urban residence, insurance, caregiver demographics, family characteristics	Caregiver interview; baseline
Reach: Sample Recruitment	Monitoring of sample representativeness; types of recruitment activities; rates of recruitment; % eligible, consented, provided with informational session	Recruitment tracking forms; quality checks by PI; weekly meetings with mentor, clinic staff, and research team
Efficacy: <u>Child (by proxy):</u> Pain Fatigue Quality of life <u>Caregiver:</u> Fatigue Emotional distress: anxiety Emotional distress: depressive symptoms <u>Measures of self-management behaviors:</u> Monitoring and tracking symptoms Attending clinic appointments Administering home medications and treatments	PROMIS Parent Proxy: Pain Interference*[21,22](age 5 and older) Self-efficacy SEMCD-6 PedsQL with Sickle Cell Disease Module (proxy = 0.97)[23] (age 2 and older) PedsQL Multidimensional Fatigue Scale in Sickle Cell Disease (proxy = 0.95)[24] (age 2 and older), PROMIS Fatigue SF, Depression SF (>0.9)[25] PROMIS Emotional Distress: Anxiety (0.97)[26] PROMIS Emotional Distress: Depressive symptoms SF (0.97)[27] Daily pain severity rating; daily pain type rating # days recorded symptoms; # days and types of recorded treatments; # scheduled clinic appointments attended; # days daily mediation administered; # days PRN medications administered	Review and content analysis of transcriptions of text messages; review and content analysis of recorded teleconferences; tracking forms; fidelity checklist; transmissions from web-based application to nurse; post-intervention interviews; weekly meeting with mentor, clinic staff, and research team; baseline, mid-intervention, post-intervention, 3-months post-intervention
Adoption: Adherence Acceptability Education	# days symptoms recorded; # times educational component accessed; length of time in minutes educational component accessed; # text messages and videoconferences with nurse Caregiver satisfaction; # problems reported; types of problems reported # times accessed educational materials; length of time in minutes educational materials accessed # days recorded symptoms; # contacts (text or videoconferencing) with nurse pertaining to symptoms	Tracking forms; content analysis from text messages and videoconferences with nurse, data transmitted from web-based application; fidelity checklist; weekly meetings with mentor and research team; caregiver interview at end of study

Symptom monitoring and tracking Patient-provider communication	# and type (screening, referring, coaching, supporting) of contacts (text or videoconferencing) with nurse Collaborate for Parents	
Implementation: Technology Consistency of intervention	# problems encountered with mobile device, # problems reported to research staff; types of problems reported instructional session conducted as planned; fidelity to protocol maintained MAPS	Tracking forms; weekly meeting with mentor and research team; caregiver interview at end of study
Maintenance: Projection of future adoption	# caregivers who would continue intervention; caregiver perception of the intervention; feasibility of nurse role	Caregiver interview at end of study; weekly meetings with mentor, clinic staff, and team

4.0 Study Endpoints

Study end points include: Successful study completions, Consent withdrawals, PI terminations, Lost contact with the patient, and unexpected adverse events.

5.0 Inclusion and Exclusion Criteria/ Study Population

- Eligible caregiver/child dyads will be identified through the staff at the MUSC Pediatric Sickle Cell Clinic. After receiving permission to approach, PI or PC will screen the potential participants against the inclusion and exclusion criteria. Screening will be documented in REDCap.

Inclusion Criteria

- Children ages 8 - 17 years and parent or primary caregiver 18 years of age or older
- Child with sickle cell disease, as reported by clinician at the MUSC Pediatric Sickle Cell Clinic

Exclusion Criteria

- Parent/caregiver or child with cognitive disability or delay that precludes ability to participate
- Lack of Wi-Fi access

Inclusion of Women and Minorities

Both women and minorities will be included in the proposed study. Women are more often than men reported to be the primary caregiver of children with chronic conditions and approximately 66% of caregivers of adults with chronic illness are women. Therefore, it is anticipated that more women will be recruited as participants than men. In addition, SCD occurs almost exclusively in African Americans; therefore, it is anticipated that all or nearly all of the caregiver participants will be African American.

Inclusion of Children

Children without cognitive delay ages between the ages of 8-17 years will be included as part of the child/caregiver dyad.

6.0 Number of Subjects

N=60 – 30 caregivers of 30 children (8-17 years) with SCD will be recruited.

7.0 Setting

- The intervention will be used by the participants in their community environments. Study visits will occur at MUSC Sickle Cell Unit and via telephone to the participant's home.

8.0 Recruitment Methods

- Parents/caregivers who participated in Phase I of the study and agreed to be re-contacted for future research will be contacted and invited to participate.
- For other potential participants, the MUSC Pediatric Sickle Cell Clinic staff will be given the inclusion/exclusion criteria and will be asked to identify eligible participants in the clinic. When potentially eligible participants attend an appointment at the clinic, the clinician/staff will approach the parent/caregiver, briefly introduce the study through an IRB approved study letter, and if interested ask if the researchers can speak with the parent/caregiver to offer additional information. For parents/caregivers who agree, the PI or PC will provide an overview of the study either by phone or face-to-face in the clinic and conduct eligibility screening. Eligible and interested parents/caregivers will proceed to the informed consent interview.
- Additionally, for the purposes of this study and in direct alignment with the mission of the CON P20 Symptom Self-Management Center, we will employ the use of MUSC Bioinformatics Center (BMIC) core services to identify and recruit patients across the MUSC Enterprise that meet the study inclusion/exclusion criteria and that have granted authorized research contact permission in MyChart through the electronic 'opt in' EPIC designation. Once these potentially eligible patients are identified, we will then contact them by telephone using a script to determine if they are interested in study participation
- Flyers will be posted in the waiting room and patient rooms at the MUSC Sickle Cell Clinic. The flyers will include the PI's contact information; interested parents/caregivers who call the PI will be screened for eligibility.

9.0 Consent Process

Since research will be conducted with caregiver/child dyads, consent will be obtained from the parent/caregiver and written assent from the child participant (12-17 years). In this study, we will employ the use of two informed consenting strategies (In-person meeting and electronically through REDCap e-Consent) so as to increase the reach of the study and to promote the generalizability of findings.

In-Person informed consent will occur in the comfort and safety of a private clinic room at the MUSC Sickle Cell Unit prior to any screening procedures being conducted and/or data collection. Potential participants will be given the informed consent document to read and review in advance, and/or may have it read to them by the researchers if they prefer. After reviewing the Consent document, both caregiver and child will be given the opportunity to ask any questions about the study that they may have, and will be requested to demonstrate what is expected from them should they enroll in the study through a questioning of their understanding of study procedures and risks. Prior to consenting, all questions will be resolved to the caregiver and child's satisfaction. If a participant does not appear to understand the information contained within the Consent document, the study coordinator will review the consent document again with the participant. If after this second review, the subject does not demonstrate an understanding, they will not be enrolled in the study. Only participants, with no

diagnosed or observed cognitive impairment, will be consented and enrolled into the study.

Electronic or e-Consenting will be performed on eligible families that want to participate in the study but are unwilling for whatever reason and/or unable to come to MUSC for a face-to-face informed consent meeting. Families identified through the study recruitment processes that fall into this category will already have spoken with the researchers by telephone, have been introduced to the study and its demands, as well as had their initial questions answered. After speaking with the researchers, families that are further interested in study participation will be asked to provide an email address at which they will receive a REDCap survey link containing a scanned image of the currently approved Informed Consent document (developed from the MUSC REDCap e-consent template). Families will be able to take as much time as they like to read the consent document together in the comfort and privacy of their own home or at a place and time of their choosing. They will be provided with the telephone and email contact details in the survey instruction header for the researchers, should they have any questions before providing their consent by adding their respective signatures to the form and submitting it. Prior to providing their physical e-consent, the researchers will coordinate with these families; so as to be on the telephone and be available to further answer any questions that they may have during the e-consent process. Should a participant have any questions or concerns about the study, the researchers will address these issues to the best of their abilities and knowledge. Upon submitting the e-consent, a REDCap trigger will immediately notify the researchers, who will then provide their countersignature to the document.

