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A. Cover Page

Title: SCD-PROMIS: A software platform that enhances self-efficacy and patient-provider engagement with the goal of reducing readmission rates in children with sickle cell pain

Grant ID number: 20083487

Main collaborators: Kevin Gary, PhD, Kevin Cleary, PhD, Pamela Hinds, RN, PhD; Randi Streisand, PhD, Michael Guerrera, MD, Jichuan Wang, PhD, Julia Finkel, MD.

Abstract: The goal of this project is to reduce pain-related, 30-day readmission rates for sickle cell disease (SCD) patients. Pain is the main reason why SCD patients are admitted and readmitted to hospitals. Often, even after several days of hospitalization, patients continue to have high levels of pain, and a large percentage of patients are readmitted within 30-days of discharge. In fact, readmission rates of SCD patients are higher than those of asthmatics and diabetics. In order to reduce 30-day hospital readmission rates and improve patient care quality, the Affordable Care Act and Centers for Medicare and Medicaid Services have established the Readmissions Reduction Program. In keeping with this effort, we propose a methodology and supporting technology that will fundamentally change the way we monitor SCD patients. This methodology has the potential to decrease SCD patients' admission/readmission rates and to enhance their quality of life, by improving patient reporting, self-efficacy, and patient/provider engagement when there is worsening pain and increased admission/readmission risk. The software platform will use validated Patient Reported Outcome Measurement Information System (PROMIS) measures to remotely monitor patients' pain and related outcomes after hospital discharge and to increase healthcare provider engagement when there is a worsening of patients' pain or an increased risk of readmission. This proposal brings together a team of engineers, hematologists, and pain researchers that have worked together before, and who collectively have the expertise to develop and test the feasibility and predictive value of the application in a large population of SCD patients.

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C. Reviewer Comments

We are grateful for the thoughtful review of our letter of intent as the reviewer's critiques (*shown in italics*) led to revisions that we believe improve our proposal. We now clearly articulate the overall goal of this proposal and describe in detail the clinical outcomes, the processes to be followed during the study, and the mobile application.

Critique 1: *Very poorly written goal (talks about the mobile web/phone based platform) with no mention of process nor clinical outcomes (vague reference to clinical care, pain monitoring and related outcomes).* We now make clear that our goal is to reduce the high readmission rates observed in SCD patients. We propose to develop a mobile platform that will facilitate the interactions between healthcare providers and SCD patients after hospital discharge. The application will have two components: a mobile phone application ("app") for patients and a web-based monitoring platform for providers. SCD patients will use the app to frequently monitor their pain and quality of life and to report weekly PROMIS measures. Healthcare providers will use the web-based platform to monitor those weekly PROMIS measures and to identify patient reported outcomes that are predictors of readmission for pain. We will identify the predictors of readmission and design alerts to be sent to health care providers, which will in turn increase patient/provider engagement. The app will increase the engagement of SCD patients and will motivate them to achieve self-efficacy regarding the management of their acute and chronic pain care.

Critique 2: - *Need more commentary on the actual tool (iPhone, IPAD, android, whatever) to be used, and how such tools might be supplied to a population which likely has an over-representation of low-income individuals.* We have added extensive details on the tools, specifically the app and web-based platform, as well as on the methodologies utilized to increase patient engagement and pain reporting. To cover the broadest subset of the population, the app is designed to be cross-platform (Android, iOS, web browsers) by leveraging the HTML5 stack. We have also requested funds in the budget to buy phones and monthly data plans to be provided to individuals who lack access to mobile devices.

Critique 3: *How will the project maintain the use of the technology by persons of low income (ie., will the hospital/clinic be responsible for providing and maintaining the service on cell-phones for these individuals?* While most of our patients have access to mobile devices, we are requesting funds to provide such devices and monthly data plans to patients who lack access to one. For those who have mobile devices, the mobile app will work on a high percentage of modern operating systems, notably Android and iOS. We believe that if our project is successful in reducing readmission rates, hospitals and health care providers will have an interest in providing such capabilities to patients to allow for remote patient monitoring for 30 days after hospital discharge.

D. Main Section of the proposal

1. Overall Goal & Objectives

The overall goal of this project is to reduce pain-related, 30-day readmission rates and to improve quality of care for patients with sickle cell disease (SCD). In the United States, sickle cell disease affects approximately 100,000 individuals, predominantly African American, who face a lifelong challenge of living with pain that results in decreases in quality of life and health care disparities[1-4]. SCD-pain is associated with repeated emergency room visits, frequent hospital admissions, and a very high hospital readmission rate[5].

We propose to develop a methodology and supporting technology that will fundamentally change the way we monitor SCD patients. This methodology has the potential to decrease SCD patients' admission/readmission rates and to enhance their quality of life, by improving patient compliance with reporting, self-efficacy, and provider engagement when there is worsening pain and increased admission/readmission risk. The targeted patient population will be SCD patients at Children's National Health System (CNHS), a major pediatric healthcare system serving the Washington DC metropolitan area. SCD is associated with acute and chronic pain, increased pain burden and pain interference with activities of daily living, high health care utilization, and very high hospital readmission rates. The mobile and web technology platform will be designed to address the challenges faced by SCD patients by increasing the engagement of less activated patients, increasing their self-efficacy, and increasing engagement between providers and patients. The platform will also be designed to be translatable to other chronic pain patient populations, including adults.

