WEB-BASED MONITORING OF PAIN MANAGEMENT IN ADOLESCENT AND YOUNG ADULT SICKLE CELL PATIENTS THROUGH DAILY SELF-ASSESSMENT

by

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There is a wide range of variability in the clinical phenotype of Sickle Cell Disease (SCD), resulting in a vast array of clinical presentations ranging from acute, recurrent vaso-occlusive pain episodes to chronic pain, increased risk of strokes, acute chest syndromes and osteonecrosis. Historically, pain crises have been defined by whether or not the patient seeks medical attention. Previous studies have shown that while patients with SCD are in pain 54.5% of the time, they are only seeking medical attention during 3.5% of these episodes. This has led to a gross underestimation of the prevalence of pain episodes, due to discrepancies in both the definition and reporting of these episodes. There is currently no utility available to accurately assess and manage pain levels in Sickle Cell patients who are not utilizing medical facilities. The implementation of a web-based application to monitor daily pain levels is relevant to public health because it is likely to provide medical teams with the tools necessary to track patient pain levels more precisely. This will also enable healthcare providers to be more proactive with regard to pain management in patients with SCD.

Twenty-nine patients were asked to record their level of pain three times daily for six months via a web-based application. The application asked patients to appraise their pain level by use of a Visual Analog Scale (VAS), ranging from 0 (no pain) to 10 (extreme pain). Each patient was assigned a non-specific identifier that enabled him or her to log into the system

without referencing any personal health information. Pain measurements were electronically time stamped and all information was filtered to ensure the protection of patient sensitive information. Authorized team members were alerted of pain episodes by email (pain levels of 5-7) or text message (pain levels of 8-10). The patient was then contacted and information was gathered regarding the location and duration of pain, the presence of other symptoms and social factors that influenced a patient's decision to seek medical intervention.

Of the 29 patients enrolled in the study, 21 patients accessed the web-based application and provided a total of 4,981 pain data entries over a six month time period. Patients reported that they were in no pain (pain score of 0) 23.4% of the days logged, in pain (pain score of 1-7) 76.6% of the days logged and in pain crisis (pain score of 8-10) 12.2% of the days logged.

This data provides proof of the principle that adolescents with SCD will provide electronic reports of their pain multiple times a day over an extended period of time. This preliminary data also suggests that the prevalence of pain in adolescents is much greater than previously reported.

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PREFACE

As I stand here on the verge of ending one chapter of my life to begin another, I find it necessary to take a moment to thank all those who have played such an intricate role in my success as a graduate student.

To the participants in my study, this study could not have made it without your eagerness to get involved. Many of you have embraced the web-site, making it a part of your everyday life. Your participation has not only provided us with invaluable knowledge, regarding pain in the pediatric and adolescent Sickle Cell population, but has also taught you lessons in your own pain patterns as well. I hope that you enthusiasm and devotion will continue throughout the duration of the study.

Dr. Lakshmanan Krishnamurti, thank you for entrusting me to see your vision through and giving me the opportunity to work with such an amazing group of patients. Over the past two years your passion and devotion to your patient population has been such an inspiration. I have gained a lifetime of knowledge in such a short amount of time.

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1.0 INTRODUCTION

Sickle Cell Disease (SCD) is one of the most common monogenic disorders worldwide[4]. SCD predominately affects individuals of African ancestry, where 1 in 8 are carriers of this condition. However, SCD can also affect persons of Mediterranean, Arabian, East Indian, South and Central American and Caribbean ancestry. In the United States alone, more than 1,100 infants are born each year with this condition[1,4].

SCD is characterized by acute, recurrent, vaso-occlusive pain episodes that often present within the first 1-2 years of life[5]. These vaso-occlusive pain episodes, termed vaso-occlusive crises (VOC), are the leading cause of morbidity and mortality associated with SCD. This is due to the fact that VOC results in a wide range of clinical manifestations such as: bone marrow infarctions, splenic sequestration, organ damage and cerebrovascular accidents (stroke)[5].

Historically, the medical community has defined a pain episode based on healthcare utilization. However, studies have shown that while patients with SCD are in pain 54.5% of the time, they only seek medical attention for 3.5% of these episodes[3,6]. This has led to a gross underestimation of the prevalence of pain episodes due to discrepancies in both the definition and reporting of pain episodes. There is currently no tool available to accurately assess and manage pain levels in Sickle Cell patients who are not utilizing medical facilities.

The purpose of this study is to determine whether the implementation of a web-based application can be used to more precisely monitor a patient's daily pain level. Healthcare providers may become more proactive with regard to pain management in Sickle Cell patients if daily pain levels are known.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 SICKLE CELL DISEASE

SCD is an autosomal recessive inherited hemoglobinopathy that was first described by physician James Herrick, in 1910, when he noted the presence of a "large number of thin, elongated, sickle-shaped and crescent-shaped" red blood cells in a young Grenadian patient's blood smear[7]. In 1949, Linus Pauling et al. were the first to suggest that the cause of SCD was the result of defective hemoglobin molecules[8].

Hemoglobin (Hb) is tetrameric protein composed of two alpha (α) and two beta (β) globin polypeptide chains[9]. The conformation of these 4 polypeptide chains provides a protective central space that enables hemoglobin to noncovalently bind to the iron-protopohyrin IX molecule, heme, without exposing it to the surrounding aqueous cellular environment[9]. The presence of the heme molecule enables hemoglobin to transiently bind and transport O_2, CO_2, CO and NO[9]. The presence of high concentrations of these hemoglobin molecules allows the red blood cells to efficiently transport oxygen from the lungs to all the cells of the body.

The α-globin like genes located on chromosome 16 encode the embryonic ζ-globin and the adult α-globin molecules[9]. The β-globin like genes located on chromosome 11 encode the embryonic ε-globin, fetal γ-globin and adult δ-globin and β-globin molecules[9]. The expression

of various α- and β-globin molecules change over the course of an individual's lifetime (Figure 1)[9].

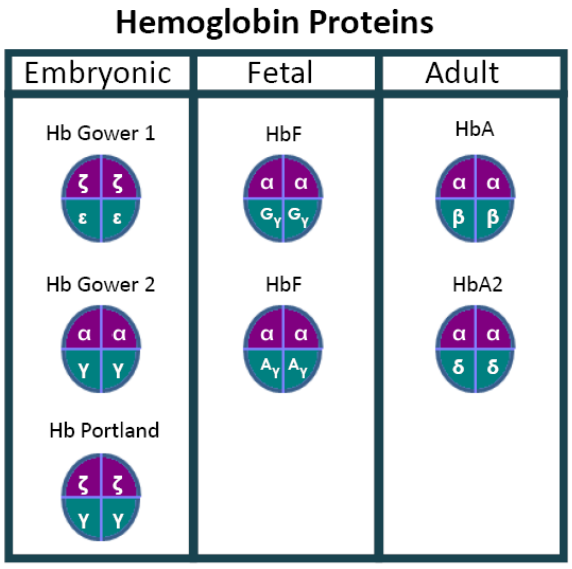

Figure 1:Genetic Expression of Human Hemoglobin[9] (adapted)

During the early stages of embryogenesis the ζ and ε globin genes are expressed to form Hb Gower 1[9]. As the embryo continues to grow there is a decrease in the expression of the ζ and ε globin genes and an increase in the expression of the α-, Gγ- and Aγ- globin genes[9]. This results in the formation of two additional embryonic hemoglobin molecules Hb Gower 2, consisting of $\alpha_2\varepsilon_2$ and Hb Portland, consisting of $\zeta_2\gamma_2$[9]. As the concentration of α- and γ-globin molecules increases, Hb Gower 2 and Hb Portland are eventually replaced with fetal hemoglobin molecules, consisting of $\alpha_2A\gamma_2$ or $\alpha_2G\gamma_2$[9].

After birth, the expression of Gγ- and Aγ- globin genes are replaced by the expression of β- and δ- globin genes leading to the formation of the adult hemoglobin molecules Hb A and Hb A_2[9]. Hemoglobin A consists of $\alpha_2\beta_2$ and accounts for 97% of the hemoglobin molecules found

in the adult human body while Hb A_2 consisting of $\alpha_2\delta_2$ accounts for 2% of the hemoglobin molecules in the human body[9].