The consent form will meet the requirements of the Code of Federal Regulations and the MUSC Institutional Review Board. The consent form will include the following:
1. The purpose, nature, and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. The name and a contact of the investigator(s) responsible for the protocol.
4. The right of the participant to accept or refuse study interactions and to withdraw from participation at any time.

The HIPPA authorization process will be conducted sequentially with the family in the same manner by the researchers. Participants will be able to download a copy of their executed informed e-consent/HIPAA authorization forms directly to their own computer, or have copies emailed to them. They will also be given the option to have a copy of their executed e-forms mailed to them should they elect to do so. A copy of the executed e-consent/HIPAA authorization forms will also be stored in the participant's electronic case record for monitoring and audit purposes.

If a child participant should reach an age of majority while enrolled in the study, they will be asked to provide written consent.

10.0 Study Design / Methods

The mHealth SCD management intervention will be delivered via an app on both the caregiver and child mobile devices over a 12-week period. This multi-component, web-based app consists of 1.) continuous access to directed educational resources on the SCD process, treatment, home management strategies, symptom prevention and management strategies; 2.) a series of pages in the app that allow for tracking and monitoring symptoms; and 3.) child/caregiver – provider communication. The educational component is based on patient-centered materials that have been developed and tested by authoritative sources. In the app, educational materials are organized by user age (for individuals with SCD) or role for parents/caregivers. Citations are provided and links to the sources are included. The symptom tracking and monitoring component consists of a customizable avatar on which the user can record the location, severity, and characteristics of pain. Users can record other concurrent or associated symptoms (such as fatigue) and can view a graph

with the pain history. This portion of the app also includes a health history page on which users can document important clinical information, such as sickle cell type, last sickle cell crisis hospitalization, medications, and allergies. The child/caregiver – provider communication component consists of the ability for the child/caregiver to send a secure message to providers within the app to communicate pain and other symptoms. Providers will have the capability to securely send a reply within the app. In addition, children/caregivers can choose to receive a daily "support" message that will be automatically sent from a list of possible messages. All communication is encrypted and sent securely within the app via a portal. Two to three providers at the MUSC Sickle Cell Clinic will participate as the designated providers in the study.

To determine feasibility, we will apply the RE-AIM framework to assess the Reach, Efficacy, Adoption, Implementation, and Maintenance of the intervention with 30 children/caregiver dyads.[18] The domains are further explicated in Table 1. The intervention will be loaded onto the child's and caregiver's tablet or smartphone (Apple or Android); participants without a device will be provided one for the duration of the study. The PI or PC will deliver detailed verbal instructions to the participants on the use of the device and the intervention. Participants will also receive written instructions and a contact number for technical assistance if needed. Baseline measures (Table 1) will be collected during the same meeting. Participants will retain the devices and will participate in the intervention over a 12 week-period. At the end of the 12-week period, the PI will conduct a post-intervention meeting with each individual caregiver and child participant during which post-intervention data collected. Caregivers will also be asked to return the mobile device at the end of the study. The PI will meet with the study provider weekly during the intervention.

Retention: To improve retention, IRB-approved personnel will contact enrolled participants at 3-week intervals between data collection points. The timeline for these points of contact are at the following weeks post baseline data collection: weeks 3, 9, 15, 18, and 21. The purpose is to maintain contact with enrolled participants, not data collection. Correspondence will be logged in REDCap. Contact will take place via text message, using the number(s) provided to study personnel upon enrollment. Examples of messages are provided in an uploaded attachment.

Post-intervention interviews. All 30 caregivers and their children will be asked if they would like to participate in the 3-month post-intervention key informant interviews with the PI to obtain more in-depth data on accessibility, usability, and adherence to intervention. However, only a subset of 15 dyads will be chosen to participate. Selection will be by computer at random. Both caregiver and child will have to agree to participate in the interview to be eligible for selection. Dyads have a 50-50 chance of being randomly selected. Semi-structured interviews will be conducted using a qualitative descriptive approach,[17] will last approximately 45-60 minutes, and will be conducted according to an interview guide with open-ended questions and prompts. These interviews will be recorded for later nVivo qualitative data analysis. Reimbursement for dyads will be a $50 gift card provided at each of the 4 data collection points, with dyads in key informant interviews receiving an additional $40 gift card. All payments will be given to the caregiver. Selected caregivers will be given the option of having the interview conducted in-person in a private room at MUSC or by telephone in the comfort and safety of their own home.

Measures. Children (8-17 years) and Caregivers will complete age-appropriate self-report assessments at baseline, mid-intervention (6 weeks), post-intervention (12 weeks), and 3 months post-intervention as previously described. Self-report and proxy assessments will be collected during meetings between the PI or PC and the participant. Depending on participants' preference and availability visit 2, 3 and 4 surveys will be completed either by phone or electronically via REDCap survey or by paper and pencil. All data will be recorded in REDCap by the PC.

11.0 Specimen Collection and Banking

Not applicable

12.0 Data Management

Sample size considerations

The purpose of this study is to establish feasibility of implementing the integrated intervention obtain estimates of variability for the primary outcome measures and obtain preliminary indicators of effectiveness of the intervention rather than to confirm or refute hypotheses. Therefore, sample size considerations focus on precision of estimates. For this feasibility study, we project that we will be able to recruit 30 child/caregiver dyads. With such a sample we will be able to estimate outcome proportions for feasibility measures including recruitment and drop-out with precision ±0.11 to ±0.16 for values of the true proportion ranging from 0.10 to 0.30 (or correspondingly, from 0.70 to 0.90). Assuming a drop-out rate of up to 30%, 95% confidence limits can be estimated for impact measures, such as change from pre-to-post in quality of life for child and caregiver with a precision ranging from ±0.43 to ±1.35 corresponding to estimated standard deviations for change in quality of life scores ranging from 0.5 to 5.0 SD units.

Demographic and clinical variables obtained at baseline will be described via measures of central tendency (mean, median), variability and frequency distributions as appropriate. Additionally, demographic and clinical characteristics for those who adhered to the study protocol (study completers) versus those who did not adhere (non-adherers and drop-outs) will be compared to better describe the population for this study. For continuous quality of life measures for the child and caregiver the difference between pre and post intervention measurements will be estimated via 95% confidence intervals. To assess preliminary intervention effects, we will conduct repeated measures ANCOVA with symptom (pain) severity and type obtained daily as dependent variable in individual models adjusting for “dose” defined as number of times education module was accessed and total time spent in education modules.

Post-intervention qualitative analyses (Aim 2): Data collected from post-intervention key informant interviews will be analyzed using directed content analysis[19] and nVivo qualitative data analysis software version 11.[20] Consistent with the directed content analysis approach, initial coding categories are identified according to the guiding theoretical model, and for this study, will reflect the RE-AIM domains.

13.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

There is a well-developed and NIH/NINR prepared SRG approved DSMP that involves the use of a Safety Monitoring Committee (SMC) that shall meet semi-annually post initial study enrollment. The Committee is comprised of key individuals that include: an independent medical safety monitor (ISM), a biostatistician (BS), and the Program Manager (PM).