This project has three main objectives**:**

Objective 1: To evaluate engagement between patients and healthcare providers by monitoring pain, anxiety, mobility, and activities of daily living in SCD patients after pain-related hospital discharge.

To realize this objective, we propose to collect PROMIS measures reports at hospital discharge and weekly thereafter from patients admitted to Children's National Health System for SCD-related pain. We will develop a mobile phone application for SCD patients and a server-side web portal and data management platform for healthcare providers to collect the data and encourage pain reporting. The platform will include the ability to adaptively deliver a small number of follow-up questions based on responses to PROMIS questions, enabling detailed data collection on pain burden factors. We will evaluate the sustained level of engagement of patients and healthcare providers, the self-efficacy (empowerment) of patients with respect to pain management, and the ability of healthcare providers to engage less activated patients. To encourage patient outcomes reporting, we will incorporate innovative strategies using advanced smartphone features including notifications and incentivization methods such as gamification and rewards.

In addition to the patient side, we will create a web portal to enable healthcare providers to better monitor their patients and improve their interaction with patients showing poor levels of engagement. The web portal will be based on a server-side data management platform that will also enable data collection regarding compliance rates, usability (e.g. notification fatigue), and PROMIS responses. We hypothesize that by implementing the methodology and technology-

supporting platform that 80% of the SCD patients will be compliant with weekly reporting. We believe that increased reporting will inform the best way to monitor patients, increase engagement between patients and health care providers, and will guide the design of interventions to improve outpatient pain management and reduce hospital admission and readmission rates in patients with SCD.

Deliverables:

1. Design and develop a mHealth mobile app using advanced smartphone features, adaptive delivery of PROMIS and extended questions, and compliance incentivization methods.
2. Develop a server-side web portal and data management platform that enables providers to track patient compliance and analyze responses collected from app-delivered questionnaires.
3. Determine compliance rates in submitting PROMIS questionnaires using the app.

Objective 2: To analyze the association between PROMIS measures and risk of 30-day readmission and to identify the predictors of hospital readmission. These data will in turn **inform the design of interventions aimed at 1) increasing provider engagement (alerts, e-mails,** text messages), 2) improving outpatient pain management, and 3) increasing patient self-efficacy and education on management of their pain. With weekly remote monitoring, we will be able to identify worsening pain conditions and pain interference with activities of daily living. Therefore we will be able to develop a prediction engine to identify the timing when interventions should be considered and implemented. The data management platform developed in Objective 1 will allow our behavioral scientist and statistician to analyze the correlations and potential causalities of these factors to hospital admission and readmission rates. We hypothesize that 1) changes in PROMIS measures will predict hospital readmission, 2) weekly pain reporting will inform the design of interventions that increase patient self-efficacy in the management of their pain, increases patient/provider engagement, and ultimately will reduce admission and readmission rates.

Deliverables:

1. Obtain IRB approval and collect PROMIS measures upon and after hospital discharge
2. Conduct an analysis to determine 30-day hospital readmission rates of SCD patients who used the mobile app and identify predictors of hospital readmission rates based on PROMIS measures.
3. Develop a prediction engine for hospital readmission that includes clinical history and weekly PROMIS measures.

Objective 3: Once the predictors of readmission are identified and interventions are designed jointly by the hematologists, behavioral scientists, and pain researchers, we will design an appropriately powered, follow-up trial to determine the efficacy of these interventions in decreasing readmission rates for SCD patients.

Deliverables:

1. Design interventions to increase patient self-efficacy targeting the predictors of readmission.
2. Design the follow-up study to determine the efficacy of the newly designed interventions.

Overall Impact: If successful, this application and its subsequent version will fundamentally change the manner in which we monitor patients' pain after hospital discharge and has the potential to improve outpatient pain management and reduce SCD admission and readmission rates. The proposed project will incorporate validated NIH Patient Reported Outcomes Measurement Information System (PROMIS) measures[6,7] to monitor patients' pain and associated outcomes (anxiety, fatigue, mobility) weekly after hospital discharge. We will extend PROMIS measures with adaptive delivery (described below in the **In-app Questionnaire** section) of a small number of questions aimed at gathering detailed information on the patient's condition. With the use of the proposed app, we expect to achieve an increase in patient/provider engagement, better patient follow-up by remote e-monitoring after hospital discharge, an increase in patient motivation and activation in pain reporting and management, and ultimately decreased readmission rates. . Further, the software platform developed will also have broad applicability for adult and children who have acute and chronic pain caused by diseases other than sickle cell as monitoring of their pain can be accomplished without visits to the hospital.

