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Enhancing Adherence to Prescribed Opioids Using a Mobile-Base Application: A Pilot Study of feasibility in Chronic Non-Cancer Pain

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Enhancing Adherence to Prescribed Opioids Using a Mobile-Base Application: A Pilot Study of feasibility in Chronic Non-Cancer Pain.

A thesis dissertation submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

by

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LIST OF ABBREVIATIONS

APP(S): Application(s)

SCD: Sickle Cell Disease

ISPOR: International Society for Pharmacoeconomics and Research outcome

US: United States

CDC: Center for Disease Control

PiSCES: Pain in Sickle Cell Epidemiology Study

NIH: National Institute of Health

SMS: Short Message Service

eMOD: Electronic Management of Diabetes

PRN: Pro Re Nata (When Necessary)

BPSS: Biopsychosocial-Spiritual

mHEALTH: Mobile Health

IOS: An operating system used for mobile devices manufactured by Apple Inc

SWIFT: General purpose, multi-paradigm, compiled programming language

HTTPS: Hyper Text Transfer Protocol Secure

SSL: Secure Socket Layer

VCU: Virginia Commonwealth University

SHIP-HU: Enhancing Use of Hydroxyurea In Sickle Cell Disease Using Patient Navigators

MARS: Mobile application rating scale

HIPAA: Health Insurance Portability and Accountability Act

IRB: Institutional Review Board

CORR: The CORR procedure is a statistical procedure for numeric random variables that computes Pearson correlation coefficients, three nonparametric measures of association, and the probabilities associated with these statistics

Abstract

ENHANCING ADHERENCE TO PRESCRIBED OPIOIDS USING A MOBILE-BASE APPLICATION: A PILOT STUDY OF FEASIBILITY IN CHRONIC NON-CANCER PAIN.

By Daniel Mouaffo Sop

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

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Nonadherence (overutilization and underutilization) to prescribed opioids underlies the current us opioid epidemic/crisis. Methods to measure opioid adherence have limitations or are only proxy measures. Examples of such methods include: patient recall, pill counts, refill rates, biological monitoring such as urine toxicology, and electronic monitoring such as mems caps. While not perfect, software programs or apps which collect instantaneous patient reports of utilization using reminders, and those that have the potential to encourage appropriate behavior, are gaining popularity as a way to monitor adherence. We were interested to develop such a software app to monitor opioid adherence. In this study we present feasibility of a mobile monitoring and reporting system that would provide an accurate unbiased screening tool to systematically analyze opioid adherence. In addition, the software simultaneously measures pain.

We developed this mobile-based application, OpPill, for the iOS and Android smartphone platforms. Development and testing consisted of using existing deep mixed methods research on pain behavior and opioid use among sickle cell disease (SCD) patients (n=21) to determine the most effective application content and/or structure. The application was used by sickle cell disease patients (n=30) at the Virginia Commonwealth University Health System (VCUHS).

The Mobile Applications Rating Scale: a new and validated tool for assessing the quality of health mobile apps for engagement, functionality, aesthetics, information quality, subjective quality, relevance and overall impact was administered post usage to evaluate the application.

A total of 28 patients were recruited to review and test the software at one sitting. Patients were equally divided among males and females, had a high school to graduate level education, with a majority having some college education. The majority of the population found the application to be relevant for their care. When surveyed to select all the items they thought the application was designed to do, 37% indicated that it was aimed at improving their physical health, and 37% thought it was designed to help them set goals, while 29.6% and 22.2% said respectively that it helped them feel happy/healthy and reduce negative emotions. In regards to the targeted population, patients where asked if the content was appropriate for sickle cell and the majority said it was well-targeted, with negligible issues (88.8%). Study participants were asked if they would recommend this application to people with sickle cell disease and 100% said they would recommend the application. Patients were also asked to report on the completeness of information within the app, the majority (96%) reported on the application's completeness while 4% estimated the information to be minimal or overwhelming. The quality of information as it pertains to sickle cell patients was overwhelimingly reported to be relevant (91.7%); only 8.3% found the application to be poorly relevant to sickle cell disease. The application's performance was positively rated at 100% while the ease of its use positively rated at 91.7%. Most participants (85.7%) found the application to be interesting to use while 74% found it entertaining. All users found the application's navigation to be logical and accurate with consistent and intuitive gestural design.

When asked how many times patients thought they would use the application in the next 12 months, results showed 24% would use it over 50 times, 36% would use it somewhere

between 10-50 times and 40% would only use it 3-10 times. Some patients reported that they would pay for the application (24%) while 44% said they might pay and 32% reported that they would not pay for this application. On a scale of 1 to 5 with 1 being the lowest and 5 being the highest, mean engagement, functionality, aesthetics and information scores were calculated and yielded the following results: mean engagement score: 3.96, mean functionality score: 4.54, mean aesthetics score: 3.96 and mean information score: 3.91.