The following members of the study’s DSMC will perform data safety monitoring of the study:

- Dr. Cristina Lopez, Independent Safety Monitor (ISM) - primary responsibility
- Mr. Mohan Madisetti, MS, Project Manager (PM)
- Ms. Mary Dooley, Biostatistician (BS) - supervised by Dr. Martina Mueller.

Independent Safety Monitor (ISM), Dr. Lopez who is Assistant Professor at Medical University of South Carolina, has a PhD and a background as a clinical psychologist with expertise in adolescent behavioral research, and will act as the study’s Independent Safety Monitor (ISM). Dr. Lopez has no real or apparent conflict of interest that would affect her performance in this role on the study.

Project Manager, (PM). Mr. Madisetti, MS, has over 20 years of research experience in study management, quality assurance and the protection of human subjects. Mr. Madisetti is CTRC, CITI /GCP and NIH trained in Human Subject Protections, and has completed MUSC's Certificate of Competence in Research Ethics (CREP) and member of the Institute of Human Values Ethics Committee. Mr. Madisetti has also been a member of over 5 federally and FDA sponsored research full DSMBs.

Biostatistician (BS) Ms. Dooley is a biostatistician and faculty at the College of Nursing at the Medical University of South Carolina. Ms. Dooley has experience collaborating with investigators in clinical trials as well as in community based participatory research. Ms. Dooley will be supervised by Dr. Martina Mueller from the College of Nursing.

From the initial screening of subject by inclusion and exclusion criteria to the informed consent process to the provision of participant study instruction to staff training in Good Clinical Practices (GCP) and regulations pertaining to the Conduct of Human Subject Research to routine contact with participants to internal quality control audits and protocol fidelity monitoring to the real-time review of AE's by the SMC to the oversight of the IRB - procedures for monitoring study safety are consistently afforded throughout the study. Specific study procedures include:

- Participants will be screened for inclusion and exclusion per the protocol
- Participants will be fully informed as to all know risks and the possibility of risk from study participation in the informed consent process. These risks are minimal.
- Participants will be instructed to notify the researchers of any/all suspected or experienced adverse events whether they believe them to be related or not to the intervention.
- The PI or PC will track all reported participant AEs through to resolution.
- All investigators and researchers will maintain active CITI and GCP training.
- The PI or PC will maintain weekly contact with all participants to elicit information about AE's and to monitor participant study progress, compliance and safety.
- The PI or PC will review participants study logs for fidelity compliance with the intervention.
- The PI or PM will conduct quarterly internal quality control audit of all participant records to ensure compliance with MUSC IRB regulations; the PI and PC will work together to correct any errors.
- The BS shall generate semi-annual AE reports for the PI, SMC and IRB to review.
- The ISM will have access to real-time study data and will be able to provide immediate recommendations to the PI and PD.
- Investigator performance and compliance will be provided for through MUSC IRB and ORI study oversight.

Protecting Confidentiality of Participant Data

Participant Screening and Enrollment. All data from participants screened for the study will be entered into an electronic study database. Designated research staff will collect, gather, and enter required data (written informed consent, HIPAA Authorization, and demographics) onto study data forms. Screened patients who do not meet study eligibility will have specific screening data entered into the study database. The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include reason for exclusion. All dates will be shifted and other Personal Health Information (PHI) will be removed from the study database upon study completion. All data obtained from this study will be used for research purposes only and will comply with Federal HIPAA regulations. Master Screening and Enrollment Logs will be maintained by the PI or PD and will be used by the PI or PD to prepare reports on accrual and attrition for the ISM and SMC.

Case Report Forms. All proposed study specific case report forms (source documents) for data collection will be designed by the PI and, when possible, transferred by the PI or PC into electronic Case Report Forms (eCRFs) for use in the study's REDCap database. These study specific eCRFs source documents (study logs for correspondence, compensation and other forms such as pre-eligibility screens) will be coded by the participant's unique study ID# for all data collected including study instruments will be maintained in the participant research record. Completed instruments that require signature on a paper CRF will be scanned and uploaded into the study database to all for remote electronic safety monitoring as well as maintained on file in accordance with MUSC policies and applicable Federal Regulations for the Conduct of Human Participant Research.

Binders. The PI or PC will prepare and maintain a participant-specific binder for each participant containing all non-eCRFs records. A regulatory file will also be maintained to include the IRB-approved Protocol, original Informed Consent documents, HIPAA forms and other study-related regulatory documents. All paper research records and CRFs will be maintained in a locked file cabinet, stored in a room for research files that is accessible only via a password protected entry system that features security cameras, within the College of Nursing. Access to the research records, study database and PHI's will be restricted to study personnel as approved by the PI and MUSC IRB. As with all studies conducted at MUSC, this study is also eligible for a random audit by MUSC Office of Compliance.

Data Processing. This study will use Research Electronic Data Capture (REDCap) for data capture and management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The study-specific REDCap electronic database will be designed and developed by the PI or PD in concert with the BS. The provision of REDCap is made available through the South Carolina Clinical & Translational Research (SCTR) Institute at MUSC with NIH Grant awards UL1RR029882 and UL1TR000062.

Data Security. Ensuring data security, compliance with 45 CFR 46 and maintaining the integrity of PHI is a top priority. MUSC has Standard Operating Procedures (SOP) to ensure a high level of data security while coordinating electronic and paper data management activities for clinical research trials. The REDCap study database will be hosted in the Biomedical Informatics secure data center at MUSC, a secure environment for data systems and servers on campus, and includes firewall, redundancy, failover capability, backups and extensive security checks. The secure data center has strict access control; only authorized core personnel may access the facility un-escorted. Only authorized users are allowed to connect to the network, and the security of the network is actively monitored. Power and environmental controls have several layers of backups, from interruptible power supplies to alternate and redundant feeds to the local utility company. The REDCap system administrator contributes to the maintenance of institutional disaster recovery and business continuity plans. Load balancers and a highly fault tolerant SAN infrastructure contribute to high availability.

The REDCap system itself has several additional layers of protection including password protection. Access to the data and its security is managed institutionally by sponsored login IDs through a Shibboleth login with an MUSC issued NetID and features a user account management filter that controls who can access the data and to what degree. All personnel must pass an employment background check before being issued an ID. Password complexity, history and expiration standards are implemented at the institutional level. Access to individual REDCap projects and their data is managed by the owner of the project. All transactions are securely delivered to the application using Secure Sockets Layer (SSL – SHA-1 with RSA Encryption; 2048-bits). It is then transmitted internally

(behind the firewall) to the database server. All transactions are logged at the server layer (httpd logging), application layers (REDCap logs activity to a database table), and the database layer, using both query and binary logging. This feature provides audit trails for all changes, queries, data exports and reports. MUSC Information security policies are available at: https://mainweb-v.musc.edu/security/policy/

Data Entry. Only MUSC IRB approved study personnel that are authorized to have access to the REDCap study database will be granted password access. Study personnel using computers that are connected to the Internet will directly enter data into the remotely housed database. As such, no electronic study data will be stored on hard drives and/or any portable electronic devices. Additionally, all personnel with access to the database will have current University of Miami CITI and GCP training in the Conduct of Human Subject Protections, and HIPAA and Information Security trainings that are completed annually. Each participant will be assigned a unique study identifier, all PHIs will be masked, and data exports will be limited to the PI or the BS for generating reports and the conduct of statistical data analysis.