2.1.1 Variant Forms of Sickle Cell Disease

Table 1: Variant Forms of Beta-Globin[4,10] (adapted)

Hemoglobin	Description
HbS	β^6 Glutamic acid (GAG)→ Valine (GTG)
HbC	β^6 Glutamic acid (GAG)→ Lysine (AAG)
Hb D Punjab	β^{121} Glutamine (GAG)→ Glutamic acid (GAG)
Hb O Arab	β^{121} Glutamine (GAG)→ Lysine (AAG)
β^o Thalassemia	Complete lack of Hb A due to the inability to produce a normal β-chain
β^+ Thalassemia	Production of a reduced amount of β-chain leads to variable amount of Hb A
HPFH	$\alpha^2\gamma_2$

The term Sickle Cell Disease is used to describe a broad range of hemoglobinopathies that are characterized by Hb S in the presence of another variant beta globin chain (Table 1)[4,10]. The majority of the cases of SCD are composed of four primary subtypes: SS, SC, $S\beta^o$ and $S\beta^+$. Less frequently, cases of Sickle Cell-Hb D Punjab and Sickle Cell-Hb O Arab have been reported[4,10].

2.2 MOLECULAR BASIS OF SICKLE CELL DISEASE

In 1957, the genetic basis of SCD was identified as a single nucleotide substitution of thymine for adenine in the sixth codon of the β-hemoglobin gene[6,8]. This change results in the translational substitution of the polar, hydrophilic, glutamic acid with the nonpolar, hydrophobic valine [6,8].

As red blood cells circulate and become deoxygenated, the HbS molecules undergo a conformational change that exposes the hydrophobic Valine residue[8,12]. The exposed hydrophobic regions of adjacent HbS molecules polymerize in the aqueous compartment of the cell. This polymerization of HbS results in the formation of rigid fibers that damage the cytoskeleton of the red blood cell increase cell permeability and cause the hallmark "sickled" appearance[8,12]. As the RBC becomes re-oxygenated it results in the dissociation of the Hb S fibers and the RBC reverts to the standard biconcave disc shape[8].

With each pass through the circulatory system, the red blood cell becomes increasingly more damaged. Increases in cell permeability result in the dehydration of the RBC thereby increase cellular viscosity and perpetuate further polymerization of Hb S molecules. As cellular damage continues, the RBC begins to express adhesion molecules and receptors that enable the RBC to adhere to circulating White blood cells (WBCs) and the cellular endothelium[8]. The presence of sickled RBCs, as well as their adherence to other cellular entities, results in a decrease in the velocity of the circulating blood. All of these factors combined lead to an increase in the likelihood of cellular adhesions that can ultimately result in the occlusion of micro- or microvasculature, known as vaso-occlusive crisis (VOC). These vaso-occlusive events are the hallmark characteristic of SCD and are responsible for most of the severe clinical manifestations of SCD[13].

2.3 INHERITANCE

SCD is inherited in an autosomal recessive manner[1,10]. This means that an individual will develop SCD when they inherit one Hb S gene from one parent and any other variant β-globin gene from the other parent (Table 1). When both parents have a Hb S gene the risk for having a child with SCD is 1 in 4 or 25% [1,10].

2.4 CLINICAL MANIFESTATIONS

The physiological changes, chronic hemolytic anemia and immunologic impairment associated with Hb S can lead to systemic damage, resulting in wide a range of phenotypic manifestations.

2.4.1 Hand-Foot Syndrome

Dactylitis, commonly referred to as Hand-Foot syndrome, is characterized by painful swelling of the hands and feet that generally resolves within one week[10,12,14]. This is one of the earliest complications of SCD with the highest incidence occurring between 6 months to 2 years of life. Studies have shown that a history of early onset dactylitis (prior to 6 months of age) serves as an indicator of severe disease manifestations later in life[14].

2.4.2 Acute Chest Syndrome

Acute Chest Syndrome (ACS) is characterized by infiltration of the pulmonary vasculature with sickled RBCs[12]. ACS is associated with: lower respiratory symptoms such as chest and/or abdominal pain, shortness of breath and fever; hypoxemia; and radiological findings that mimic pneumonia on chest X-ray[1,4]. ACS is the second most common cause of hospitalizations in SCD occurring in 40% of patients and is a major cause (25%) of death in childhood[1,4,15]. ACS often develops during a vaso-occlusive event and is the result of a combination of factors such as: bacterial or viral infection, VOC of the pulmonary vasculature, pulmonary infarction, or the presence of a fat/bone marrow or sickled RBC emboli[1,5,12].

2.4.3 Hemolytic Anemia

Hemolytic anemia is evident beginning within the first year of life. The physiological changes and cellular damage associated with Hb S reduce the lifespan of a RBC from 90-120 days to 10-20 days[5]. The rate of erythropoiesis is increased to compensate for the peripheral destruction of RBCs. This leads to an increase in the amount of RBC precursors within the bone marrow and the introduction of immature reticulocytes into the blood stream[5]. The increased rate of hemolysis also results in the accumulation of indirect (unconjugated) bilirubin[5]. High levels of indirect bilirubin are responsible for the increased prevalence of jaundice and gall stones seen in SCD patients[5].

2.4.4 Infection

Infections are a major cause of morbidity and mortality in SCD. Studies have shown that infections have been linked to 20-50% of all deaths reported in prospective cohort studies over the past 20 years[15]. Impaired splenic functioning, tissue ischaemia, micronutrient deficiencies and defects in the activation of the complement pathway, are believed to result in an increased risk of bacterial and viral infections. Streptococcus, pneumonia, influenzae, salmonellae, malaria, hepatitis, parvovirus and chlamydophila are the most commonly reported infections reported in SCD patients[4,15].

2.4.5 Pulmonary Hypertension

Approximately 33% of adult patients suffer from pulmonary hypertension as a result of damage to the pulmonary vasculature[16,17]. High blood pressure in the lungs is a major risk factor for death in SCD and greatly increases the mortality rate in SCD patients[16,17].

2.4.6 Splenic Sequestration

Splenic sequestration is a life threatening condition that is most common in the first 5 years of life but can be seen at any age in patients with Hb SC or Hb Sβ thalassemia[18]. Splenic sequestration may be associated with fever, pain and respiratory problems. Sequestration is characterized by the sudden entrapment of blood within the spleen resulting in the rapid onset of

severe anemia and enlargement of the spleen[18]. If left untreated, this can result in circulatory collapse and death in less than thirty minutes.

2.4.7 Renal Involvement

The renal micro-environment promotes Hb S polymerization due to low partial oxygen pressure, low pH and high osmolality[4,19]. This results in a range of renal manifestations that can include: chronic renal failure, hematuria, renal medullary carcinoma and nocturnal enuresis[4,19].

2.4.8 Avascular Necrosis

Avascular necrosis of the joints occurs in adolescent and young adult SCD patients[20]. This is a bone disorder of the hips, femoral and humeral heads that is caused by temporary or permanent blood loss due to vaso-occlusive events[20]. Most patients that present with avascular necrosis experience progressive deterioration of the femoral head and require a total hip arthroplasty[20]. Fifty percent of all patients with SCD will develop avascular necrosis by 35 years of age[20].

2.4.9 Cerebrovascular Accidents (CVA)

Cerebrovascular accidents (strokes) are a leading cause of death in both pediatric and adult patients with SCD[19,21]. Eleven percent of all patients will have a stroke by 20 years of age. Once a stroke has occurred, the risk for recurrence is greater than 60%[4,5]. Silent cerebral infarcts (SCI) are the most common form of CVA occurring in 22% of all children with SCD[22].

2.4.10 Proliferative Sickle Retinopathy (PSR)

The physiological changes that occur in the RBCs of SCD patients lead to damage in the blood vessels of the eye[23]. This results in the formation of new blood vessels that are weaker and prone to rupture[23]. Retinopathy can compromise the vision of SCD patients. Studies have shown that the frequency of PSR within SCD patients varies depending of the patient's genotype and can be as high as 70%[23].