We conclude that surveyed patients believe it is feasible to use a smartphone application specifically targeted to monitor opioid use and behavior in patients with sickle cell disease (SCD)-associated pain. Results are limited in that these feasibility results are based on a one-time survey of patients shown the software app at one sitting, and not on repeated app use over time. Future work should include validation via quantifying repeated app use over time, as well as reported behaviors such as opioid use while using the software app.

Vita

Daniel Mouaffo Sop was born on March 28th, 1985, in Bafoussam, Cameroon, and is a Cameroonian resident with permanent residence in the United States. He graduated from Tidewater Community college, Virginia Beach, Virginia where he received an Associate Degree in Sciences in 2008. He received his Bachelor of Sciences from Old Dominion University, Norfolk, Virginia in 2011. During that time, he was inducted in the Beta Beta Beta, Pi Delta Phi & Alpha Epsilon Delta honor societies. He subsequently volunteered as an Emergency Medical Technician for the Virginia Beach EMS while interning at Medical Center Radiologists. While pursuing his master's degree, he published 16 Abstracts on issues surrounding pain, quality of life, quality of care, resource utilization and opioids adherence and behavior in Sickle Cell disease. He led authorship on a manuscript regarding clinician's opioids prescription behavior in the emergency room. He competed in the NSF sponsored DC-I corps program and was one of 5 selected in his entire institution. He has presented his work and research related to his work at the American Society of Hematologists conference, The Foundation for Sickle Cell Disease Conference and the National Institute of Health. The Content of this research has also been selected for presentation at the 2018 mHealth Technology showcase hosted by the NIH.

Chapter 1

Introduction

American health literacy is poor. In 2004, the Institute of Medicine's report on health literacy estimated that more than 90 million people have difficulty understanding, using and acting on health information (David Kindig MD, 2004)[1]

Prescriptions and prescription errors are common. According to the Patient-Centered Primary Care Collaborative, more than 3.5 billion prescriptions are written annually in the United States, and four out of five patients who visit a physician leave with at least one prescription. Medications are involved in 80 percent of all treatments and impact every aspect of a patient's life[2]. The Institute of Medicine conducted five separate studies that placed the rate of medication errors per 100 doses from 2.4 percent to 11.1 percent in inpatient hospital settings[3].

Patient safety and important health outcomes are compromised by poor health literacy, leading to poor adherence, medication errors by patients, and medication misuse. According to the International Society for Pharmacoeconomics and Outcome Research (ISPOR), adherence is "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen"[4]. Poor adherence causes approximately 33% to 69% of medication-related hospitalizations and accounts for $100 billion in annual healthcare costs.[5] Irrespective of disease, medication complexity, or how adherence is measured, the average adherence rate to chronic medication therapy is approximately 50%.[6]. Medication nonadherence can affect patient health adversely, negatively impact a patient's relationship with his/her care provider, skew results of clinical therapy trials, and increase health resource consumption.[7,8]

Mobile health (mHealth), the general term for the use of mobile phones and other wireless technology in medical care (http://www.himss.org/mhealth), is being sought to improve prescribing, adherence, patient safety, and health outcomes. Research

conducted in 2016 by Park Associates found that more than 10 percent of the nation's caregivers are also using mHealth tools to track medications for their charges. That same study found that almost 30 percent of caregivers would be interested in using those tools, as would 41 percent of Americans who expect to care for a loved one in the future[9].

Perhaps nowhere is medication nonadherence more in the news than in opioid nonadherence, specifically opioid misuse. Currently opioids are prescribed using conventional intervals, for example, every 4 hours as needed for pain in the case of a short-acting opioid, and every 12 hours in the case of a long-acting opioid[10]. Patients may deviate from their prescribed specific dosing instructions.

It is well-recognized there is an opioid prescription epidemic in the US. Accordingly, the CDC has issued guidelines that recommend against the use of high dose opioids[11]. In addition, efforts are underway to promote safe opioid use, to improve opioid adherence, and to prevent prescription opioid diversion by identifying high-risk patients and by educating patients as well as families regarding the safe use, storage, and disposal of opioids.

A significant portion of Patients with sickle cell disease (SCD), the most common inherited blood disorder, use prescribed opioids regularly. SCD affects the hemoglobin structure of red blood cells such that they form a sickle shape. SCD produces a progressively disabling illness with severe clinical consequences. Symptoms of SCD vary but are highlighted by sudden acute unbearable pain throughout the body, known as crises in addition to profound, hemolytic anemia. A large descriptive diary study of pain and opioid use in SCD found that opioid use was prevalent including short acting and long acting. The unbearable and unpredictable pain puts patients with SCD at risk of being deprived of effective pain management because of the more recent heightened scrutiny on prescription opioid use. In a study aiming to understand adherence to opioids in sickle cell disease, results showed that many patients with SCD take their

medication differently than instructed on the prescription during and between painful episodes, both underusing and overusing their opioids, when compared to the clinician's instructions[12]. Because of the high prevalence of opioid use in patients with SCD, they are often stigmatized as drug-seeking[13]. Thus, when using the ISPOR definition, many SCD patients exhibit medication nonadherence.