2. Technical Approach

a. Current Assessment of need in target area

At the Children's National Health System (CNHS) main campus in Washington, DC, we attend to approximately 1500 SCD patients per year. Our Emergency Department cares for approximately 1300 SCD patient visits yearly. The reason for 65% of those visits is severe pain, and half of those visits will result in hospital admission, which in turn, amounts to over 400 pain-related admissions per year. We conducted a study between January 2010 and December 2012 to examine the rates and to identify factors associated with hospital readmission among our SCD patients [8]. That study showed that at CNHS, our patient-level readmission rate was 33%, while the visit level readmission rate was approximately 16% [8]. In fact, at CNHS, the readmission rate for SCD patients is second only to readmissions for chemotherapy-related treatment, which are scheduled treatment-related readmissions. These data are in concert with those across the United States as another study examining the readmission rate across 40 pediatric hospitals showed that approximately 17% of hospitalizations for SCD crisis resulted in hospital readmission within 30 days[9]. In addition, for approximately 70% of the patients readmitted within 30 days, the readmission occurred within 14 days[5]. Therefore, to improve the quality of life of our patients, we need to decrease the admission and readmission rates as hospitalizations increase school absences, lead to social isolation, and are detrimental to normal development.

Interestingly, researchers showed that a significant risk factor for readmission was lack of follow-up within 30 days of discharge, and that an outpatient visit within 30 days was associated with lower 30-day readmission rates[10,11]. It is noteworthy that this lack of follow-up is in part related to difficulties patients have in complying with medical appointments. For example, parents having to take off work to bring their child to the clinics, children having to miss school days, and unavailability of rides to appointments are among many reasons for lack of follow-up and missed appointments. In our study at CNHS, we found that patients who lived within five miles from the main campus and with ready access to specialized health care

facilities had a significantly lower likelihood of being readmitted by 30 days than those patients living beyond that five mile perimeter [8]. Taken together, these data suggest that close monitoring and follow-up of SCD patients after discharge can improve patient care and decrease readmission rates. Therefore, the ability to monitor patients without requiring a visit to the hospital or clinic, as we propose in this project, has a high probability to address the lack of follow-up during the 30-day period after hospital discharge**.**

In this proposal, we will target SCD patients ages 8-17 since their lives are profoundly impacted by recurrent pain, they are likely to have access and/or be comfortable working with mobile phones, and they are capable of pain self-reporting. Further, the use of PROMIS measures has been validated in this age group. We will supply mobile phones and monthly data plans for the portion of the patient population lacking access to mobile technology. We plan to enroll and follow 150 SCD patients after hospital discharge to test our hypothesis that with our software platform we will be able to detect worsening pain, increase patient/provider engagement, increase patient self-efficacy, and in turn reduce pain burden and readmission rates.

b. Project Design and Methods

Preliminary data: At CNHS, in a study of quantitative sensory testing in pediatric SCD patients, we are currently collecting weekly pain and related outcomes reporting for 90 days. For this study, our co-investigator Dr. Kevin Gary developed an android-based mobile app including some PROMIS measures. We found that weekly pain reporting is feasible and well received among our SCD patients. Pain reporting is significantly higher in patients using the mobile app (75%) than in patients using conventional paper reporting (12.5%). In this proposal, we will develop and expand the use of mobile phone based monitoring to SCD patients at and after hospital discharge using PROMIS measures.

In a recent study of existing pain apps, researchers showed that there are nearly 300 patient-focused pain management apps available[12]. However, most existing pain management apps are too simplistic, have not engaged health care providers in their development, and their efficacy on pain-related outcomes has not been tested [12]. Further, the literature on e-Health and mHealth apps focuses on various mechanisms that are already dated in today's mobile landscape such as roto-dialing, SMS, and email, and suggests that modern smartphone features are not being fully utilized in the practice of mHealth [13,14] . Improvements in all of these areas could make a difference in the acceptance of the technology and subsequent clinical outcomes.

The use of mobile and web-based applications has been tested in SCD patients. Small studies have shown that the completion of an e-diary for pain reporting and self-monitoring is feasible in SCD patients[15-17]. Other studies have shown that children with SCD can communicate with advance practice nurses and establish communications about their health and symptoms[17,18]. Our proposed approach builds on the findings of these studies and incorporates validated PROMIS measures, in addition to empowering and increasing self-efficacy.

Health care providers and behavioral scientists have been engaged in the development of the proposed application since its early stages, and only validated patient reported outcome measures (PROMIS) will be incorporated. During the design process, there will be rigorous validation of its acceptability, usability, and efficacy. As suggested by the Milestones under Objectives 1 and 2, there are activities related to technology development, patient and provider

evaluation for compliance, analysis of readmission rates, and design of new interventions to reduce admission/readmission rates.

The following section lays out the project design and implementation strategies for the in-app questionnaire, mobile app development, and server-side healthcare provider web portal and data management platform components. The next section (1.c.) describes the design and implementation strategies for the evaluation study.