2.5 PAIN IN SICKLE CELL DISEASE

"Sickle Cell pain is unique and, like other types of pain, is a complex human experience that is strongly affected not only by pathophysiologic factors but also by psychological, social, cultural and spiritual ones[24]." Acute painful episodes are the most common clinical manifestations of SCD, resulting in 90% of hospital admissions among adult SCD patients[25]. While the exact sequence of events leading to a pain episode are not well understood, it is thought to be a continuous cycle where by vaso-occlusion results in tissue ischemia and damage, leading to a secondary inflammatory response, triggering the release of norepinephrine which ultimately leads to further tissue ischemia[24].

Studies have shown that pain episodes can be triggered by a wide range of factors including but not limited to: dehydration, stress, alcohol consumption, extreme temperatures, changes in humidity, menstrual cycle, infection, obstructive sleep apnea and cardiac or pulmonary impairments[25–34]. The pain experienced in SCD is further complicated by its unpredictable nature. Pain crises are known to vary in location, severity and duration.

Furthermore, it can become hard for healthcare professionals to accurately identify patients at the early stages of a pain crisis due to the fact that 50% of patients do not show any objective signs at the beginning stages of a pain episode[24].

2.5.1 Landmark Sickle Cell Pain Studies

Two hallmark studies have been conducted to study prevalence of pain in SCD: the Cooperative Study of Sickle Cell Disease (CSSCD) and The Pain in Sickle Cell Epidemiology Study (PiSCES). The CSSCD study was a federally funded multicenter study that followed the natural history of SCD in a total of 3,578 patients over a 10-20 year time period[6,35]. Among many other issues, researchers wanted to identify possible events that led to the onset of a pain crisis. The PiSCES study was a prospective cohort study conducted in the state of Virginia that asked 232 SCD patients to complete daily pain diaries over a six month time period to determine the correlation between the pain they were experiencing and their response to this pain[3].

While these studies are informative, they both have weaknesses that need to be addressed. The main weakness of the CSSCD study is that the classification of pain episodes was limited to "the occurrence of pain in the extremities, back, abdomen, chest or head that lasted at least 2 hours led to a clinic visit and could not be explained except by SCD[6,35]." This is a weakness because 39% of participants in this study never sought medical attention and so were classified as having no pain episodes[6]. This may be an underrepresentation of the pain episodes in this population, due to the fact that the study does not take into account self-treated pain episodes. Another weakness of the CSSCD study is that it counted pain episodes that occurred within a 2 week timeframe as one episode[6,35]. Based on this classification, 74 patients were excluded from the final analysis due to the fact that they presented with "greater than 10 closely

spaced pain episodes[6]." The PiSCES study sought to address these weaknesses by utilizing daily pain diary journaling, allowing the patient to assess whether or not they were experiencing a pain episode[3].

While the CSSCD study showed an average of less than 1 pain episode per year, the PiSCES study has shown this to be a gross underestimate of pain episodes. Rather, the PiSCES study demonstrated that patients reported experiencing pain 54.5% of the time but only sought medical attention 3.5% of the time[3,6,35]. The PiSCES study is limited by the accuracy of journaling and the reliance on patients to mail in monthly submissions. It has been suggested that patients may misrepresent their compliance by backfilling or forward filling diary entries. With no mechanism to validate when each entry was completed, one can call into question the validity of the data collected.

2.5.2 Compliance in Pain diaries

Patient self-reports have become a vital aspect to clinical research with 25% of all clinical and pharmaceutical trials utilizing some form of a diary [36]. Many have expressed concern in the validity of paper diaries due to the inability to validate patient reported compliance. In 2003, Stone et al. utilized paper diaries equipped with photo sensory technology to investigate the validity of patient reported compliance[36]. During the study, patients were asked to log their pain levels three times daily in either a paper diary or an electronic diary[36]. Participants were informed that compliance would be based on whether the participant made an entry within the fifteen minutes surrounding each of the three designated time periods (10:00 am, 4:00 pm, 8:00 pm)[36]. While the reported compliance rate in the paper diary group was comparable to that of the electronic diary group (90.5% vs. 93.6% respectively) the actual compliance, based on photo

sensory data, was determined to be only 10.9%[36]. This data suggests that 75-80% of dates and times listed in the paper diary entries were falsified by backfilling or forward filling[36].

This has lead to a push in the research community to find a tool that would allow for the validation of patient reports[37–40]. Many companies now offer handheld devices that provide an electronic time stamp for each entry and allow researchers to set desired perimeters such as how often and when the patient can enter data. The downside to this technology is that it can be very expensive with start up costs and rental fees ranging from $200 to $2,000 per device[39].

2.6 USE OF MOBILE PHONES IN US TEENS

The use of cellular phones have become an integral part of the lives of American teenagers with 75% of all 12-17 year-olds now owning cell phones[41]. The use of these mobile devices allow teenagers to keep in touch with family and friends, coordinate their schedules, browse the internet, send emails and entertain themselves. Studies have shown that 41% of teens from low-income households (income less than $30,000 annually) use their cell phones to access the Internet[41]. This influx in technology within the general public provides clinical investigators with an inexpensive resource that was not available a few decades ago. Researchers have been given an opportunity to design research tools that can be seamlessly incorporated into patients' daily lives.

3.0 SPECIFIC AIMS

3.1 AIM #1: STUDY FEASIBILITY

To determine the feasibility of obtaining pain severity scores from adolescents and young adults using a web based tool.

3.2 AIM #2: PATIENT SATISFACTION

To determine patient satisfaction with a web based pain monitoring application.

4.0 METHODS AND PROCEDURES

4.1 WEBSITE DESIGN

Data Warehouse Consultants was commissioned to design a web-based application and database that allowed for pain measurements to be electronically time stamped and recorded on a secure SQL server 2008 database. The application consisted of several basic components: the patient website and database and the administrative website.

4.1.1 Patient Website and Database

This website was available on the Internet and asked participants to appraise their pain level by use of a Visual Analog Scale (VAS), ranging from 0 (no pain) to 10 (extreme pain) (Figure 6). For security reasons, participants were assigned a unique patient identification number (UPIN), which enabled them to log into the system without referencing any personal health information. Pain measurements were electronically time stamped and all information was filtered to ensure the protection of patient sensitive information. Only non-specific patient information was stored in the database.

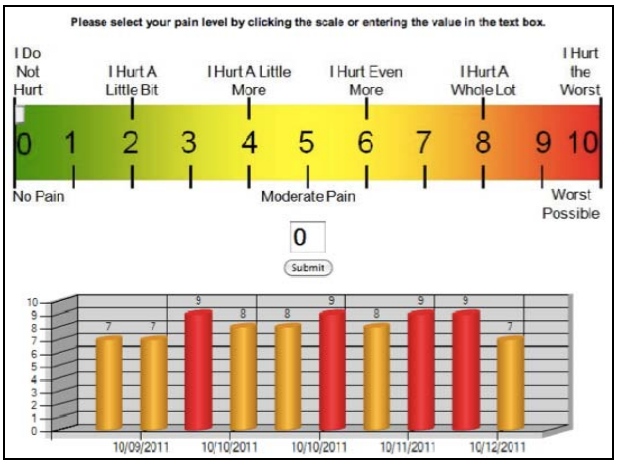

Figure 2: Depiction of Web-Based Application

4.1.2 Administrative Website

This website was created for the project administrators to manage the participants in the study. It contained web forms for enrolling patients in the study, participation statistics and provided authorized team members with each participant's contact information and pain plans. This website was available only on the CHP intranet which allowed it to leverage the existing CHP security infrastructure to maintain the highest levels of security for this type of application. The database for this application extracts data directly from the patient database so that no direct access to patient-sensitive data is possible via the Internet.

4.2 PARTICIPANT RECRUITMENT

Patients attending The Children's Hospital of Pittsburgh of UPMC Sickle Cell Clinic were approached and considered for enrollment into the University of Pittsburgh IRB approved study #PRO10110214 based on the following criteria.