Even though SCD is a unique condition as it relates to pain, in many ways it typifies chronic non-cancer pain. Clinicians who prescribe opioids to patients with chronic non-cancer pain must be concerned about the opioid epidemic and about patient safety, while simultaneously addressing patients' pain needs.

Currently popular methods to measure adherence, including patient self-reports, pill counts, refill rates, biological monitoring, and electronic monitoring, have limitations and are only proxy measures.[14,15,16] Patient self-reports rely on memory and are prone to inaccuracies and recall bias.[17] Pill counts are unreliable if patients fail to return bottles or discard pills before the count. Research in Sickle cell disease has shown that biological monitoring such as urine toxicology screens are not very precise at quantifying medication use.[18]

The use of electronic monitoring devices that detect the opening and closing of a medication bottle, such as the Medication Event Monitoring System (MEMS), has shown validity in providing an adequate representation of the complexities of patient adherence in a trial of patients undergoing remission with ulcerative colitis[19]. However, these devices do not reflect direct medication ingestion, and could be thwarted by patients attempting to hide overuse or underuse.

Currently, the most reliable way to quantify medication adherence are digital pill or ingestible biosensor systems. These systems rely on a radiofrequency emitter which directly measures medication ingestion. A study utilizing a digital pill to Assess Real-Time Medication Adherence[20] found the system also was an adequate representationof patient adherence. But although reliable, this system is impractical for use in SCD.

These systems are currently poorly available, still largely experimental, and too expensive for wide-spread use[21], especially for SCD care, due to the financial disparities of these patients.

In order to safely start, adjust, taper, and stop opioids, clinicians need to better understand contextual opioid adherence—just how and under what circumstances their patients use their prescribed opioids. Ideally, clinicians need to know when a patient takes the opioid, what dose is taken at the time, and the biopsychosocial and environmental context around that particular opioid dose. Context should include. the level of pain that triggered the opioid use, the weather at the time, and momentary stress surrounding the dose. All are known to affect pain in SCD.[22,23] With a better understanding of the opioid use pattern and context, clinicians can better identify pain triggers or exacerbating factors unique to each patient, develop a better individualized opioid management plan, and more intelligently apply non-pharmacologic interventions to mitigate pain and opioid use.

To supply this information, mHealth, specifically smartphone applications, offers a potentially useful technology. mHealth Apps are already widely used for health improvement in other chronic diseases. For example, current data demonstrate that electronic mobile devices using reminder systems through traditional means of telecommunication, like Short Message Service (SMS) text messaging, improve adherence and behavior and can be useful in measuring adherence[24]. One study found that teenagers with asthma who used a specialized system to create and schedule personal text message reminders gave the system high ratings for acceptability, ease of use, and usefulness; however, asthma control was not impacted[25]. Further, in a study to help control blood glucose levels in patients with diabetes using a comprehensive, Web-based education system and cellular phone access, the frequency of accessing the eMOD (electronic Management of Diabetes) software was significantly correlated to the change in glycosylated hemoglobin levels[26].

mHealth can offer numerous special techniques for helping patients take their medications given their customizable content, affordability and portability. Furthermore, with a medicinal services industry seeing non-adherence rates of as high as 50 percent and yearly expenses of between $100 billion and $300 billion, the potential return on investment from utilizing cell phone adherence applications could potentially outweigh the burden of non-adherence. This accessible innovation offers numerous highlights that can enable patients and healthcare providers in improving medication taking behavior.

Thus, the goal of our project was to develop and test the acceptability and usability of a mobile software application among adult patients with Sickle cell disease (SCD) to increase adherence to prescribed Opioids. Additionally, the application would allow them to report context-specific data surrounding their medication intake behavior, self-reported pain and Vaso-Occlusive crises.

Chapter 2

Literature Review

I. Sickle Cell Disease and Pain

(Samir K. Ballas, 2012) [27]Many individuals with SCD experience daily pain, which affects all aspects of life. There is great variability in the rate of recurrence and severity of pain in a SCD patient's experience. Acute and/or chronic pain may be hard to tolerate and mentally exhausting. Furthermore, this pain may limit the quality of life of patients' daily activities. Additionally, the constant pain is significantly associated with depression, anxiety, cognitive development, weight loss, disturbance in sleep, mood swings and distorted communication, and possibly loss of employment and productivity. Moreover, mistrust from other patients, caregivers, family members, and friends may lead to negative psychological effects[28].