Data Monitoring. Ongoing quality control procedures will be implemented for data collection, storage and processing. The PI or PD will conduct monitoring of the study database and generate a report for review at team meetings. Standing agenda items for these meetings will include participant recruitment and retention, AE's, protocol deviations, data integrity and overall study conduct. The PI and PD will work to resolve and validate discrepant data. Discrepancies that warrant clarification will be sent to appropriate parties for review and resolution. All data entry and changes made in the study database by authorized study personnel will be automatically logged by REDCap, and provide a transparent visible audit trail for reviewers.

14.0 Withdrawal of Subjects

The PI may withdraw a participant from the study at any time if they decide it is in their best interest, if they do not follow the investigator's instructions, or if they fail to keep study visits. This may also occur if there is a protocol violation or early closure of the study.

15.0 Risks to Subjects

Based on Phase I of the study, we do not anticipate any significant risks related to the completion of the surveys and key informant interviews in this study. However, as with any research study there is a risk of disclosure of information that can lead to a loss of confidentiality. As well as having a comprehensive DSMP that details data safety, handling, monitoring, storage and security procedures, we will further minimize the potential for loss of confidentiality through the physical separation of participant names from their research record.

Additionally, it is possible that a participant might experience some emotional distress while responding to the survey questions or participating in key informant interviews. If this were to occur, the participant would be referred to a psychologist or psychiatrist for counseling. Reactions will be monitored by the PI (who will be conducting the interviews) and signs of significant distress will be followed-up to identify any serious psychological problems. In the rare and unexpected event of serious or life threatening level of distress, a psychologist or psychiatrist will be contacted as well as the participant's primary care provider of record.

16.0 Potential Benefits to Subjects or Others

If a participant agrees to take part in this study, there will be no direct medical benefit to them. We hope the information learned from this study will aid patients and clinicians in the future. The data collected from this study will not directly affect the treatment being given to the patients. The risks associated with the proposed study are minimal and include psychological and physical strains that

might be encountered in everyday life. The benefits of the study outweigh the risks.

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PROTOCOL TITLE:

A Family-Centered Self-Management Program for Young Children with Sickle Cell Disease: Phase II

PRINCIPAL INVESTIGATOR:

Shannon Phillips, PhD, RN

1.0 Objectives / Specific Aims

Specific Aims: Few family-centered self-management interventions exist to assist children with sickle cell disease (SCD) and their families, which deprive this population of skills that may improve symptom management and quality of life. SCD is an inherited complex chronic condition (CCC) that leads to adverse health outcomes such as pain and organ damage affecting approximately 100,000 people in the US. In addition to living with pain and negative health outcomes, children and adults with SCD also face disparities in access to care. Infants and young children with more complicated CCCs, such as SCD, and those who have fewer resources are at greater risk for adverse outcomes such as increased hospital and emergency department (ED) utilization and physical and psychosocial morbidity. Children with SCD and their families, particularly those who are underserved, would benefit from interventions designed to bolster self-management skills and enhance preventive management of the disease to reduce negative complications. Importantly, caregivers of young children with SCD are often new to the disease process and have unique needs and challenges.

Interventions designed to address the unique needs of and barriers encountered by this population could improve effective management of the disease in the home setting. In addition, technology-based resources such as mobile health applications for symptom tracking, may allow intervention delivery to typically difficult-to-reach populations, thereby reducing access barriers to care, including lack of transportation and obtaining childcare. Further, incorporating theory-based family-centered self-management strategies is crucial to support families in developing sustainable, improved self-management behaviors (e.g. monitoring symptoms, and attending clinic appointments) which will ultimately improve symptom management (e.g. pain, fatigue) and quality of life, and decrease costly emergency department (ED) visits and hospitalizations.

The interprofessional team of investigators for this study includes a mentee (Phillips) with a clinical background as a pediatric acute care nurse and research experience with exploring barriers in access to care among children with CCC. Mentors include an R01 funded nurse scientist who is an expert in intervention development and the conduct of clinical trials (Kelechi: primary mentor), an R01 funded clinical psychologist with extensive expertise in technology, user-based design, and intervention adaptation (Ruggiero: co-mentor), a pediatric hematologist/oncologist specializing in clinical care and research with populations with SCD (Kanter: co-mentor), and a biostatistician with extensive research experience (Mueller: co-mentor). This complementary interdisciplinary team has the knowledge, skills, and access to the population to successfully conduct this study, but will also provide the mentee with mentorship and training experiences in theory-based, technology-enhanced intervention research among a population of children with a CCC and their caregivers.

There are three main components within the study intervention: previously tested educational materials for adults with SCD and their families, a publicly available mHealth application for tracking pain in SCD, and a model of patient-provider communication delivered via mHealth that has been tested with older children with SCD. The goal of the proposed research is to use the theory-based Pediatric Self-Management Model to tailor and pilot test the effect of an integrated intervention on psychosocial and physical symptom management and quality of life for children with SCD ages 0-7 years and their caregivers.

During Phase I of this study, we refined the development and design of the intervention under study, by conducting user focus groups and pilot testing the app with provider feedback among a target population of end-users. Now, in Phase II, we aim to deploy the intervention in a real-world setting. The purpose of this second phase of this study is to conduct feasibility testing of an innovative, technology-based intervention to improve self-management behavior, quality of life, and symptom management in a sample of children with SCD and their families.

During this second phase of this study, we seek to achieve the following aims:

Primary Aim: *Assess feasibility of implementation processes including reach, enrollment, fidelity, adoption, acceptability, and satisfaction using the RE-AIM framework with process measures, surveys, and key informant interviews.*

Secondary Aim: *Investigate the presence of signals of efficacy on measures of self-management, and physical and psychological symptoms and quality of life.*

2.0 Background

Importance of the problem. The significance of this project lies in the fact that it is the first step (adaptation and feasibility testing) in a research continuum that will lead to validation of a technology-based intervention for improving self-management, symptom management, health care utilization and ultimately quality of life among populations of children with complex chronic conditions (CCC) and their caregivers. As such, this project is directly in line with the stated core mission of the NIH's National Institute of Nursing Research.

Sickle cell disease (SCD) is a highly complex and challenging chronic disorder that negatively influences quality of life in children and families of those with the disorder.[1] SCD is a hereditary CCC that almost exclusively affects African Americans. Nationwide, an estimated 72,000 to 98,000 individuals have SCD; >90% of these are African American.[2] Symptoms of SCD often occur within the first year of life and require lifelong preventive management. SCD is a hemoglobinopathy characterized by an altering in the shape of red blood cells in response to hypoxia, stress, or acidosis.[3,4] These abnormally shaped cells occlude small vessels and cause inflammation, pain, infarction, and ultimately, organ damage.[3,4] The physiological sequelae of SCD lead to high health care needs and utilization, and often, to comorbidities and early death.[5,6] Many children with CCC, particularly SCD, and their families have high health care needs that are frequently unmet or inadequately met. SCD is one of several CCCs affecting children that could benefit from improved self and family management care, such as epilepsy, cerebral palsy, and chronic respiratory disease.[7,8]

SCD as a CCC based in health disparity. Because children with SCD and their families have high health care and "other" needs that endure throughout their lifetime, preventive actions are necessary in early childhood to avoid or mitigate adverse effects of the disease process. For optimal management and minimal adverse effects, persons with SCD and/or caregivers must coordinate appointments with various providers, continuously monitor symptoms, and obtain preventive home therapies. Often, challenges are pronounced early in the disease process as caregivers learn about the disease and treatments. Typically, a multidisciplinary team is established and caregivers learn to coordinate and maintain care. However, SCD primarily affects an underserved population (i.e., African Americans) who disproportionately face barriers such as transportation, obtaining childcare, and taking time from work. In fact, low-income children with SCD have significantly higher hospitalizations and ED visits than other children in general.[9]

Methods to enhance self-care of SCD by affected individual and the family are needed. Self-care interventions to prevent adverse effects of the disease process have not been well implemented for children with SCD. Fortunately, assistance with providing reliable sources of disease and treatment related information, decision-making, and communication with the care team via technology improve family-centered self-management behaviors in older children (ages 10-17 years) with SCD.[10] Assisting families caring for an infant or young child with SCD via a similar technology-based model may lead to improved self-management and quality of life outcomes. Providing resources via this mechanism may reduce burden and maximize outreach

to this difficult to reach, underserved, high needs population. Traditional barriers to care such as transportation, childcare, and work conflicts can be overcome. Long-term management of SCD and prevention of adverse outcomes also requires support for self-management skill development. Through technological resources and collaborative relationships with providers, caregivers can receive support to develop self-management skills.