4.2.1 Inclusion Criteria

1. Patients with SCD
2. Patients ranging from 12-22 years of age, on date of enrollment
3. Patients who attend the Children's Hospital of Pittsburgh's Sickle Cell Clinic
4. Patients who have access to a cellular telephone with Internet capability or computer with internet access

4.2.2 Exclusion Criteria

1. Sickle Cell patients less than 12 yrs of age or older than 22 yrs of age, on date of enrollment
2. Sickle Cell patients who do not attend the Children's Hospital of Pittsburgh's Sickle Cell Clinic
3. Sickle Cell patients who do not have access to a cellular phone with internet capabilities or a computer with internet access
4. Sickle Cell patients with severe medical complications

4.2.3 Ethical Considerations

Every possible effort was taken to include gender and racial equality into this study. Both female and minority participants were eligible for this study and encouraged to participate.

4.3 CONSENT PROCESS

All eligible participants, as specified by the above criteria, were fully briefed on the criteria, risks and benefits of the study. They were provided with an IRB approved consent form (Appendix A and Appendix B) that fully described the study and provided the participant with ample information to make an informed decision regarding their participation in the study. Subjects were assured that their participation was voluntary and that withdrawal from the study would not jeopardize current or future treatment.

Formal consent was obtained prior to any involvement in the study. The participant was provided with a copy of the consent form and the original consent was retained as part of the study records (Appendix A and B).

4.4 COMPENSATION

Participants were asked to access and enter their pain levels, on a scale of 0-10, three times a day on the web-based application. A minimum of 4 hours was required between entries. All participants in the study have been compensated in the form of a WePay® gift card. Participants who successfully reported 3 consecutive days worth of web entries had $1.50 applied to their gift card. After one week's worth of consecutive web entries participant's compensation rate was increased to $4.50 and after a month's worth of consecutive web entries compensation were increased to $19.50. If at any point the participant skipped an entry period, they were reverted back to the base compensation rate of $1.50, while still retaining the existing balance on their gift

card. Based on this scale, a participant who completed all entries over the one-year study time period would have the potential of earning $231.00 in the form of a WePay gift card.

4.5 PAIN INTERVENTION

Each participant worked with team members to define their individual baseline pain level, the level of pain at which they would like medical intervention and their self-defined pain crisis level. When a participant logged pain levels of 5.0 through 10.0 it resulted in the generation of an email/text message, alerting authorized team members of potential pain crises. An authorized team member contacted participants, when they reported pain levels equal to or greater than their previously defined medical intervention level. Participants were asked to provide details regarding the type and location of their pain, treatments they had tried and whether these treatments alleviated their pain. All contacted participants were offered the opportunity to speak with a medical professional that would provide further instructions on how to alleviate their pain.

4.6 SATISFACTION SURVEY

Six months into the study all participants were asked to complete a brief 4-point likert scale survey (Appendix C), which consisted of eleven questions. These questions addressed topics such as the user-friendliness of the application, the impact the study had on the participant's everyday life and their behavioral patterns.

4.7 STATISTICAL ANALYSIS

All data manipulations and descriptive statistics were performed with SAS 9.3. The frequency and percentages for pain entries were computed across all data, per patient and per day. The median across pain entries per patient was computed. A daily pain score was summarized as the maximum pain entry reported in a single day. The pain score was categorized into 3 groups: no pain for a pain score of 0, pain for pain scores 1-7 and crisis for pain scores 8-10. Frequency of pain days (days with a daily pain score of 1-10) and days without pain (a score of 0) were compiled and percentages computed. Means of daily pain levels were computed across all days with pain score submission, as well as across all pain days.

5.0 RESULTS

5.1 POPULATION DEMOGRAPHICS

Two hundred and fifty three patients attend the Sickle Cell clinic at The Children's Hospital of Pittsburgh of UPMC. One hundred and thirty of these patients were between 12 years and 22 years of age during the study enrollment period. Of these 130 patients, 60 (46%) attended a clinic appointment between March 17, 2011 and September 19, 2011. Thirty-one (52%) of the 60 patients approached declined to participate in the study. Reasons for not participating in the study included: lack of access to a computer or mobile device; parental restriction due to behavioral issues; and perceived burden of logging levels three times daily.

Twenty-nine patients (48%) were enrolled in the web-based study. Seven of these patients (24%) did not log any pain score for the duration of the study. Of the remaining 22 patients (76%), we excluded one (5%) because they consistently disregarded the time restriction between pain entries. The data gathered from the remaining 21 patients served as the analysis sample.

Table 2 lists the population demographics of the analysis sample (n=21). Approximately two-thirds of the study participants were female (66.7%), with a median age of 17 years. Fifty-two percent of participants (n=11/21) were diagnosed with Sickle Cell Anemia, 29% (n=6/21) of participants were diagnosed with Hemoglobin SC, 14% (n=3/21) were

diagnosed with Hemoglobin $S\beta^+$ and the remaining 5% (n=1/21) of participants were diagnosed with Hemoglobin S-HPFH.

Table 2: Participant Demographics

Genotype	n	%
Hb SS	11	52.4
Hb SC	6	28.6
Hb $S\beta^+$	3	14.3
Hb S-HPFH	1	4.8
Gender	**n**	**%**
Female	14	66.7
Male	7	33.3
Age		
Median	17	
Std Dev	2.37	
Youngest	14	
Oldest	21	

5.2 STUDY FEASIBILITY

A total of 4,981 pain entries (129 patient days) were included in this analysis. The median number of pain scores entered was 275, representing 71% of requested scores. Figure 7 depicts the distribution of pain entries based on submission type. More than half (63%) of all scores and 86% of all patient initiated submissions, were entered using the online application. Ten percent of all scores, 14% of all patient initiated submissions, were received by text message due to the participant's inability to log onto the website. Twenty-seven percent of all scores were retrieved from electronic hospital records due to the patient being hospitalized for a Sickle Cell related complication.

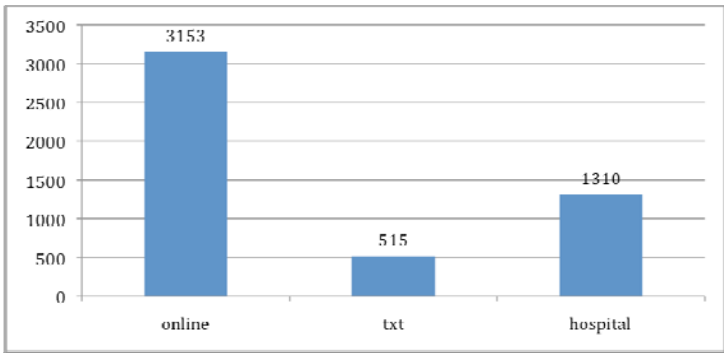

Figure 3: Distribution of Entries by Submission Type

Figure 8 represents the number of occurrences where a participant reported pain entries one, two, or three times daily. Over the course of 129 days, participants reported pain levels three times daily 67% of the time. Participants reported twice daily 21% of the time and once daily 12% of the time.

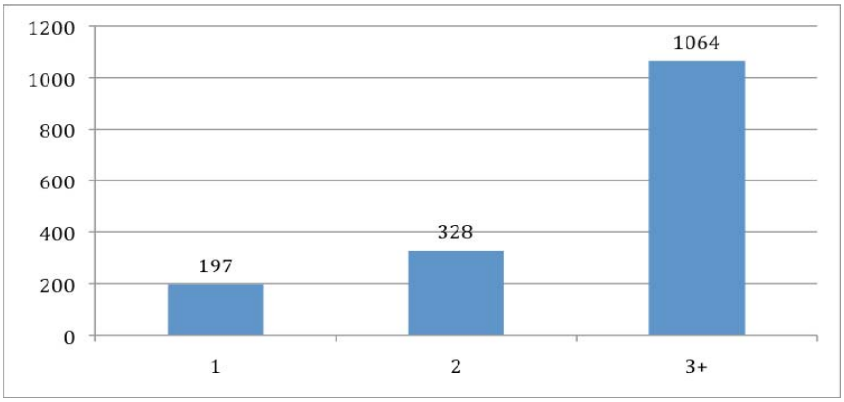

Figure 4: Frequency of Pain Entries per Day

5.3 ANALYSIS OF PAIN

Figure 9 depicts the breakdown of each individual participant's pain experience. Throughout the length of the study (n=129), a quarter of all participants reported some level of pain, with the highest mean pain level reported as an 8. One participant never reported experiencing any level of pain.