II. Opioid analgesics in pain management for sickle cell pain

(I Boyd, 2014)[29]Prescription opioids minimize the chronic disease pain by providing pain control to SCD patients. Thus, opioid analgesics are the most commonly accepted method of pain management for sickle cell. Chronic and acute opioid treatment have been accepted as a suitable and effective method in pain management. Many studies, theories, and anecdotes demonstrate clinically significant pain relief from stable doses of opioid medication. Reduced length of hospital stay and reduced resource use of health care systems result from effective pain management and mobility. At-home pain relief using "as-needed" (PRN) analgesics for severe sickle cell pain is common; however, long-acting "scheduled" medication is more effective and could provide more consistent pain relief, generate less euphoria upon administration, allow slower development of tolerance, and offer more favorable side-effect profiles than short-acting counterparts. Many of these individuals with SCD manage pain at home using

prescribed opioid analgesics, which have been found to give significant pain relief when used appropriately[30].

III. Opioid use in sickle cell disease is controversial

(T.R. Kotila, 2015)[31]Opioid use in sickle cell disease (SCD) is controversial. SCD patients may distrust physicians and exhibit pseudo-addiction behaviors, including hoarding and going to several physicians to acquire more medication. As with other patients using prescribed opioids, SCD patients may become addicted or manifest criminal behavior with opioid use, although this is a rare occurrence. A few studies regarding long-term opioid use in SCD patients have been published[32], but an in-depth analysis of how and why SCD patients use prescribed opioids on a daily and continuous basis has not been done.

These prescription opioids are often under-prescribed due to physicians' reluctance to prescribe adequate dosages of opioid analgesia and concerns about addiction, tolerance, and side effects[33] .Physicians tend to overestimate the prevalence of opioid dependence in patients with sickle cell crises despite a low 3% incidence of opioid analgesic addiction and may even harbor negative attitudes towards SCD patients in general[34]. Nevertheless, the recent rise in prescription opioid use for cancer and non-cancer pain management remains controversial due to widely divergent perspectives and evidence regarding inadequate and unnecessary treatment of pain. Over the last two decades, the proportion of office visits in which prescriptions for potent opioids were given increased from 2% to 9%[35]. Despite this rise in rate of opioid prescription and use, there is still a significant data showing inadequate pain management[36].

To address this gap in the pain management literature for SCD and perhaps relevant to opioid use in non-cancer, chronic pain disorders, there is a need to explore how and why patients use their prescribed opioids.

IV. Momentarily Biopsychosocial-Spiritual (BPSS) Reasons

(Lou Ella V. Taylor, 2014)[37]Research on opioid use has not yet focused on time- or context-specific use of opioids and motivation to deviate from prescribed opioid regimens. In part, this is due to the irreducible nature of pain. Several models have been created to describe the nature of pain; one of the most prominent models is the Biopsychosocial Model, which divides pain into biological, psychological, and social components. Some researchers consider spirituality another component of pain management due to the nature of religious and spiritual coping methods many chronic pain sufferers utilize. The Biopsychosocial-Spiritual (BPSS) model when describing reasons behind different methods of opioid medication use in sickle cell disease because chronic pain in adults with sickle cell disease (SCD) is a complex multidimensional experience that includes biological, psychological, sociological, and spiritual factors.

V. Why adherence to prescribed opioid in SCD?

(Alsalman AJ 1, 2013)[38]Despite wide-spread acceptance in the use of opioids for chronic, non-cancer pain, there is a concern for the possibility of abuse, misuse, and diversion. In order to resolve this controversy, we must explore the motivation for patients to experience adequate pain control versus any adverse effects and the potential for abuse. It is important to evaluate medication-taking behaviors, including adherence to an established regimen, normal non-adherence to that daily regimen, and any aberrant behavior.

However, use of opiates is controversial due to its side effects and risk of addiction. Distrust from physicians and peers may lead some SCD patients to improperly use opioids and exhibit pseudo-addiction behaviors, leading to discord between healthcare providers and SCD patients. This indicates the need for effective pain management, in particular, research analyzing the motivations behind opioid use.

Despite the pain and medication adherence models in the literature, current models fail to capture time- or context-specific use of opioids. The unpredictable and severe nature of SCD pain crises as well as the conventional use of short-acting (and sometimes long-acting) opioids in the SCD patient population presents as an ideal disease paradigm in which patterns of opioid usage and adherence may be studied. Also, despite nearly a century of common use of opioids to treat pain, there is surprisingly scarce research on improving adherence to prescribed opioid in non-cancer pain and the relationship between this pain and opioids intake. Additionally, patterns underlying opioid use under specific contexts (environmental, emotional) such as those in most BPSS phenomena have not yet been tested. Alsalman AJ (1, 2013) used a confidential mixed-methods study where short surveys were utilized to quantitatively examine patterns of adherence (or nonadherence) motivations with qualitative exploration of these reasons for a more comprehensive analysis.

VI. Smartphones, Applications and Medicine

(Lindsey Dayer, 2013)[39]With the increased adoption of smartphones, there has been a simultaneous explosion of health focused mobile applications. A report from the IMS Institute for Healthcare Informatics counted over 165,000 healthcare apps available for download, many of which can be used to improve adherence for patients taking daily medications.