Theoretical Framework. The Pediatric Self-Management Framework[7] guides the present study and provides an ideal underpinning to our proposed methods because it outlines multilevel influences that affect self-management and family-centered self-management behaviors through multiple processes, and guides prediction of the outcomes associated with influences, behaviors, and processes. According to this framework, self-management influences, processes, and behaviors exist on the individual, family, community, and health care system domains. Because this study will focus on children ages birth-7 years and their caregivers, and on the caregiver-provider relationship, we will target the family and health care system domains. Specific influences, processes, and behaviors addressed in this study are outlined in Table 1.

Table 1: Intervention Self-Management Influences, Processes, and Behaviors

Self-management Influences	Self-management Processes	Self-management Behaviors
• Family disease and treatment knowledge • Parental monitoring and supervision • Parental involvement • Patient (parental)-provider communication	• Determining child's health care needs • Communication with medical team • Seeking disease and treatment related information • Determining child's health care needs • Allocation of treatment responsibility • Learning about patient's disease and treatments • Provision of support for treatment regimens • Modification of communication styles • Shared decision making	• Giving medication and treatments such as home physical and respiratory therapy • Attending clinic appointments • Monitoring and tracking symptoms • Introducing and supporting lifestyle modifications • Providing recommended therapies

3.0 Intervention to be studied

The intervention is a multicomponent (3-part) technology-based package. The intervention targets influences and processes informed by the Pediatric Self-Management framework (Table 1). Component 1 (education) consists of continuous access to directed educational resources on the SCD process, treatment, home management strategies, symptom prevention and management strategies. These materials are easily accessible via a mobile device given to caregivers and will include patient-centered PDF files and links to websites developed and tested by authoritative sources. An example includes the patient education materials provided by NIH NHLBI such as the Sickle Cell Disease Infographic: Monitoring Pain (Figure 1). To address potential literacy barriers, an

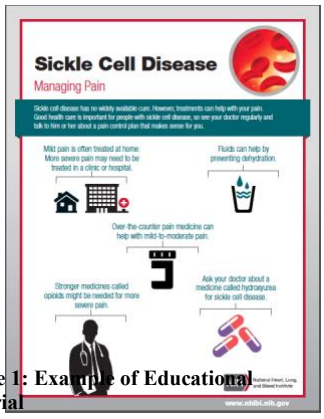

Figure 1: Example of Educational Material

application that reads PDF files aloud (e.g. @Voice Aloud Reader) is downloaded onto caregiver devices. Component 2 (symptom monitoring and tracking) consists of a mobile-device based publicly available application for tracking and monitoring pain in SCD that also permits upload of symptom logs and text alerts to a health care provider (Voice Crisis Alert). Component 3 (caregiver-provider communication) is based on Jacob et al. (2013)'s intervention with an mHealth intervention for older children with SCD. This component consists of a technology-based connection with a provider who will: respond to alerts delivered via the mHealth application, monitor pain symptoms delivered via the mHealth application, and respond to messages. A provider at the MUSC Pediatric Sickle Cell Clinic will collaborate with caregivers to coach caregivers on the care of the child and provide support to the caregiver.[10] Caregivers will receive a daily message using a semi-structured protocol to "check in" with participants and promote engagement. All components are integrated into the web-based app. A secure portal is in place for messaging that encrypts all messages and protects confidentiality.

During Phase I of this study, using an iterative design process and guided caregiver, child and clinician feedback, we developed and refined the intervention by conducting user focus groups and pilot testing the app among a target population of end-users. Specific tasks accomplished during this Phase I, included developing and incorporating age specific language into the app, refining the user graphical user interface, developing and integrating the provider communication component to include clinically relevant disease specific symptoms, and build-out of the clinician's patient portal – where individual patient's data can be accessed for summary viewing. Now, in Phase II, we aim to deploy the intervention in a real-world setting.

Children (5-7) with SCD and their caregivers will complete self-report and proxy assessments as described in Table below; data will be recorded in REDCap by the PI or project coordinator

Major tasks and domains	**Measures/instruments/ questions and Cronbach's alpha ( )**	**Data sources and time points**
Demographics/clinical characteristics	Age, child age, health history, race/ethnicity, medications, health care utilization, rural/urban residence, insurance, caregiver demographics, family characteristics	Caregiver interview; baseline
Reach: Sample Recruitment	Monitoring of sample representativeness; types of recruitment activities; rates of recruitment; % eligible, consented, provided with informational session	Recruitment tracking forms; quality checks by PI; weekly meetings with mentor, clinic staff, and research team
Efficacy: <u>Child (by proxy):</u> Pain Fatigue Quality of life <u>Caregiver:</u> Fatigue Emotional distress: anxiety Emotional distress: depressive symptoms	PROMIS Parent Proxy: Pain Interference*[21,22] (age 5 and older) PedsQL with Sickle Cell Disease Module (proxy = 0.97)[23] (age 2 and older) PedsQL Multidimensional Fatigue Scale in Sickle Cell Disease (proxy = 0.95)[24] (age 2 and older) PROMIS Fatigue SF (>0.9)[25]	Review and content analysis of transcriptions of text messages; review and content analysis of recorded teleconferences; tracking forms; fidelity checklist; transmissions from web-based application to nurse; post-intervention interviews; weekly

Measures of self-management behaviors: Monitoring and tracking symptoms Attending clinic appointments Administering home medications and treatments	PROMIS Emotional Distress: Anxiety (0.97)[26] PROMIS Emotional Distress: Depressive symptoms SF (0.97)[27] Daily pain severity rating; daily pain type rating # days recorded symptoms; # days and types of recorded treatments; # scheduled clinic appointments attended; # days daily mediation administered; # days PRN medications administered	meeting with mentor, clinic staff, and research team; baseline, mid-intervention, post-intervention, 3-months post-intervention
Adoption: Adherence Acceptability Education Symptom monitoring and tracking Patient-provider communication	# days symptoms recorded; # times educational component accessed; length of time in minutes educational component accessed; # text messages and videoconferences with nurse Caregiver satisfaction; # problems reported; types of problems reported # times accessed educational materials; length of time in minutes educational materials accessed # days recorded symptoms; # contacts (text or videoconferencing) with nurse pertaining to symptoms # and type (screening, referring, coaching, supporting) of contacts (text or videoconferencing) with nurse Collaborate for Parents	Tracking forms; content analysis from text messages and videoconferences with nurse, data transmitted from web-based application; fidelity checklist; weekly meetings with mentor and research team; caregiver interview at end of study
Implementation: Technology Consistency of intervention	# problems encountered with mobile device, # problems reported to research staff; types of problems reported instructional session conducted as planned; fidelity to protocol maintained MAPS	Tracking forms; weekly meeting with mentor and research team; caregiver interview at end of study
Maintenance: Projection of future adoption	# caregivers who would continue intervention; caregiver perception of the intervention; feasibility of nurse role	Caregiver interview at end of study; weekly meetings with mentor, clinic staff, and team

4.0 Study Endpoints

Study end points include: Successful study completions, Consent withdrawals, PI terminations, Lost contact with the patient, and unexpected adverse events.