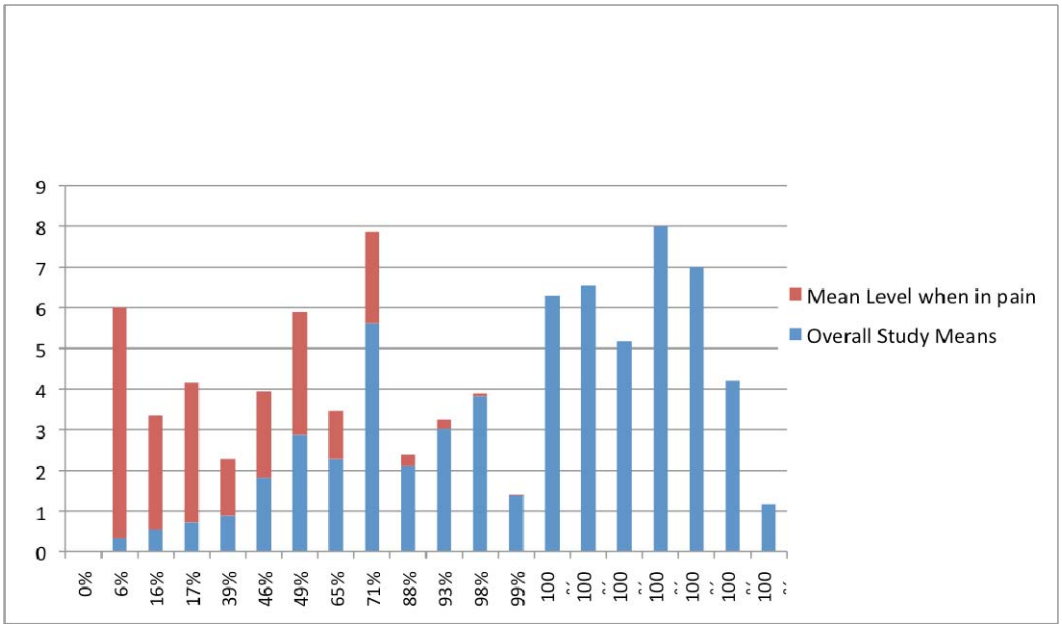

Figure 5: Individual Mean Pain Intensity

Pain entries were broken down into three ordinal, mutually exclusive categories of No "Pain", "Pain-No Crisis" and "Crisis". The category of No pain was associated with a pain score of 0. The "Pain-No Crisis" category was associatd with a pain score of 1-7 and the "Crisis" was associated with a pain score of 8-10. The "Crisis" category was further broken into "Crisis-No Utilization" and "Crisis-Utilization" based on whether the participant's pain crisis was associated with an unplanned healthcare utilization. Figure 10 depicts the percentage of patient days

(n=129) as broken down into these 4 exclusive categories. Patients reported no pain 23.4% of 129 analyzed patient days. This means that the participants were in pain 86.6% of the analyzed days. On 64.4% of these days participants reported pain without crisis. Participants reported pain with crisis 12.2% of the analyzed days but only sought medical attention 8.5% of the time.

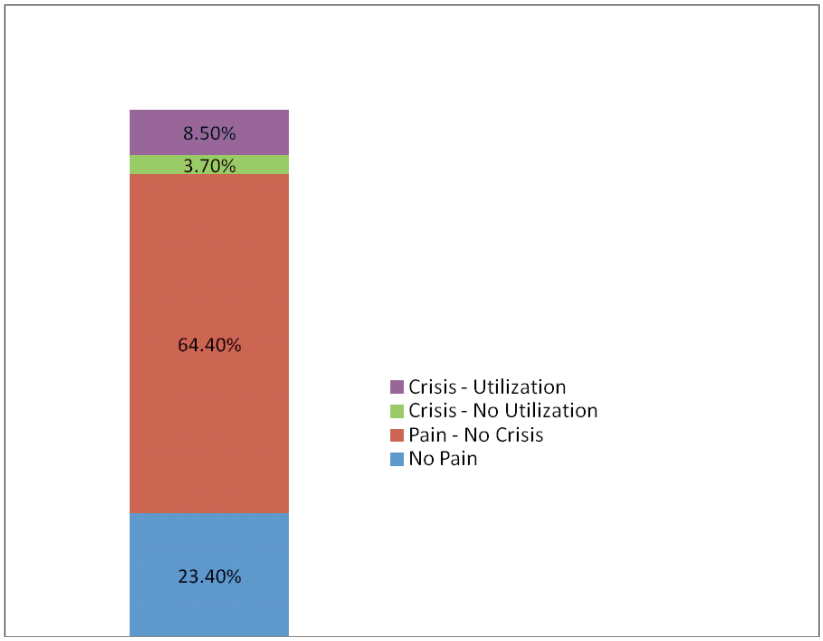

Figure 6: Frequency of Pain Episodes

5.4 SATISFACTION SURVEY

Telephone interviews were conducted to provide a 5 month interim analysis regarding participants overall satisfaction with the web-based application. The questions addressed three keys areas of interest: the user-friendliness of the web-based application, participant's immediate compliance with online monitoring and the impact of the web-based application on the participant. Responses were based on a 4-point likert scale with 1 indicating no/not at all, 2 indicating somewhat, 3 indicating considerably and 4 indicating yes/always.

All twenty-one participants were contacted, with 12 participants (57%) responding. Table 3 reports the results of the survey. Possible reasons for not responding to the survey may include: inability to be reached by telephone, discontinuation of phone service and lack of interest in participating in survey. Forty-two percent (n=5/12) of all respondents indicated that they did not have trouble accessing the web-based application from their cellular phone. Eighty-three percent (n=10/12) of respondents reported that they had no difficulty in viewing or answering the application from their cell phone or electronic device. All respondents indicated that the instructions were clear to them. Seventy-five percent of respondents (n=9/12) indicated that receiving text message reminders were beneficial in the timely submission of pain entries.

All respondents reported that they did not feel the study was a burden and would agree to participate again in a comparable study. Roughly half of all respondents (58%) indicated that this study influenced their life, by identifying patterns in their pain. Sixty-seven percent of respondents (n=8/12) reported that the application assisted them in detecting early symptoms of a pain episode and 75% of respondents (n=9/12) felt that the feedback they received from the medical team assisted them in preventing a pain episode.

Table 3: Satisfaction Survey Results

N= 11	1 (no /not at all)	2 (somewhat)	3 (considerably)	4 (yes/always)
User-friendliness of the Web-Based Application				
Did you have trouble accessing the application from your cell phone?	5	2	1	4
Did you have difficulties reading or viewing the application from your cell phone/ electronic device?	10	1	0	1
Could you conveniently answer the application from your cell phone/ computer?	1	1	0	10
Were the instructions clear to you?	0	0	0	12
Immediate compliance with online monitoring				
How often did you fill out the application directly after being prompted?	1	2	4	5
Impact of Web-Based Application				
Did you feel that participating in this study was a burden?	12	0	0	0
Did the study influence your life?	3	2	1	6
Was the number of times required to log onto the web-based application annoying?	9	3	0	0
Would you agree to participate again in a comparable study?	0	0	0	12
Web-based Application support of behavioral training				
Did the application help detect early symptoms of pain episodes?	1	3	0	8
Did the medical teams' feedback help you to take actions to prevent a pain episode?	0	2	1	9

6.0 DISCUSSION

The increase in the development of mobile devices with Internet capabilities has greatly impacted the realm of clinical research. Researchers can now utilize mobile devices in place of paper diaries to monitor participants. This study set out to determine the feasibility of using a web-based tool to monitor pain scores of adolescents and young adults with SCD. While 33% (4 out of 12 respondents) of respondents indicated that they could not access the application from their cellular phone, all four of these individuals were able to use other electronic devices (i.e. computer, iPod, etc.) to access the application. Three out of four of these respondents indicated that the lack of an adequate data package on their phone prevented them from being able to access the application. One participant had the appropriate data package in place but due to the age of their phone, had compatibility issues with accessing the application.