Medication nonadherence is a significant barrier to disease management, with estimates of nonadherence ranging from 25% to 50% depending on factors such as disease, insurance coverage, and patient characteristics. Medication nonadherence also affects health outcomes and healthcare costs. The US spends $100-$300 billion annually on avoidable health care costs due to nonadherence[40]. In response to the costs and poor health outcomes, various tailored interventions have been developed and tested to improve poor medication adherence including electronic pill boxes, text

messaging, online interventions (such as assessments), and counseling. However, despite these efforts, we still need additional tailored and effective tools to improve adherence[41].

The prevalence of smartphone usage has dramatically increased over the past several years. Presently, 77% of US adults own a smartphone, which is a big jump from the 35% who owned a smartphone in 2011. With smartphone use on the rise, Dayer and colleagues published a 2013 article about the potential benefits of mobile apps: they are relatively inexpensive, easily accessible, and available 24/7. These software interface can provide tailored reminders (both for dosages and refills), and can function as a repository for medication and user-specific information.[42]

Medication management and adherence doesn't just affect patients and their doctors. Research conducted in 2016 by Park Associates found that more than 10 percent of the nation's caregivers are also using mHealth tool to track medications for billing purposes. That same study found that almost 30 percent of caregivers would be interested in using those tools, as would 41 percent of Americans who expect to care for a loved one in the future[43].

Chapter 3

Methods

I. A rationale

Although reliable and top of the line systems such as MEMScaps and Biosensor ingestible pills exist and can provide close to or real-time adherence information, their implementation for sickle cell disease care as a method for measuring adherence is virtually impossible for several reasons. The first and main reason being the disparities that surround Sickle Cell disease and the population it affects. For example, the funding disparities for research on sickle cell compared to other pediatric diseases are very large. Cystic fibrosis, a disease that affects primarily Caucasians, occurs in only a third of the numbers affected by SCD, but received 3.5 times more NIH funding. Private funding from foundations was about 400 times higher for cystic fibrosis[44].The disparities associated to Sickle cell Disease are not limited to SCD care, research or funding. The debilitating aspect of the disease and the unpredictability of onset for associated vaso-occlusive crisis severely limits SCD patients' ability to secure and maintain gainful employment thus causing reliance on government subsidized programs, decreased quality of care and decreased quality of life[45] . These programs such as Medicare, Medicaid and other disability programs have reimbursement and category limits which would exclude Ingestible Biosensor and MEMScap implementation. The above noted adherence monitoring systems burden of costs would become patients' responsibility, a responsibility that could not be met due to their inability to secure and maintain gainful employment. Furthermore, there are challenges associated with the use and implementation of MEMScaps and ingestible sensors. In a study aiming to understand the challenges of using MEMScap, results show that acceptance of this technology proved difficult, as many patients either declined upfront or dropped out because they did not want to use the MEMS. Outcome of the final survey indicated, 41% found

transferring medication into the MEMS bottle difficult and 27.2% reported that the MEMS was a burden and/or difficult to transport. Another 22% of the patients reported that using the MEMS changed their routine, and 10.2% worried about missing their medications[46]. Ingestible biosensor also known as the digital pill is a newly FDA approved technology that records when a dose has been taken via electronic signals sent to a wearable patch (and then, to a smartphone), via a safe-for-consumption sensor inside the pill. Although the generated data is objective, this technology would incur high costs that SCD patients may not afford and raises several new questions and concerns such as privacy and HIPPA related concerns. Ingestible technology will put meaningful statistics and metrics in front of patients and doctors, in real time, from anywhere in the world. Arlyn Scales also highlights the fact that we don't know exactly what would happen if it malfunctioned, and the only way to find out is to use the technology. It's tricky, however, because the stakes are higher for a medical tool than if an iPhone dies or malfunctions[47]. Data from previous studies demonstrate that electronic mobile devices using reminder systems through traditional means of telecommunication, like Short Message Service (SMS) text messaging, improve medication adherence and patient behavior and can be useful in measuring adherence in the short term[48]. Investigators determined that sending photographs of medication capsules through cellular phones before ingestion provided more accurate time measures of adherence[49]. One study found that teenagers with asthma who used a specialized system to create and schedule personal text message reminders gave the system high ratings for acceptability, ease of use, and usefulness; however, their asthma control was similar to baseline[50]. In a study using a comprehensive, Web-based education system cellular phone access to help control blood glucose levels in patients with diabetes, the frequency of accessing the eMOD (electronic Management of Diabetes) system through a cellular phone was directly related to the change in glycosylated hemoglobin levels[51]. Although a systematic review of Internet-based

adherence interventions found promising results, it also found that the 13 studies lacked quality measurements of adherence[52]. Various studies of the use of smartphones in the clinical setting have been performed[53], but studies empirically testing smartphone apps acceptability in chronic pain with aims to improve adherence are lacking. Thus, the rationale behind our study design.