5.0 Inclusion and Exclusion Criteria/ Study Population

- Eligible caregiver/child dyads will be identified through the staff at the MUSC Pediatric Sickle Cell Clinic. After receiving permission to approach, PI or PC will

screen the potential participants against the inclusion and exclusion criteria. Screening will be documented in REDCap.

Inclusion Criteria

- Children ages 0 – 7 years and parent or primary caregiver 18 years of age or older
- Child with sickle cell disease, as reported by clinician at the MUSC Pediatric Sickle Cell Clinic

Exclusion Criteria

- Parent/caregiver with cognitive disability or delay that precludes ability to participate
- Lack of access to Wi-Fi

Inclusion of Women and Minorities

Both women and minorities will be included in the proposed study. Women are more often than men reported to be the primary caregiver of children with chronic conditions and approximately 66% of caregivers of adults with chronic illness are women. Therefore, it is anticipated that more women will be recruited as participants than men. In addition, SCD occurs almost exclusively in African Americans; therefore, it is anticipated that all or nearly all of the caregiver participants will be African American.

Inclusion of Children

Children ages 0-7 years will be included as part of the child/caregiver dyad. Proxy data will be collected on children younger than 5 years, and older children (ages 5-7 years) without developmental delay will be invited to complete surveys and participate in key informant interviews with the caregiver.

6.0 Number of Subjects

- N=60 – 30 caregivers of 30 children (0-7 years) with SCD will be recruited.

7.0 Setting

- The intervention will be used by the participants in their community environments. Study visits will occur at MUSC Sickle Cell Unit and via telephone to the participant's home.

8.0 Recruitment Methods

- Parents/caregivers who participated in Phase I of the study and agreed to be re-contacted for future research will be contacted and invited to participate.
- For other potential participants, the MUSC Pediatric Sickle Cell Clinic staff will be given the inclusion/exclusion criteria and will be asked to identify eligible participants in the clinic. When potentially eligible participants attend an appointment at the clinic, the clinician/staff will approach the parent/caregiver, briefly introduce the study through an IRB approved study letter, and if interested ask if the researchers can speak with the parent/caregiver to offer additional information. For parents/caregivers who

agree, the PI or PC will provide an overview of the study either by phone or face-to-face in the clinic and conduct eligibility screening. Eligible and interested parents/caregivers will proceed to the informed consent interview.

- Additionally, for the purposes of this study and in direct alignment with the mission of the CON P20 Symptom Self-Management Center, we will employ the use of MUSC Bioinformatics Center (BMIC) core services to identify and recruit patients across the MUSC Enterprise that meet the study inclusion/exclusion criteria and that have granted authorized research contact permission in MyChart through the electronic 'opt in' EPIC designation. Once these potentially eligible patients are identified, we will then contact them by telephone using a script to determine if they are interested in study participation
- Flyers will be posted in the waiting room and patient rooms at the MUSC Sickle Cell Clinic. The flyers will include the PI's contact information; interested parents/caregivers who call the PI will be screened for eligibility.

9.0 Consent Process

Since research will be conducted with caregiver/child dyads and no research will be conducted without the caregiver present, consent will be obtained from the parent/caregiver for both him/herself and the child participant (0-7 years). In this study, we will employ the use of two informed consenting strategies (In-person meeting and electronically through REDCap e-Consent) so as to increase the reach of the study and to promote the generalizability of findings.

In-person informed consent will occur in the comfort and safety of a private clinic room at the MUSC Sickle Cell Unit prior to any screening procedures being conducted and/or data collection. Potential participants will be given the informed consent document to read and review in advance, and/or may have it read to them by the researchers if they prefer. After reviewing the Consent document, both caregiver and child will be given the opportunity to ask any questions about the study that they may have, and will be requested to demonstrate what is expected from them should they enroll in the study through a questioning of their understanding of study procedures and risks. Prior to consenting, all questions will be resolved to the caregiver and child's satisfaction. If a participant does not appear to understand the information contained within the Consent document, the study coordinator will review the consent document again with the participant. If after this second review, the subject does not demonstrate an understanding, they will not be enrolled in the study. Only participants, with no diagnosed or observed cognitive impairment, will be consented and enrolled into the study.

Electronic or e-Consenting will be performed on eligible families that want to participate in the study but are unwilling for whatever reason and/or unable to come to MUSC for a face-to-face informed consent meeting. Families identified through the study recruitment processes that fall into this category will already have spoken with the researchers by telephone, have been introduced to the study and its demands, as well as had their initial questions answered. After speaking with the researchers, families that are further interested in study participation will be asked to provide an email address at which they will receive a REDCap survey link containing a scanned image of the currently approved Informed Consent document (developed from the MUSC REDCap e-consent template). Families will be able to take as much time as they like to read the consent document together in the comfort and privacy of their own home or at a place and time of their choosing. They will be provided with the telephone and email contact details in the survey instruction header for the researchers, should they have any questions before

providing their consent by adding their respective signatures to the form and submitting it. Prior to providing their physical e-consent, the researchers will coordinate with these families; so as to be on the telephone and be available to further answer any questions that they may have during the e-consent process. Should a participant have any questions or concerns about the study, the researchers will address these issues to the best of their abilities and knowledge. Upon submitting the e-consent, a REDCap trigger will immediately notify the researchers, who will then provide their countersignature to the document.

The consent form will meet the requirements of the Code of Federal Regulations and the MUSC Institutional Review Board; and, include the following elements:
1. The purpose, nature, and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. The name and a contact of the investigator(s) responsible for the protocol.
4. The right of the participant to accept or refuse study interactions and to withdraw from participation at any time.

The HIPPA authorization process will be conducted sequentially with the family in the same manner by the researchers. Participants will be able to download a copy of their executed informed e-consent/HIPAA authorization forms directly to their own computer, or have copies emailed to them. They will also be given the option to have a copy of their executed e-forms mailed to them should they elect to do so. A copy of the executed e-consent/HIPAA authorization forms will also be stored in the participant's electronic case record for monitoring and audit purposes.

10.0 Study Design / Methods

The mHealth SCD management intervention will be delivered via an app on the caregiver's mobile device over a 12-week period. This multi-component, web-based app consists of 1.) continuous access to directed educational resources on the SCD process, treatment, home management strategies, symptom prevention and management strategies; 2.) a series of pages in the app that allow for tracking and monitoring symptoms; and 3.) child/caregiver – provider communication. The educational component is based on patient-centered materials that have been developed and tested by authoritative sources. In the app, educational materials are organized by user age (for individuals with SCD) or role for parents/caregivers. Citations are provided and links to the sources are included. The symptom tracking and monitoring component consists of a customizable avatar on which the user can record the location, severity, and characteristics of pain. Users can record other concurrent or associated symptoms (such as fatigue) and can view a graph with the pain history. This portion of the app also includes a health history page on which users can document important clinical information, such as sickle cell type, last sickle cell crisis hospitalization, medications, and allergies. The child/caregiver – provider communication component consists of the ability for the child/caregiver to send a secure message to providers within the app to communicate pain and other symptoms. Providers will have the capability to securely send a reply within the app. In addition, children/caregivers can choose to receive a daily "support" message that will be automatically sent from a list of possible messages. All communication is encrypted and sent securely within the app via a portal. Two to three providers at the MUSC Sickle Cell Clinic will participate as the designated providers in the study.