While this is a small study, the data suggests that the use of a web-based application is both feasible and user-friendly with 86% of all patient-initiated submissions being entered via the web-based application. This suggests that this application provides an economical alternative to previously available handheld devices. As a means of addressing some of the initial connectivity issues, participants were provided with the option of texting pain scores to the research coordinator. Reasons for texting pain scores rather than accessing the web site directly included: cell phone compatibility issues, inaccessibility due to traveling and internet connectivity.

The second goal of this study was to determine patient satisfaction with a web-based pain monitoring application. The analysis is limited by the fact that nearly half (43%) of all participants did not respond to the satisfaction survey. Possible reasons for not responding to the survey may include: inability to be reached by telephone, discontinuation of phone service and lack of interest in participating in survey. Of the 12 participants that responded, the majority (83%) felt that they could conveniently access the web-application and all respondents stated that the instructions were clear to, they did not feel that the study was a burden and they would agree to participate again in a comparable study.

When comparing our findings with those of Smith et al., our data reinforces the results that were previously reported in the adult Sickle Cell population[3]. While Smith et al. found that patients were in pain 54.5% of analyzed patient days but only sought medical attention 3.5% of the time[3], our data shows that participants were in pain 76.6% of analyzed patient days and sought medical attention 8.5% of the time. This serves to further suggest that the use of a web-based application has a viable place in the clinical research setting.

Future plans include the expansion of the web-based application to incorporate Patient Report Outcome Measurement Information System (PROMIS®) and to encompass multiple Sickle Cell clinics nationwide. PROMIS® was developed and validated by the NIH funded patient reported outcomes consortium and incorporates highly reliable and precise measurements of the effect of pain on a patient's physical, mental and social well being.

In conclusion, this study has successfully illustrated that the incorporation of a web-based application can be utilized to provide a more reliable monitoring of pain thresholds in the Sickle Cell population. The current data also suggests that participants were provided with invaluable

knowledge regarding their pain patterns and the recognition of symptoms indicative of an impending pain episode.

APPENDIX A

MINOR PARTICIPANT CONSENT FORM

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM
Parents of Minor

TITLE: Web-Based Monitoring of Pain Management in Adolescent and Young Adult Sickle Cell Patient's through Daily Self-Assessments

INVESTIGATOR: Lakshmanan Krishnamurti, M.D.
4401 Penn Avenue
Pittsburgh, Pennsylvania 15224
United States

SITE(S): Children's Hospital of Pittsburgh of UPMC
4401 Penn Avenue
Pittsburgh, Pennsylvania 15224
United States

STUDY-RELATED PHONE NUMBER(S): Lakshmanan Krishnamurti, M.D.
412-692-5055
412-692-5325 (24 hours)

SUB-INVESTIGATOR(S): Paul Pilkonis,PhD.
Nathan Dodds
Sriya Gunawardena, M.D.
Patricia McLendon, CRNP
Mary Campbell, BSN, RN
Kimberly Washington, LSW

STUDY COORDINATOR: Meagan Smith

SPONSOR: Hemostasis and Vascular Biology Research Institute
University of Pittsburgh, Pittsburgh Pennsylvania
United States

This consent form may contain words that you or your child do not understand. Please

take the time to read it carefully and ask the study doctor or study staff to explain any words that you or your child do not understand. Please get all your questions answered before you sign this consent form.

Your child is being invited to participate in a clinical research study at the University of Pittsburgh Medical Center sponsored by the University of Pittsburgh's Hemostasis and Vascular Biology Research Institute (the "Sponsor"). You are being asked if you would like your child to take part in this study because your child has sickle cell disease. Before you agree for your child to participate in this study, you need to know the risks and benefits of being in the study so you can make an informed decision about participating. This is known as "informed consent".

This consent form will tell you and your child about the study. The purpose of the study, risks, benefits, inconveniences, discomforts, and other pertinent information are discussed below. You and your child, should read it and ask the study doctors or study staff as many questions as needed before you and your child decide if you want him/her to take part in the study. You do not need to sign the consent form now. You may take the consent form home with you and talk with your child, family members and friends about the study. Once you and your child know about the study and have had all of your questions about the study answered and decide that you would like your child to participate in the study, you will be asked to sign this consent form while at a study doctor's visit with a member of the study team. A signed copy of this consent form will be given to you to keep. You or your child may have questions about this study later. There are also names and telephone numbers of people you can call to get answers to any questions you or your child may have now or at any time during or after the study. You or your child may change your mind about having him/her participate in the study at any time. You do not have to give a reason.

Your child's participation in this research study is entirely voluntary. That means you and/or your child are free to decide not to take part in or to withdraw from this study at any time, and your child will not lose any benefits of his/her routine medical care.

Why is this research being done?

The reason for this study is to collect information about the use of a web-based application to monitor the level of pain experienced in patients with sickle cell disease. This information will help us to determine whether or not this application is an appropriate method for pain monitoring and management in patients with sickle cell disease. This study will not make any specific changes to the therapy selected by your child's doctor as standard of care.

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

This study is open to males and females ages 12 years to 22 years with sickle cell disease.

How many subjects will be in this study?

Approximately 30 subjects from The Children's Hospital of Pittsburgh Sickle Cell Clinic may take part in this study.

What procedures will be performed for research purposes?

If you decide to have your child take part in this study, you, your child and your child's doctor will decide what treatment your child will receive. This decision will not be affected by your child's participation in this study. If your child is currently receiving treatment for sickle cell disease, this treatment will not be affected or changed as a result of his/her participation in this study.

Your child will be asked to complete a web-based survey, accessed from either a mobile device or computer, to identify the level of pain they are currently experiencing. S/he will be asked to access the survey three times daily for eighteen (18) months. Your child will be asked to answer a questionnaire about the web-based application after he/she has participated in the study for six (6) months and then again after twelve (12) months. Your child will also be asked to answer a short web-based survey about how pain affects their daily activities and sleeping habits. Your child will be asked to complete this survey once (1) per day for thirty (30) days.

By enrolling your child in this study, you will also authorize this research team to access your child's medical records. The information we will obtain from the medical record will focus on the your child's pain status for one year before s/he was enrolled in this study. We will also indicate, in your child's medical records, any time s/he reports a pain rating of moderate to severe.

To be a part of this study, your child will not have to make any extra office visits to see your child's study doctor, have any extra tests performed, or take any specific or additional drug.

How long will my child be in the study?

The information collection will continue for as long as you and your child feel it is appropriate or until your child has participated for eighteen (18) months.

Can I stop my child from being in the study?

Yes. You may decide to stop your child's participation in the study at any time. Tell the study doctor if you are thinking about stopping or decide to stop your child's participation.

What are the risks or possible side effects, and discomforts of this research study?

There is no risk of discomfort connected with your child providing information about their pain level, due to sickle cell disease. There is a minimal risk of a breach of confidentiality that would allow someone other than your child's study doctor and his/her study staff to link your child's information in the online application with his/her name.

Your child will be assigned a non-specific identifier when they enroll in the study. This identifier will allow him/her to log into the system without giving any personal information. All pain measurements will be stored on a secure database. All information will be filtered so that your child's personal information will only be available, behind the UPMC firewall, so that participating research staff can directly monitor his/her pain status. Your child's name and social security number would not be entered into the online database and would not be used for any other reason. If at any time you withdraw your consent for your child to continue in the study, the study staff would not request your child's social security number for any reason.

What if there are new findings?

We may learn new things about your child's health during the study that you and your child may need to know. We can also learn about things that might change your decision to allow your child to be in this study. If so, you will be notified about any new information.

What are the possible benefits from my child taking part in this study?

Your child will not receive any direct benefit by participating in this study. However, your child's participation in this program may help us understand how the pain associated with sickle cell disease is most effectively managed in the future.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?

Since we are gathering information your child's doctor would normally gather during

his/her routine care, there are no additional costs associated with participation in this study.