II. Specific Aims

- To develop an Electronic Data Capture platform using the OpPill mobile application to capture context-specific data associated with prescription opioid use.
- To test the acceptability and usability of the OpPill mobile application among adult patients with Sickle cell disease (SCD) to report context-specific data.

III. Study Design

The OpPill mobile application (app) was designed and built to contain the following design features: (1) An opioid use diary to allow the user to report (a) the type of opioid used, (b) the dose taken, (c) the time the medication was taken, and (d) context specific information associated with the opioid use (2) A pain diary to allow the user to report (a) pain intensity levels, (b) the time pain intensity is being experienced and (c) context specific information associated with the pain intensity level. (3) The ability for researchers to monitor and track pain level, opioid use, and context-specific information overtime. (4) The ability for the research team to communicate and provide feedback to the user. (5) The ability for the application to alert the research team of various conditions such as (a) the user's failure to access the application within a specified period of time, and (b) if opioid use exceeds a specified dose amount over a specified period of time.

1) Phase 1: Focus Groups

Phase 1 conducted by another researcher involved the recruitment of 21 patients for individual interviews to gain knowledge about sickle cell patients' typical contexts and activities reported associated with their pain and opioid use. The results of this work (Abdulkhaliq J. Alsalman, 2013) reported the following: population studied consisted of 52% (n=11) men and 48% (n=10) women with a mean age of 36 years, ranging from a diverse background of socioeconomic and educational levels. Medical history and psychological variables were assessed at baseline time. Relevant medical history predictors included history of pain days and history of analgesics medications[54]. This multi-phase mixed method study described the opioid taking behavior and the reasons for adherence to prescribed opioid of 21 SCD patients in the Adult Sickle Cell Anemia Clinic at Virginia Commonwealth University Health System (VCUHS) in Richmond, Virginia. Adherence was described and assessed by the investigator following an extensive semi-structured interview and preliminary survey regarding adherence behavior. The investigator used 24 questions in an open-ended, face-to-face interview and preliminary survey to collect data about adherence to the prescribed opioid regimens. Qualitative thematic analysis uncovered several patterns of opioid-taking behavior and several related biopsychosocial-spiritual phenomena. These patterns and phenomena portrayed a new six-domain conceptual framework that addresses the complex individual, relational, environmental, cultural, and systemic issues surrounding opioid taking-behavior in SCD. From this six-domain framework, the investigator organized the explanatory factors into a new method of classification, which included two overarching domains: intra-patient (biological, psychological, spiritual), extra-patient (social support, provider relationships, institutional norms, culture, legal and governmental policy). This classification provided a roadmap for future research that led to phase 2 of our project. The six domains explored in the research offered guidance towards understanding a complex explanation of the effect of pain, its

pharmacotherapy, and medication taking behaviors on an individual's health that simultaneously bridges all healthcare domains. The context themes and activity themes that emerged were programmed as pre-populated lists into the application.

2) Phase 2: Prototype Development

Phase 2 of the research study involved actual software application development. The OpPill application was developed to be accessible using an IOS or android powered device. The application was built using client-server architecture. The client component was built in native SWIFT code and the server component using Google Cloud Next Enterprise server to broker data exchange. The system contains a password-protected Web-interface allowing safeguards to protect users while enabling researchers the ability to create studies, add new study participants, and access results. Data entered by participants regardless of the device used will be transmitted to the server using an encrypted (HTTPS) protocol over a Secure Socket Layer (SSL) connection. The server was hosted on the Google Cloud behind a firewall in a network secure environment. A username and password was required to access data on the user end and the researcher's end. Following the development of the OpPill prototype, feedback was obtained, and a subsequent final model was built based on the feedback provided. Suggested recommendations were addressed before proceeding to high-fidelity testing.

3) Phase 3: Low-Fidelity Testing

Following the development, the app was trialed with SCD adults to determine the application content and/or structure's accuracy and appeal. The application was also demonstrated to experienced SCD clinicians for content validity evaluation and clinical significance. Input received from patients and clinicians was included in the final phases of the application's development.

4) Phase 4: High-fidelity Testing

Phase 4 involved applying the application developed to additional evaluation for its Usability, Clinical Feasibility and Compliance (High fidelity User-Centered Design parameter). This was done through an approved Institutional Review Board application to assess the application's quality at the Sickle Cell Clinic within the VCU Ambulatory care center using a Cross-sectional cohort design. We recruited a purposive, heterogeneous sample of 30 adult SCD patients for this study.