In-app Questionnaire

As previously stated, in this app, we will incorporate only validated NIH PROMIS measures, a collection of precise and highly reliable responsive assessment tools that measure patient–reported health status. PROMIS was developed using item response theory and has been tested and validated as a monitoring tool for patients with several chronic illnesses including cancer, diabetes, sickle cell disease, rheumatic and kidney diseases [7]. Dr. Pam Hinds, the Director of Nursing Research at CNHS and one of the investigators in this proposal, has validated this tool in children with several chronic illnesses, and she has shown its validity and reliability for the estimation of treatment effect[6]. In SCD patients, PROMIS measures were shown to correlate with biochemical[19] and clinical markers of the disease[7]. Among SCD patients, those with recent pain episodes had worse PROMIS measures scores that evaluate physical functioning, emotional distress, fatigue, and pain interference [7]. Their validity and reliability make PROMIS measures an ideal tool for collecting pain reporting information, contrary to current commercially available pain reporting apps that include non-validated and non-tested measurements[12].

In addition to the PROMIS questions, we will also include a short number of follow-up questions using adaptive delivery techniques to inform the design of the next generation of interventions. . Adaptive delivery means the follow-up questions will be determined dynamically based on the responses to PROMIS questions provided by the patient. These questions will be designed by the PI, Dr. Quezado, and will include qualitative responses that allow the patient to richly describe the nature of her/his pain and how it is affecting her/his quality of life.

Mobile App Development

A significant innovation of the proposed mobile app is its design, implementation, and evaluation of a hybrid strategy combining aspects of *enhanced content*, *notifications*, *gamification*, and *rewards* to achieve higher patient reporting rates. Asking subjects to complete a repetitive task with potentially negative connotations (a reminder of their pain and health conditions) will be mitigated by periodically educating, reminding, and rewarding participation. *Enhanced and targeted multimedia content* will be used to describe the need for compliance to the patient on-demand; if the subject wonders why s/he has to do this at any time, the enhanced content will serve to re-educate and re-motivate the subject. *Notifications* (reminders) will remind the subject to complete the questionnaire at a scheduled time in a non-intrusive manner. *Gamification*, the technique of embedding game-related activities and rewards into a separate process or service, is an increasingly popular technique for enhancing engagement in mHealth apps[13,14] . In this mobile app, patients will be able to earn *rewards* in the form of badges that indicate levels of sustained compliance with pain reporting. The badges

by themselves motivate compliance as they are a physical persistent representation of an achieved status. Badges and rewards can be used in the context of a mobile game to enhance game play, such as so-called "power-ups".

Another significant innovation will be the monitoring of user interactions with the app. This data is commonly referred to as clickstream data, meaning it records each user interaction event of significance. This will let providers and app designers know if notification fatigue is occurring, if PROMIS measures reporting is left incomplete, or if advanced features such as enhanced content or gamification are not utilized. This user interaction data will provide the basis for refining the design of the app for future interventions involving pain reporting.

The preliminary data that support this proposal has been and is being collected with a version of the mobile app that leverages the HTML5 technology stack to support cross-platform deployment. The app has been tested on Android 4.0.x and up, iOS 7.x and up, and HTML5 compatible desktop browsers such as Google Chrome, Mozilla Firefox, and Apple Safari (IE10+ should work as well). Native code around the HTML5 component is used to produce the app and supports specific features such as notifications and event tracing. This proposal will support the most recent versions of the Android, iOS, and Web platforms currently in use to cover our patient population. This coverage of major mobile operating system platforms will assist in patient recruitment efforts.

Server-side Web Portal and Data Management Platform

A server-side implementation of a web portal and data management platform for healthcare providers will collect PROMIS response data and usability events such as notification views, times app started, and every tap event. Figure 1 shows the system architecture of the proposed platform. The portal will provide a user interface with a set of embedded tools enabling the management of pain reporting studies with the ability to enroll new patients and track the compliance status of enrolled patients. The user interface will provide features that enable a healthcare provider to identify patients at risk of non-compliance quickly, to view submitted patient questionnaire responses, and to customize the use of alerts to the provider for particularly high-risk cases. Further, the healthcare provider will see on the portal when notifications were issued and whether the patient activated the in-app questionnaire from the notification or dismissed the notification without action. The data management platform will provide simple data reporting and exporting capabilities for offline usability and response analysis, and will also support the querying and exporting of data required for the readmission prediction analysis (Objective