To determine feasibility, we will apply the RE-AIM framework to assess the Reach, Efficacy, Adoption, Implementation, and Maintenance of the intervention with 30 children/caregiver dyads.[18] The domains are further explicated in Table 2. The intervention will be loaded onto the

caregivers' tablet or smartphone (Apple or Android); participants without a device will be provided one for the duration of the study. The PI or PC will deliver detailed verbal instructions to caregivers on the use of the device and the intervention. Caregivers will also receive written instructions and a contact number for technical assistance if needed. Baseline measures (Table 2) will be collected during the same meeting. Caregivers will retain the devices and will participate in the intervention over a 12 week-period. At the end of the 12-week period, the PI will conduct a post-intervention meeting with each individual caregiver participant during which data will be collected. Caregivers will also be asked to return the mobile device at the end of the study. The PI will meet with the study provider weekly during the intervention.

Retention: To improve retention, IRB-approved personnel will contact enrolled participants at 3-week intervals between data collection points. The timeline for these points of contact are at the following weeks post baseline data collection: weeks 3, 9, 15, 18, and 21. The purpose is to maintain contact with enrolled participants, not data collection. Correspondence will be logged in REDCap. Contact will take place via text message, using the number(s) provided to study personnel upon enrollment. Examples of messages are provided in an uploaded attachment.

Post-intervention interviews. At the end of the 12-week study, all 30 caregivers will be asked if they would like to participate in a 3-month post-intervention key informant interviews with the PI to obtain more in-depth data on accessibility, usability, and adherence to intervention; however, only 15 will be chosen to participate. This subset will be selected randomly by computer. Dyads have a 50-50 chance of being randomly selected if all dyads express interest. Semi-structured interviews will be conducted using a qualitative descriptive approach,[17] will last approximately 45-60 minutes, and will be conducted according to an interview guide with open-ended questions and prompts. These interviews will be audio recorded for later nVivo qualitative data analysis. Selected caregivers will be given the option of having the interview conducted in-person in a private room at MUSC or by telephone in the comfort and safety of their own home.

Reimbursement for dyads will be a $50 gift card provided at each of the 4 data collection points, with dyads in key informant interviews receiving an additional $40 gift card. All payments will be given to the caregiver.

Measures. Older children (5-7 years) and their caregivers will complete age-appropriate self-report and proxy assessments at baseline, mid-intervention (6 weeks), post-intervention (12 weeks), and 3 months post-intervention as previously described. Self-report and proxy assessments will be collected during meetings between the PI or PC and the participant. Depending on participants' preference and availability visit 2, 3 and 4 surveys will be completed either by phone or electronically via REDCap survey or by paper and pencil. All data will be recorded in REDCap by the PC.

11.0 Specimen Collection and Banking

Not applicable

12.0 Data Management

Sample size considerations

The purpose of this study is to establish feasibility of implementing the integrated intervention obtain estimates of variability for the primary outcome measures and obtain preliminary indicators of effectiveness of the intervention rather than to confirm or refute hypotheses.

Therefore, sample size considerations focus on precision of estimates. For this feasibility study, we project that we will be able to recruit 30 child/caregiver dyads. With such a sample we will be able to estimate outcome proportions for feasibility measures including recruitment and drop-out with precision ±0.11 to ±0.16 for values of the true proportion ranging from 0.10 to 0.30 (or correspondingly, from 0.70 to 0.90). Assuming a drop-out rate of up to 30%, 95% confidence limits can be estimated for impact measures, such as change from pre-to-post in quality of life for child and caregiver with a precision ranging from ±0.43 to ±1.35 corresponding to estimated standard deviations for change in quality of life scores ranging from 0.5 to 5.0 SD units.

Demographic and clinical variables obtained at baseline will be described via measures of central tendency (mean, median), variability and frequency distributions as appropriate. Additionally, demographic and clinical characteristics for those who adhered to the study protocol (study completers) versus those who did not adhere (non-adherers and drop-outs) will be compared to better describe the population for this study. For continuous quality of life measures for the child and caregiver the difference between pre and post intervention measurements will be estimated via 95% confidence intervals. To assess preliminary intervention effects, we will conduct repeated measures ANCOVA with symptom (pain) severity and type obtained daily as dependent variable in individual models adjusting for "dose" defined as number of times education module was accessed and total time spent in education modules.

Post-intervention qualitative analyses (Aim 2): Data collected from post-intervention key informant interviews will be analyzed using directed content analysis[19] and nVivo qualitative data analysis software version 11.[20] Consistent with the directed content analysis approach, initial coding categories are identified according to the guiding theoretical model, and for this study, will reflect the RE-AIM domains.

Data sharing with the NINR/NIH: As a condition of this National Institutes of Nursing Research (NINR) award, de-identified patient data will be shared by the researchers with the NINR and stored electronically on an NIH password protected secure server (https://cdrns.nih.gov/). The purpose of sharing this information is to build a NINR repository of data using Common Data Elements (CDE) for future research purposes among the general scientific community and for public health benefit. Patients will be allocated a random identifier through the NIH supported GUID Tool. The GUID Tool (https://cdrns.nih.gov/node/39) is a customized software application that generates a Global Unique Identifier for each study participant. The GUID is a subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII). The GUID is made up of random alpha-numeric characters and is NOT generated from PII/PHI. As such, it has been approved by the NIH Office of General Counsel. GUID Generation complies with HIPPA regulations for the protection of PII/PHI. Patients are made aware of this data sharing agreement with the NINR/NIH in the study's Informed Consent document.

13.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

There is a well-developed and NIH/NINR prepared SRG approved DSMP that involves the use of a Safety Monitoring Committee (SMC) that shall meet semi-annually post initial study enrollment. The Committee is comprised of key individuals that include: an independent medical safety monitor (ISM), a biostatistician (BS), and the Program Manager (PM).

The following members of the study's DSMC will perform data safety monitoring of the study:
- Dr. Cristina Lopez, Independent Safety Monitor (ISM) - primary responsibility
- Mr. Mohan Madisetti, MS, Project Manager (PM)

• Ms. Mary Dooley, Biostatistician (BS) - supervised by Dr. Martina Mueller.

Independent Safety Monitor (ISM), Dr. Lopez who is Assistant Professor at Medical University of South Carolina, has a PhD and a background as a clinical psychologist with expertise in adolescent behavioral research, and will act as the study's Independent Safety Monitor (ISM). Dr. Lopez has no real or apparent conflict of interest that would affect her performance in this role on the study.

Project Manager, (PM). Mr. Madisetti, MS, has over 20 years of research experience in study management, quality assurance and the protection of human subjects. Mr. Madisetti is CTRC, CITI /GCP and NIH trained in Human Subject Protections, and has completed MUSC's Certificate of Competence in Research Ethics (CREP) and member of the Institute of Human Values Ethics Committee. Mr. Madisetti has also been a member of over 5 federally and FDA sponsored research full DSMBs.

Biostatistician (BS) Ms. Dooley is a biostatistician and faculty at the College of Nursing at the Medical University of South Carolina. Ms. Dooley has experience collaborating with investigators in clinical trials as well as in community based participatory research. Ms. Dooley will be supervised by Dr. Martina Mueller from the College of Nursing.