Will my child be paid if they take part in this study?

If you choose to have your child participate in the study they will be paid in the form of a WePay gift card, for the first twelve (12) months of the eighteen (18) month study. If your child reports their pain level three times a day for three days in a row they will have $1.50 applied to their gift card. If your child reports their pain level three times a day for seven days in a row they will then have $4.50 applied to their gift card. After reporting their pain levels three times a day for one month the amount applied to their card will be increased to $19.50. If your child skips an entry period they will start back at the base pay rate of $1.50, while still keeping the existing balance on their gift card. Based on this scale, if your child reports their pain levels over the full one year time period, they will receive $231.00 towards a WePay gift card. In addition, your child has the potential to earn an additional $50.25 towards a WePay gift card by completing the web-based survey once a day for first seven (7) months of the remaining thirteen (13) months of the study. Your child will receive $0.25 per day for completion of this survey. This means that if your child reports their pain level three times a day for one year and complete the web-based survey every day for thirty days she/he will earn $281.25 towards a WePay gift card.

Who will know about my child's participation in this research study?

All records pertaining to your child's involvement in this study are kept strictly confidential (private) and any data that includes your child's identity will be stored in locked files and will be kept for a minimum of seven years. Your child's identity will not be revealed in any description or publications of this research.

It is possible that authorized representatives from the University of Pittsburgh Research Conduct and Compliance Office may review your child's data for the purpose of monitoring the conduct of this study. In very unusual cases, your child's research records may be released in response to an order from a court of law.

If information collected in this study is shared with other researchers, the information will not include anything that will directly identify your child.

Is my child's health information protected after it has been given to others?

If you give permission to give your child's identifiable health information to a person or business, the information may no longer be protected. There is a risk that your child's information will be released to others without your permission.

May I withdraw, at a future date, my permission for my child's participation in this Research study?

Yes. To do so, you must contact the investigators who are listed on the first page of this consent form. If you withdraw your daughter or son from this study, we will continue to use the information we have collected from your child's medical records and any of the pain assessments s/he has already completed.

Is my child's participation in this study voluntary?

Yes. Your child's participation in this study is completely voluntary. Your child may refuse to take part in it, or s/he may stop participating at any time, even after signing this form. Your child's decision will not affect your relationship with or the care you receive from the UPMC/Children's Hospital Sickle Cell Clinic or the University of Pittsburgh.

If I agree to have my child take part in this research study, can my child be removed from the study without my consent?

Your child's study doctor or The University of Pittsburgh's Hemostasis and Vascular Biology Research Institute may decide to take your child out of the study at any time without your consent for any of the following reasons:

- Patients who are unable to access the internet based application within one week of the start of the study
- Patients who experience a major medical complication during the study timeframe
- Patients whose parents refuse to allow them to participate

Who should I call if my child or I have any questions?

You can talk with the study doctor about any questions or concerns you have about this study. Contact your child's study doctor, Dr. Lakshmanan Krishnamurti, at 412-692-5055 or 412-692-5325 (24 hours) for any of the following reasons:

- if you or your child have any questions about your child's participation in this study,
- if at any time you feel your child has had a research-related problem, or
- if you or your child have questions, concerns or complaints about the research.

Call the study doctor if you change your mind and decide that you no longer want your child to take part in the study.

If you have questions about your child's rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Pitt IRB
3500 Fifth Ave.
Hieber Building, Suite 106
Pittsburgh, PA 15213
Telephone: (412) 383-1480
Fax: (412) 383-1508

The University of Pittsburgh IRB is a group of people who perform independent review of research.

The University of Pittsburgh IRB will not be able to answer some study-specific questions. However, you may contact The University of Pittsburgh IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you and your child have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to allow your child to be in this study, you will receive a signed and dated copy of this consent form for your records.

VOLUNTARY PARENTAL PERMISSION

The above information has been explained to me and to my child. All of our current questions have been answered. We understand that we are encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. We understand that we may always request that our questions, concerns, or complaints be addressed by a listed investigator. We also understand that we may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

I understand that, as a minor (age less than 18 years), my child, named below, is not permitted to participate in this research study without my permission. Therefore, by signing this form, I give my permission for his/her participation in this research study.

_____
Name of Minor participant

_____
Signature of Parent

_____ _____
Printed Name of Parent Date

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

_____
Signature of Minor Participant

ASSENT SECTION:

Statement of person conducting assent discussion:

1. I have explained all aspects of the research to the subject to the best of his or her ability to understand.
2. I have answered all the questions of the subject relating to this research.
3. The subject agrees to be in the research.
4. I believe the subject's decision to enroll is voluntary.
5. The study doctor and study staff agree to respect the subject's physical or emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

_____ _____

Signature of Person Conducting Assent Discussion Date

Statement of Parent:

My child appears to understand the research to the best of his or her ability and has agreed to participate.

_____ _____

Signature of Parent or Guardian Date

CONSENT FOR CONTINUED RESEARCH PARTICIPATION
(FOR SUBJECTS WHO TURN 18 WHILE ON STUDY)

You are currently participating in a research study. Consent for your participation in this research study was initially obtained from one of your parents. You have now reached the age of 18 and you are able to provide direct consent for continued participation in this research study.

If you agree to be in this study, a signed and dated copy of this consent form will be given to you.

CONSENT

The above information has been explained to me. All of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns, or complaints be addressed by a listed investigator. I also understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I give consent to participate in this research study.

_____
Printed Name of Subject

_____
Subject's Signature Date

INVESTIGATOR'S CERTIFICATION

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been explained to the above individual and that any questions about this procedure have been answered.

Investigator's Signature (if different from above) Date

Printed Name and Role in Research Study

APPENDIX B

ADULT PARTICIPANT CONSENT FORM

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM
Adult Participant Consent Form

TITLE: Web-Based Monitoring of Pain Management in Adolescent and Young Adult Sickle Cell Patient's through Daily Self-Assessments

INVESTIGATOR: Lakshmanan Krishnamurti, M.D.
4401 Penn Avenue
Pittsburgh, Pennsylvania 15224
United States

SITE(S): Children's Hospital of Pittsburgh of UPMC
4401 Penn Avenue
Pittsburgh, Pennsylvania 15224
United States

STUDY-RELATED PHONE NUMBER(S): Lakshmanan Krishnamurti, M.D.
412-692-5055
412-692-5325 (24 hours)

SUB-INVESTIGATOR(S): Paul Pilkonis,PhD.
Nathan Dodds
Sriya Gunawardena, M.D.
Patricia McLendon, CRNP
Mary Campbell, BSN, RN
Kimberly Washington, LSW

STUDY COORDINATOR: Meagan Smith

SPONSOR: Hemostasis and Vascular Biology Research Institute
University of Pittsburgh, Pittsburgh Pennsylvania
United States

This consent form may contain words that you do not understand. Please take the time to read it carefully and ask the study doctor or study staff to explain any words that you

do not understand. Please get all your questions answered before you sign this consent form.

You are being invited to participate in a clinical research study at the University of Pittsburgh Medical Center sponsored by the University of Pittsburgh's Hemostasis and Vascular Biology Research Institute (the "Sponsor"). You are being asked if you would like to take part in this study because you have sickle cell disease. Before you agree to participate in this study, you need to know the risks and benefits of being in the study so you can make an informed decision about participating. This is known as "informed consent".

This consent form will tell you about the study. The purpose of the study, risks, benefits, inconveniences, discomforts, and other pertinent information are discussed below. You should read it and ask the study doctors or study staff as many questions as needed before you decide if you want to take part in the study. You do not need to sign the consent form now. You may take the consent form home with you and talk with your family members and friends about the study. Once you know about the study and have had all of your questions about the study answered and decide that you would like to participate in the study, you will be asked to sign this consent form while at a study doctor's visit with a member of the study team. A signed copy of this consent form will be given to you to keep. You may have questions about this study later. There are also names and telephone numbers of people you can call to get answers to any questions you may have now or at any time during or after the study. You may change your mind about having him/her participate in the study at any time. You do not have to give a reason.