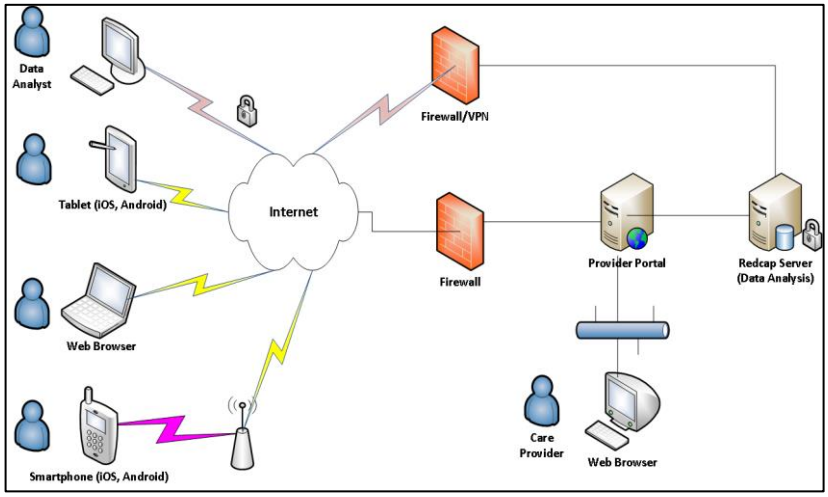

Figure 1. System architecture for the platform.

2). Collection of personalized health information (PHI) will occur securely and privately through the following means:

- The app will require a secret individual PIN code to be entered before starting the survey.
- Survey response data will not be stored on the mobile/tablet device. If a device is lost or stolen, recovery of previously entered data is impossible to recover from the device. Transmissions between the patients and the server will be encrypted.
- The server will be placed behind a firewall configured to only allow data from provisioned clients over a preconfigured network port. Providers will only be able to access the portal from behind the firewall.
- The server will be monitored for irregular transmissions, such as probing attacks.
- Data will be de-identified during the patient-provider workflow and only re-identified on a secure REDCap server for analysis. REDCap is the de facto open platform for managing clinical data for research studies. Our eventual goal is to move the entire platform directly onto REDCap, but for the purposes of this project we will leverage our existing work on a web portal and push data to REDCap for full deferred analysis.

Enrollment of SCD patients and collection of PROMIS measures

Figure 2 illustrates the study flow chart. IRB and institutional approvals for the patient trial will be obtained during the first six months of the project. From months 6 to 18, 150 SCD patients ages 8-17 will be recruited upon hospital discharge to participate in the study. Patient's clinical data will be retrieved from our Electronic Health Record and recorded in RedCap for subsequent analysis. The recruitment will be led by Dr. Quezado, in concert with Dr. Michael Guerrera, the Director of the Sickle Cell Anemia Program in the Department of Hematology. After enrollment, the application will be installed on the patient's cell phone by the technical team or on a hospital provided phone, if required. Patients and their parents will be instructed on how to use the app and baseline PROMIS measures will be obtained. The app will incorporate a total of 24 PROMIS questions drawn from the Pediatric Item Bank v.1.0 Short Forms that have been validated for the age group that will be enrolled: Pediatric Physical Function – Pediatric Mobility (6 questions), Pediatric Pain Interference (6), Pediatric Anxiety (6), and Pediatric Fatigue (6). In addition, the app will have enhanced capabilities such as the ability to report pain scores using a visual analog scale,

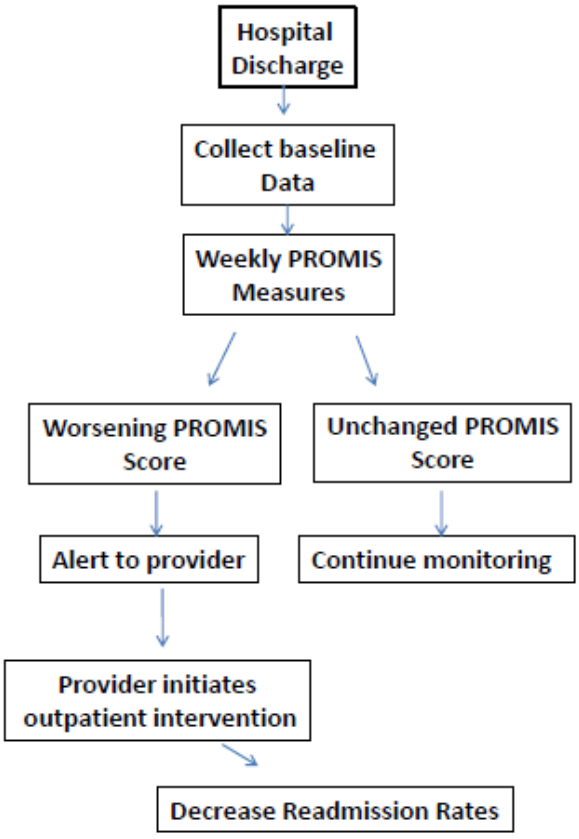

Figure 2: Study flow chart

adaptive delivery of drill-down questions based on current responses, and multimedia help and motivational content. As an example of adaptive delivery, when a patient indicates that he/she was able to attend school, the app will have a follow up questions to ascertain the reasons for school absences. When a patient report of medications is not in keeping with initial prescription, a follow up questions as to the reason for lack of compliance will follow.
We will also follow readmission rates in a standard of care control group. The patients in this standard of care group will receive the current standard of care and will not use the proposed app either because they refused to participate on the study or were not screened for study entry by the research team.