From the initial screening of subject by inclusion and exclusion criteria to the informed consent process to the provision of participant study instruction to staff training in Good Clinical Practices (GCP) and regulations pertaining to the Conduct of Human Subject Research to routine contact with participants to internal quality control audits and protocol fidelity monitoring to the real-time review of AE's by the SMC to the oversight of the IRB - procedures for monitoring study safety are consistently afforded throughout the study. Specific study procedures include:

- Participants will be screened for inclusion and exclusion per the protocol
- Participants will be fully informed as to all know risks and the possibility of risk from study participation in the informed consent process. These risks are minimal.
- Participants will be instructed to notify the researchers of any/all suspected or experienced adverse events whether they believe them to be related or not to the intervention.
- The PI or PC will track all reported participant AEs through to resolution.
- All investigators and researchers will maintain active CITI and GCP training.
- The PI or PC will maintain weekly contact with all participants to elicit information about AE's and to monitor participant study progress, compliance and safety.
- The PI or PC will review participants study logs for fidelity compliance with the intervention.
- The PI or PM will conduct quarterly internal quality control audit of all participant records to ensure compliance with MUSC IRB regulations; the PI and PC will work together to correct any errors.
- The BS shall generate semi-annual AE reports for the PI, SMC and IRB to review.
- The ISM will have access to real-time study data and will be able to provide immediate recommendations to the PI and PD.
- Investigator performance and compliance will be provided for through MUSC IRB and ORI study oversight.

Protecting Confidentiality of Participant Data

Participant Screening and Enrollment. All data from participants screened for the study will be entered into an electronic study database. Designated research staff will collect, gather, and enter required data (written informed consent, HIPAA Authorization, and demographics) onto study data forms. Screened patients who do not meet study eligibility will have specific screening data entered into the study database. The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include reason for exclusion. All dates will be shifted and other Personal Health Information (PHI) will be removed from the study database upon study completion. All data obtained from this study will be used for research purposes only and will comply with Federal HIPAA regulations. Master Screening and Enrollment Logs will be maintained by the PI or PD and will be used by the PI or PD to prepare reports on accrual and attrition for the ISM and SMC.

Case Report Forms. All proposed study specific case report forms (source documents) for data collection will be designed by the PI and, when possible, transferred by the PI or PC into electronic Case Report Forms (eCRFs) for use in the study's REDCap database. These study specific eCRFs source documents (study logs for correspondence, compensation and other forms such as pre-eligibility screens) will be coded by the participant's unique study ID# for all data collected including study instruments will be maintained in the participant research record. Completed instruments that require signature on a paper CRF will be scanned and uploaded into the study database to all for remote electronic safety monitoring as well as maintained on file in accordance with MUSC policies and applicable Federal Regulations for the Conduct of Human Participant Research.

Binders. The PI or PC will prepare and maintain a participant-specific binder for each participant containing all non-eCRFs records. A regulatory file will also be maintained to include the IRB-approved Protocol, original Informed Consent documents, HIPAA forms and other study-related regulatory documents. All paper research records and CRFs will be maintained in a locked file cabinet, stored in a room for research files that is accessible only via a password protected entry system that features security cameras, within the College of Nursing. Access to the research records, study database and PHI's will be restricted to study personnel as approved by the PI and MUSC IRB. As with all studies conducted at MUSC, this study is also eligible for a random audit by MUSC Office of Compliance.

Data Processing. This study will use Research Electronic Data Capture (REDCap) for data capture and management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The study-specific REDCap electronic database will be designed and developed by the PI or PD in concert with the BS. The provision of REDCap is made available through the South Carolina Clinical & Translational Research (SCTR) Institute at MUSC with NIH Grant awards UL1RR029882 and UL1TR000062.

Data Security. Ensuring data security, compliance with 45 CFR 46 and maintaining the integrity of PHI is a top priority. MUSC has Standard Operating Procedures (SOP) to ensure a high level of data security while coordinating electronic and paper data management activities for clinical research trials. The REDCap study database will be hosted in the Biomedical Informatics secure data center at MUSC, a secure environment for data systems and servers on campus, and includes firewall, redundancy, failover capability, backups and extensive security

checks. The secure data center has strict access control; only authorized core personnel may access the facility un-escorted. Only authorized users are allowed to connect to the network, and the security of the network is actively monitored. Power and environmental controls have several layers of backups, from interruptible power supplies to alternate and redundant feeds to the local utility company. The REDCap system administrator contributes to the maintenance of institutional disaster recovery and business continuity plans. Load balancers and a highly fault tolerant SAN infrastructure contribute to high availability.

The REDCap system itself has several additional layers of protection including password protection. Access to the data and its security is managed institutionally by sponsored login IDs through a Shibboleth login with an MUSC issued NetID and features a user account management filter that controls who can access the data and to what degree. All personnel must pass an employment background check before being issued an ID. Password complexity, history and expiration standards are implemented at the institutional level. Access to individual REDCap projects and their data is managed by the owner of the project. All transactions are securely delivered to the application using Secure Sockets Layer (SSL – SHA-1 with RSA Encryption; 2048-bits). It is then transmitted internally (behind the firewall) to the database server. All transactions are logged at the server layer (httpd logging), application layers (REDCap logs activity to a database table), and the database layer, using both query and binary logging. This feature provides audit trails for all changes, queries, data exports and reports. MUSC Information security policies are available at: https://mainweb-v.musc.edu/security/policy/

Data Entry. Only MUSC IRB approved study personnel that are authorized to have access to the REDCap study database will be granted password access. Study personnel using computers that are connected to the Internet will directly enter data into the remotely housed database. As such, no electronic study data will be stored on hard drives and/or any portable electronic devices. Additionally, all personnel with access to the database will have current University of Miami CITI and GCP training in the Conduct of Human Subject Protections, and HIPAA and Information Security trainings that are completed annually. Each participant will be assigned a unique study identifier, all PHIs will be masked, and data exports will be limited to the PI or the BS for generating reports and the conduct of statistical data analysis.

Data Monitoring. Ongoing quality control procedures will be implemented for data collection, storage and processing. The PI or PD will conduct monitoring of the study database and generate a report for review at team meetings. Standing agenda items for these meetings will include participant recruitment and retention, AE's, protocol deviations, data integrity and overall study conduct. The PI and PD will work to resolve and validate discrepant data. Discrepancies that warrant clarification will be sent to appropriate parties for review and resolution. All data entry and changes made in the study database by authorized study personnel will be automatically logged by REDCap, and provide a transparent visible audit trail for reviewers.

14.0 Withdrawal of Subjects

The PI may withdraw a participant from the study at any time if they decide it is in their best interest, if they do not follow the investigator's instructions, or if they fail to keep study visits. This may also occur if there is a protocol violation or early closure of the study.

15.0 Risks to Subjects

Based on Phase I of the study, we do not anticipate any significant risks related to the completion of the surveys and key informant interviews in this study. However, as with any research study there is a risk of disclosure of information that can lead to a loss of confidentiality. As well as having a comprehensive DSMP that details data safety, handling, monitoring, storage and security procedures, we will further minimize the potential for loss of confidentiality through the physical separation of participant names from their research record.

Additionally, it is possible that a participant might experience some emotional distress while responding to the survey questions or participating in key informant interviews. If this were to occur, the participant would be referred to a psychologist or psychiatrist for counseling. Reactions will be monitored by the PI (who will be conducting the interviews) and signs of significant distress will be followed-up to identify any serious psychological problems. In the rare and unexpected event of serious or life threatening level of distress, a psychologist or psychiatrist will be contacted as well as the participant's primary care provider of record.

16.0 Potential Benefits to Subjects or Others

If a participant agrees to take part in this study, there will be no direct medical benefit to them. We hope the information learned from this study will aid patients and clinicians in the future. The data collected from this study will not directly affect the treatment being given to the patients. The risks associated with the proposed study are minimal and include psychological and physical strains that might be encountered in everyday life. The benefits of the study outweigh the risks.

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