Your participation in this research study is entirely voluntary. That means you are free to decide not to take part in or to withdraw from this study at any time, and you will not lose any benefits of your routine medical care.

Why is this research being done?

The reason for this study is to collect information about the use of a web-based application to monitor the level of pain experienced in patients with sickle cell disease. This information will help us to determine whether or not this application is an appropriate method for pain monitoring and management in patients with sickle cell disease. This study will not make any specific changes to the therapy selected by your doctor as standard of care.

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

This study is open to males and females ages 12 years to 22 years with sickle cell disease.

How many subjects will be in this study?

Approximately 30 subjects from The Children's Hospital of Pittsburgh Sickle Cell Clinic may take part in this study.

What procedures will be performed for research purposes?

If you decide to take part in this study, you and your doctor will decide what treatment your will receive. This decision will not be affected by your participation in this study. If you are currently receiving treatment for sickle cell disease, this treatment will not be affected or changed as a result of your participation in this study.

You will be asked to complete a web-based survey, accessed from either a mobile device or computer, to identify the level of pain you are currently experiencing. You will be asked to access the survey three times daily for eighteen (18) months. You will be asked to answer a questionnaire about the web-based application after you have participated in the study for six (6) months and then again after twelve (12) months. You will also be asked to answer a short web-based survey about how pain affects you daily activities and sleeping habits. You will be asked to complete this survey once (1) per day for the remainder of the study (thirteen (13) months).

By enrolling in this study, you will also authorize this research team to access your medical records. The information we will obtain from the medical record will focus on the your pain status for one year before you were enrolled in this study. We will also indicate, in your medical records, any time you report a pain rating of moderate to severe.

To be a part of this study, you will not have to make any extra office visits to see your study doctor, have any extra tests performed, or take any specific or additional drug.

How long will I be in the study?

The information collection will continue for as long as you feel it is appropriate or until you have participated for eighteen (18) months.

Can I stop participating in the study?

Yes. You may decide to stop your participation in the study at any time. Tell the study doctor if you are thinking about stopping or decide to stop your participation.

What are the risks or possible side effects, and discomforts of this research study?

There is no risk of discomfort connected with you providing information about your pain level, due to sickle cell disease. There is a minimal risk of a breach of confidentiality that would allow someone other than your study doctor and his/her study staff to link your information in the online application with your name.

You will be assigned a non-specific identifier when they enroll in the study. This identifier will allow you to log into the system without giving any personal information. All pain measurements will be stored on a secure database. All information will be filtered so that your personal information will only be available, behind the UPMC firewall, so that participating research staff can directly monitor your pain status. Your name and social security number would not be entered into the online database and would not be used for any other reason. If at any time you withdraw your consent to continue in the study, the study staff would not request your social security number for any reason.

What if there are new findings?

We may learn new things about your health during the study that you may need to know. We can also learn about things that might change your decision to be in this study. If so, you will be notified about any new information.

What are the possible benefits from my taking part in this study?

You will not receive any direct benefit by participating in this study. However, your participation in this program may help us understand how the pain associated with sickle cell disease is most effectively managed in the future.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?

Since we are gathering information your doctor would normally gather during you routine care, there are no additional costs associated with participation in this study.

Will I be paid if I take part in this study?

If you choose to participate in the study you will be paid in the form of a WePay gift card, for the first twelve (12) months of the eighteen (18) month study. If you report your pain level three times a day for three days in a row you will have $1.50 applied to your gift card. If you report your pain level three times a day for seven days in a row you will then have $4.50 applied to your gift card. After reporting your pain levels three times a day for one month the amount applied to your card will be increased to $19.50. If you skip an entry period you will start back at the base pay rate of $1.50, while still keeping

the existing balance on your gift card. Based on this scale, if you report your pain levels over the full one-year time period, you will receive $231.00 towards a WePay gift card. In addition, you have the potential to earn an additional $50.25 towards a WePay gift card by completing the web-based survey once a day for first seven (7) months of the remaining thirteen (13) months of the study. You will receive $0.25 per day for completion of this survey. This means that if you report your pain level three times a day for one year and complete the web-based survey every day for thirty days you will earn $281.25 towards a WePay gift card.

Who will know about my participation in this research study?

All records pertaining to your involvement in this study are kept strictly confidential (private) and any data that includes your identity will be stored in locked files and will be kept for a minimum of seven years. Your identity will not be revealed in any description or publications of this research.

It is possible that authorized representatives from the University of Pittsburgh Research Conduct and Compliance Office may review your data for the purpose of monitoring the conduct of this study. In very unusual cases, your research records may be released in response to an order from a court of law.

If information collected in this study is shared with other researchers, the information will not include anything that will directly identify you.

Is my health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

May I withdraw, at a future date, my participation in this Research study?

Yes. To do so, you must contact the investigators who are listed on the first page of this consent form. If you withdraw from this study, we will continue to use the information we have collected from your medical records and any of the pain assessments you have already completed.

Is my participation in this study voluntary?

Yes. Your participation in this study is completely voluntary. You may refuse to take part in it, or may stop participating at any time, even after signing this form. Your decision

will not affect your relationship with or the care you receive from the UPMC/Children's Hospital Sickle Cell Clinic or the University of Pittsburgh.

If I agree to take part in this research study, can I be removed from the study without my consent?

Your study doctor or The University of Pittsburgh's Hemostasis and Vascular Biology Research Institute may decide to take you out of the study at any time without your consent for any of the following reasons:

- Patients who are unable to access the internet based application within one week of the start of the study
- Patients who experience a major medical complication during the study timeframe

Who should I call if I have any questions?

You can talk with the study doctor about any questions or concerns you have about this study. Contact your study doctor, Dr. Lakshmanan Krishnamurti, at 412-692-5055 or 412-692-5325 (24 hours) for any of the following reasons:

- if you have any questions about your participation in this study,
- if at any time you feel have had a research-related problem, or
- if you have questions, concerns or complaints about the research.

Call the study doctor if you change your mind and decide that you no longer want to take part in the study.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Pitt IRB
3500 Fifth Ave.
Hieber Building, Suite 106
Pittsburgh, PA 15213
Telephone: (412) 383-1480
Fax: (412) 383-1508

The University of Pittsburgh IRB is a group of people who perform independent review of research.

The University of Pittsburgh IRB will not be able to answer some study-specific questions. However, you may contact The University of Pittsburgh IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

VOLUNTARY CONSENT

The above information has been explained to me. All of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns, or complaints be addressed by a listed investigator. I also understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I give consent to participate in this research study.

_____

Printed Name of Subject

_____

Subject's Signature Date

INVESTIGATOR'S CERTIFICATION

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been explained to the above individual and that any questions about this procedure have been answered.

Investigator's Signature (if different from above) Date

Printed Name and Role in Research Study

APPENDIX C

PARTICIPANT SATISFACTION SURVEY

Participant Satisfaction Survey

Please take a few moments to provide us with your feedback regarding your experience with the web-based application:

User-friendliness of the Web-Based Application accessed by cell phone?	**No/not**	**Somewhat**	**Considerably**	**Very Much**
Did you have trouble accessing the application from your cell phone?	**1**	**2**	**3**	**4**
Did you have difficulties reading or viewing the application from your cell phone/ electronic device?	**1**	**2**	**3**	**4**
Could you conveniently answer the application from your cell phone/ electronic device?	**1**	**2**	**3**	**4**
Were the instructions clear to you?	**1**	**2**	**3**	**4**
Immediate compliance with online monitoring				
How often did you fill out the application directly after being prompted?	**1**	**2**	**3**	**4**
Impact of Web-Based Application				
Did you feel that participating in this study was a burden?	**1**	**2**	**3**	**4**
Did the study influence your life?	**1**	**2**	**3**	**4**
Was the number of times required to log onto the web-based application annoying?	**1**	**2**	**3**	**4**
Would you agree to participate again in a comparable study?	**1**	**2**	**3**	**4**
Web-Based Application support of behavioral training				
Did the application help detect early symptoms of a pain episode?	**1**	**2**	**3**	**4**
Did the medical teams' feedback help you to take actions to prevent a pain episode?	**1**	**2**	**3**	**4**

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