Inclusion Criteria: 1) Subjects with SCD (HbSS, HbSβ0 thalassemia, HbSOArab, HbSC) within age range of 8-17 years; 2) Subjects admitted to CNHS with SCD-related pain 3) Ability to comply with study related evaluations and follow-up.

Exclusion Criteria: Inability to give informed consent/assent.

Planned analysis of the association between PROMIS measures and hospital readmission
Dr. Jichuan Wang, a biostatistician with vast experience in the analysis of PROMIS measures, will conduct the statistical analysis[6,20-22]. Various statistical methods will be applied to analyze the association between PROMIS measurements and readmission risk. First, the rate of hospital readmission will be estimated by time periods (e.g., 1, 2, 3, and 4 weeks after discharge). Considering the PROMIS measures to be predictive of readmission, a Receiver-Operator Characteristic (ROC) analysis with the PROMIS measures will be used to evaluate the discriminatory ability that PROMIS measures to correctly predict hospital readmission among children with SCD [23-25]. We will conduct ROC analysis for each of the four PROMIS symptom measures by time period. The area under the ROC curve (AUC), which is commonly used as a summary measure of diagnostic accuracy, will be estimated. If the AUC for a PROMIS measure is computed to be 0.70, it indicates that the measure would have a 70% chance of correctly predicting the likelihood of hospital readmission. The threshold of each PROMIS ROC curve that yields the optimal sensitivity and specificity of predicting readmission will be identified [24,25]. Both the AUCs and thresholds will be compared between the PROMIS measures by time period. From the ROC analysis, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) will be estimated by time period.

We will also conduct a latent profile analysis (LPA))[26-29] to identify potential latent profiles, where individuals are similar within group, but different across groups, in regard to the levels of PROMIS measures. A series of LPA models with an increasing number of latent profiles will be estimated, and iteratively comparing each successive K-profile model with the previous (K-1)- profile model using AIC, BIC, SABIC, the Lo-Mendell-Rubin likelihood ratio (LMR LR) test, the adjusted LMR LR (ALMR LR) test, and the bootstrap likelihood ratio test (BLRT). Patients will be classified into their most likely latent profile using the estimated posterior membership probabilities. The quality of profile membership classification will be assessed by examining average posterior probabilities and the entropy statistics. The LPA will be conducted using the PROMIS measures by time period. Considering the relatively small sample size (N=150), we will use MCMC Bayesian approach for LPA model estimation, and the plausible values of the latent profile variable will be imputed and saved for further analysis [7,26,27,30]. Finally, the likelihood of

hospital readmission will be analyzed using a Cox hazards model [31-33]. As readmission can occur any time after discharge and the information on readmission will be censored after the end of the observation period (i.e., 30 days in this study), two pieces of event history information (i.e., event occurrence and exposure time) will be collected and analyzed together in the model; and individuals who are not re-hospitalized in 30 days will be treated as censored cases. The PROMIS measures, as well as the latent profiles of PROMIS symptoms estimated for LPA, will be used in the Cox model to predict the hazard of readmission, controlling for covariates (e.g., gender, ethnicity, age). Based on the results of the Cox model, the conditional probability that an individual could be re-hospitalized will be estimated any time after discharge, corresponding to specific values of PROMIS measures. Such estimated probability of readmission, as well as the sensitivity, specificity, PPV and NPV estimated from ROC analysis, will be tabulated corresponding to specific values of PROMIS measures, as well as the latent profiles estimated from LPA.

Readmission prediction engine (Figure 3).

Once PROMIS measures are collected and analyzed, we will develop the framework for a novel prediction engine that assesses the risk of hospital readmission and informs providers that intervention may be necessary. This system support structure will accept answers from PROMIS questions, tracking changes from week to week, and will also include patient clinical information as indicated in Figure 2. We will consider several modeling techniques that incorporate cluster analysis, inductive logic programming, and Bayesian networks. First we will finalize the structure of the network and will populate the probability distribution tables though the assignment of beta distributions for each node based solely on subject matter expertise. At the end of the data collection period, we will analyze the robustness of the network by assessing predicted outcome of a fixed data set compared to the actual outcomes. We propose to demonstrate that the network has the ability to successfully predict that the patient is at a high risk for hospital readmission and suggests when intervention is necessary. As this tool evolves, it will eventually be used to intervene with patients before they are admitted to the hospital.