Patients were asked to use the application during their clinic visit recording their own pain, opioid use, and circumstances surrounding their input while accessing the application for engagement, functionality, aesthetics, information quality, and subjective quality. At the end of each user's trial, The Mobile Application Rating Scale (MARS), a newly validated tool was used to assess patient's feedback regarding the app (See Appendix); notably: Engagement, Functionality, Aesthetics, Information accuracy, Subjective Quality, and Perceived Impact. Responses were evaluated to explore emerging themes and field notes on 1) ease of app use, 2) general endorsement of the app (i.e. The features of the app whether it is appealing to adults with SCD or not), 3) rewarding and trust building aspects of the app, and 4) recommendations for improving the user-interface of the app. The MARS tool was first published in 2015 explaining the process used for its development and validation, thus its rarity. The MARS tool development involved a comprehensive literature search to identify articles containing explicit Web- or app-related quality rating criteria. English-language papers from January 2000 through January 2013 were retrieved from PsycINFO, ProQuest, EBSCOhost, IEEE Xplore, Web of Science, and ScienceDirect. The search terms were, "mobile" AND "app*" OR "web*" PAIRED WITH "quality" OR "criteria" OR "assess*" OR "evaluat*[55]". Per Stoyanov, criteria for the assessment of app quality were categorized by an expert panel to develop the new Mobile App Rating Scale subscales, items, descriptors, and anchors. Derivation of the MARS tool involved selecting 10 apps from

a sample of 60 apps that were randomly selected using an online randomizer. The 10 Applications were used to pilot the MARS rating procedure and the remaining 50 Applications provided data on irater reliability.

IV. Assurance of Access to Patient Sample

For pilot studies, a sample size in the range of 10 to 20 subjects is sufficient for feasibility assessments. 21 patients participated in phase1 and 30 patients in phase 4. Adults SCD subjects came from a mixture of the (Pain In Sickle Cell Epidemiologic Study) PiSCES and (Start Healing In Patients with HydroxyUrea) SHIP-HU cohort but were enriched by new adult SCD patients. Patients in this cohort met conceptually either the American Pain Society definition or the International Association for the Study of Pain's definition of chronic pain.

V. Data Collection

We collected participants demographics and Pain Characteristics to include age, race, gender, education (highest completed) and self-reported income (in categories). Opioids adherence and disease characteristics were also collected in the form of phenotypic manifestation of pain and patient's disease genotype. Acceptability, Usability and efficacy of the OpPill was tested using the validated Mobile Application Rating Scale (MARS) tool. The MARS tool was designed by a research team involved in the development and validation of eHealth and mHealth interventions, or 'eTools'[55]. The scale aimed to provide researchers, clinicians and developers with a list of evaluation criteria, and a gradient response scale for their objective evaluation. There are three main MARS factors: 1, the MARS mean; this is the mean of four objective subscales (Engagement, Functionality, Aesthetics, and Information). 2, Subjective Quality. 3, Perceived Impact. Subjective Quality and Perceived Impact are based on the rater's' own impression of the eTool, including its usability and perceived

effectiveness. Additionally, alternative pain quenching practices along with body temperature at the time of collection was captured.

VI. Data and Safety Monitoring

The research involved no more than minimal risk to the subjects. All patient data were de-identified. Patient medical records were used partly to pre-screen patients for eligibility. As part of conditions for treatment, patients sign authorization for this use. All de-identified information was maintained in a HIPAA-compliant manner.

VII.Institutional Data and Safety Monitoring Board

The VCU IRB served as the institutional review board for this study.

Chapter 4

Analysis

Characteristics and demographics of patient participants were determined using simple descriptive statics, as was the mobile application rating scale. The application's quality criteria were clustered within the engagement, functionality, aesthetics, information quality, and subjective quality categories. The subjective qualities were customized to be sickle cell disease specific in order to relate to the patient population that was evaluating the OpPill application. Each MARS item used a 5-point scale (1-Inadequate, 2-Poor, 3-Acceptable, 4-Good, 5-Excellent), descriptors for these rating anchors were written for each item. In cases where an item may not be applicable for all apps, an option of not applicable was included.

Following the MARS tool guidelines, scores were obtained by individually computing the mean scores for engagement, functionality, aesthetics, and information quality. Additionally, an overall mean app quality total was calculated. Mean scores instead of total scores are used because an item can be rated as not applicable. Additionally, mean scores are used to provide quality ratings corresponding to the familiar format of star ratings. The subjective quality sickle cell specific items were analyzed separately by computing the mean and applying the CORR procedure to evaluate the correlation of demographics, engagement, function, aesthetics and information with SCD outcomes of the OpPill application. The MARS app classification section was analyzed using simple statistics for descriptive purposes only.

Chapter 5

Results

I. Patient Population: Focus group and Low Fidelity testing – Phase 1

Study participation consisted of a one-time, approximately 1.5 hour in-person interview using interview guide (see Figure 1). The interviews were audio-recorded and subsequently transcribed for qualitative analysis. Among other inclusion and exclusion criteria, eligible subjects were to be between the ages 18 and 65 years, Having SCD diagnosis, African-American patients and feeling pain for > 30% of days in the last month. All recruited subjects have received opioid outpatient prescriptions within the previous 12 months.