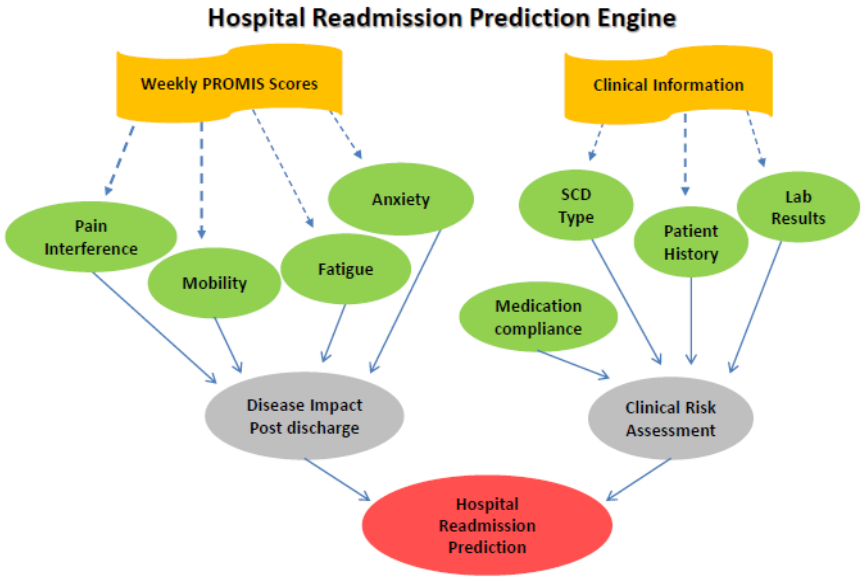

Figure 3: Readmission prediction engine uses the patient data collected throughout the study that is input into a network. The structure of the network infers that hospital readmission is dependent on clinical risk and PROMIS measures

Sample Size and Statistical Power

For the purpose of power analyses, we assume a probability of 0.10 of readmission among children with SCD. Our proposed sample of N=150 patients would achieve a power of 0.95 to detect an AUC value of 0.75 that is better than chance (AUC=0.50) at α=0.05 level. Based on the proposed sample of N=150 and an anticipated event rate of 0.10, the Cox regression would achieve 99% of power at a 0.05 significance to detect a small log hazard ratio of 0.10 (or hazard ratio of 1.105) on a covariate with a standard deviation of 11.50 (e.g., the standard deviation of PROMIS symptom measure varies approximately from 10.7 to 13.5 among children with cancer[6]. The power was adjusted assuming an R-Squared of 0.15 of regressing the variable of interest on the other covariates in the Cox regression. The proposed sample size is relatively small for the mixture model (e.g., LPA). We propose using a Bayesian approach, which is not based on large sample theory, for LPA modeling. In addition, with Bayesian method, data non-normality can be handled under the very plausible assumption of missing at random (MAR) (i.e., missingness is allowed to be a function of observed covariates and observed outcomes) rather than missing completely at random (CMAR)[34,35].

Design of a follow up study to determine the efficacy of newly developed interventions to reduce readmission rates.

By integrating the results from objectives 1 and 2 we will identify the predictors of readmission. Accordingly, we will design interventions targeting those predictive factors. These interventions will be designed with input from team members, including the hematologists, pain management experts, behavioral psychologists, and software engineers. Interventions to be considered include increasing patient education about their pain and pain interference, development of skype consultation templates to be conducted between patients and providers when PROMIS scores are suggestive of worsening clinical conditions, setting up transportation for onsite visits if there is further deterioration of clinical condition, and the development of a home treatment plan to increase hydration, ensure medication compliance, and closer patient monitoring when pain condition is shown to be worsening.

After completing the studies outlined in Objectives 1 and 2**,** we expect to have an improved understanding of the factors contributing to readmissions, and therefore we will be able to design effective interventions to reduce the readmission rate by at least 50%. By integrating the results and designing targeted interventions, we will be able to design appropriately powered trials to reduce the pain-related readmission rates in SCD patients. We will work with our statistician Dr. Wang who has expertise in multicenter clinical trial design to test the efficacy of newly designed interventions in SCD patients in future work, as we intend to apply for an NIH R01 grant for follow-on funding.

Potential Difficulties

While we admit over 400 patients/year to CNMC for sickle cell related pain, it is possible that enrolling 150 patients during months 6 to 18 of the project might prove challenging. However, our experience with ongoing studies of quantitative sensory testing in SCD patients suggests that most of our patients have access to mobile devices and that even if we only enroll 50% of patients discharged from the hospital over a 6-month period, we will meet the enrollment goal. In addition, while we are confident that most of our patients have access to mobile devices, if that proves not to be the case, we have asked for funds to provide mobile devices to complete

the proposed enrollment.

In summary, the successful completion of this study will provide us with a monitoring tool that will increase patient motivation, self-reporting and self-efficacy, and will generate provider alerts to increase provider engagement at times when interventions are warranted (such as when PROMIS measures analysis predicts increased readmission risk or worsening pain condition). This will improve our care of SCD patients, increase patient engagement and self-efficacy, and position us to developing a system that will focus on decreasing hospital readmissions in the follow up study.

C. Evaluation Design

i. Addressing the practice gap in the target group

Evaluation of pain reporting compliance using the app

We will evaluate the clinical feasibility of monitoring pain and associated clinical outcomes in SCD patients upon hospital discharge using PROMIS measures delivered via the mobile app developed in objective 1. To that end, we will determine the number of patient responses obtained every week monitoring the server side and will in turn determine the compliance rate with reporting. We will also monitor the number of reminders necessary to obtain weekly patient response. We expect to have an 80% reporting compliance rate. For the duration of the study, we will monitor readmission rates for all SCD patients admitted to CNHS. As only 150 will be enrolled and therefore use the app, patients not enrolled in the study will serve as a control group that receives current standard of care without scheduled weekly monitoring. We hypothesize that patients using the proposed app will have a higher engagement rate with providers than those who do not. Engagement rate will be measured by the number of encounters (electronic or otherwise) between patients and providers.

Evaluation of the effect of using the application on readmission rates

As described in the Current Assessment of Need section of this application, we currently have extensive baseline data on hospital readmission rates for SCD patients at the CNHS campus in Washington, DC. If this proposal is funded, we will start enrolling patients on month six of the project and at that point we will start monitoring admission and readmission rates of patients using the mobile application. Among the 150 patients enrolled to use the application, we will have two groups, one that will be readmitted by 30 days of discharge and another that will not. As we admit approximately 400 SCD patients/year for pain at CNHS, there will be approximately 250 patients/year who will not use the app and will serve as a current standard of care control group.

ii. Amount of change expected

We expect that the use of the app will reduce readmission rates by increasing patient engagement and self-efficacy and patient/provider engagement. Our baseline data indicates that the visit level readmission rate for SCD is approximately 16% [8] and that patients who live more than five miles from the main campus have higher odds of readmission. Therefore, we

will measure the compliance and engagement of patients according to their geospatial distribution. We will monitor readmission rates using our patient's Electronic Health Records, to which we will have access once IRB approval is obtained. It is our expectation that we will be able to reduce readmission rates by at least 50%.

iii. Engagement of target audience

As discussed in the Mobile App Development section of this application, we will be closely monitoring user engagement. We will collect data on each user interaction event of significance. This will let providers and app designers know if notification fatigue is occurring, if PROMIS measures reporting is left incomplete, or if advanced features such as enhanced content or gamification are not utilized. This user interaction data will provide the basis for refining the design of the app for future interventions involving pain reporting.

iv. Dissemination of project outcomes

The project team will disseminate the results of this study locally, at institutions caring for SCD patients (NIH Clinical Center, Howard University) and nationally, at annual meetings of the American Society of Hematology and American Pain Society. Once data are analyzed, manuscripts will be prepared to report the outcomes in peer-reviewed journals.

3. Detailed Workplan and Deliverables Schedule

Timeline

		Timeline: Month											
	Objectives	2	4	6	8	10	12	14	16	18	20	22	24
1	**To evaluate patients and healthcare providers engagement by monitoring PROMIS measures**												
1.1	Develop mHealth mobile app												
1.2	Server-side web portal and data management platform												
1.3	Determine reporting rates												
2	**Collect PROMIS measures and develop prediction engine**												
2.1	Obtain IRB approval and collect PROMIS measures												
2.2	Statistical analysis												
2.3	Develop prediction engine												
3	**Design interventions and follow-up study and disseminate results**												

This is a 24-month project with three objectives: 1) develop the mobile app and web-based provider platform; 2) evaluate the app and platform in the clinic and develop the prediction engine; and 3) design interventions that target the predictors of readmission and design the follow up study to determine the efficacy of new interventions to reduce readmission rates. In a subsequent proposal, we will make system improvements, expand clinical use, and explore broader implementation opportunities.

Research Team

The research team has expertise in all areas needed and has collaborated previously. Zena Quezado, MD, PI, CNHS, is an anesthesiologist and pain expert with extensive experience with SCD patients who will lead the study. She will obtain IRB approval for the study protocol, recruit patients and oversee the overall conduct of the study. Kevin Gary, PhD, Technical Lead, Arizona State University, is a computer science professor with expertise in software development for mobile apps, will be responsible for the app development. Kevin Cleary, PhD, co-investigator, CNHS, is the Technical Director of Bioengineering and will provide application support for the trial at Children's. Pamela Hinds, PhD, RN, Associate Director, Center for Translational Science has had a pivotal role in the development of PROMIS measures and will provide guidance on the use of PROMIS measures. Dr. Michael Guerrera, the Director of our Sickle Cell Anemia program at CNHS, will recruit patients and advise on the design of interventions. Dr. Randi Streisand, a world renowned behavior scientist with expertise in behavior in children with chronic illnesses, will advise on the behavior modification interventions to improve self-efficacy in pain management. Dr. Julia Finkel, a pain researcher, will recruit patients and advise on the design of interventions. The research coordination will be responsible for patient recruitment, patient follow up, monitoring of compliance rates and exporting data to RedCap. Dr. Jichuan Wang, the lead statistician will design the statistical analysis and oversee its execution. Yao Chen a research Data Analyst will assist Dr. Wang with the data analysis. The team will hold bi-weekly teleconferences to discuss hardware and software requirements, review status, and make decisions. We will set up a project-dedicated Wiki where project plans, requirement discussions, teleconference agendas, and minutes will be regularly posted.

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