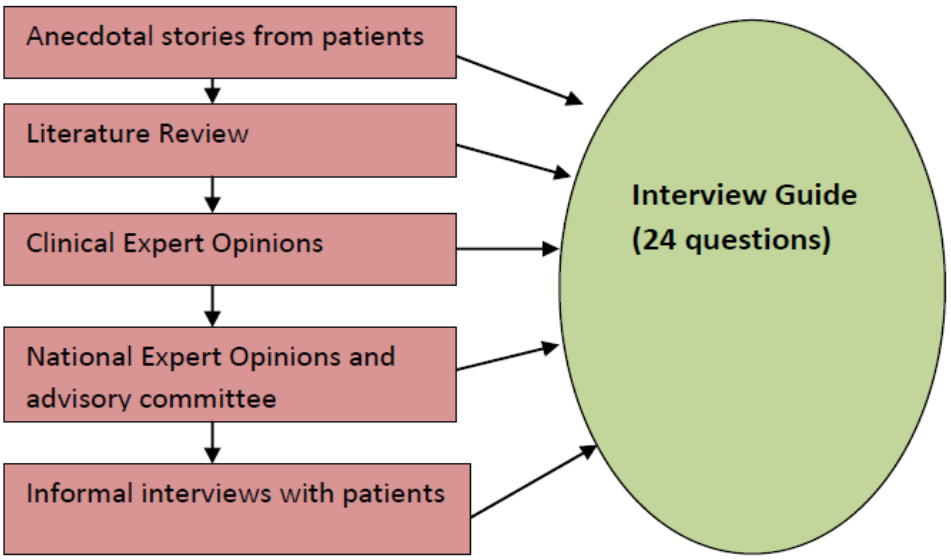
Qualitative thematic analysis revealed three phenomena: 1) SCD patients exhibited various opioid-taking behavior patterns including adherence, overuse, underuse, and erratic use; 2) Several biopsychosocial factors hindered or motivated opioid use: severe pain intensity, side effects, stress, family gatherings, unplanned meetings, religious attendance, and anticipatory fear adverse outcomes; 3) Behaviors varied based on the time of day, week, month, or year, and also based on the momentary contexts at times of actual and projected doses. Approximately 57% (n=12) of the participants were women. Patients ranged in age from 18 to 58 years. Of the 21 patients, 5 (24%) participants were married. More than half (57%) of the participants have the SS genotype of SCD. While approximately one-third (33%) of the participants have the SC genotype of SCD. When asked about rating their pain intensity on the average in last 30 days, the mean reported pain intensity was 5.5 (SD=1.7). A higher proportion (62%) of the study reported more than >50% of pain days in the last 30 days. More than half (52% (n=11)) of the participants were on both long-acting and short-acting prescribed. Notably a higher proportion (62%) of the participants have either college or some college education. Approximately 57% of the sample reported their income to be in the

range of $0 to $25,000. Approximately 24% of the patient samples are smokers. Similarly, around 24% of sample reported drinking alcohol. The interview was added below in appendix 1 and demographics representing the patient population is summarized in table 1 below.

Table1: Phase 1 demographics and Other Characteristics for Respondents

Variables	Frequency (%)
	n = 21
Age Mean (SD)	35.4 (11.4) years
Gender	
Female	57%
Marital Status	
Married	24%
Education	
High school or less	38%
College or some college	62%
Family income	
$ 0 to $25,000	56%
$25,001 to $50,000	19%
$50,001 and Over	25%
Pain Days	
≥ 30-50 days	38%
>50 days	62%
Average Pain intensity (1-10) Mean (SD)	5.5 (1.7)
Prescribed Opioid Regimen	
Short-acting (PRN) Only	52%
Both short- and long-acting	48%
Drink Alcohol	
Yes	24%
Smoke Cigarette	
Yes	24%

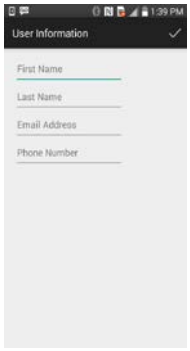
Figure 1: Developing the interview guide



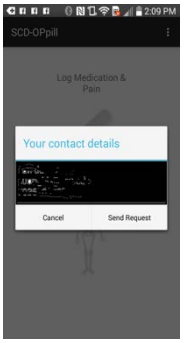
II. OpPill Application Development Phase 2

The application was designed to reflect the needs and allow for input related to recurring topics gathered from phase 1. The Application was designed to be implemented for android and apple smartphone devices. The application was built using rapid prototyping techniques. The application's screenshots for both the prototype and final product are presented in figure 2 and 3 below. A wireframe of the final product is shown below in figure 4.

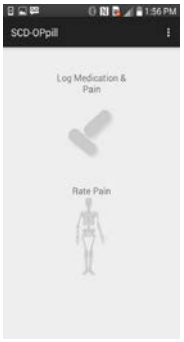
Figure 2: Prototype Screenshots



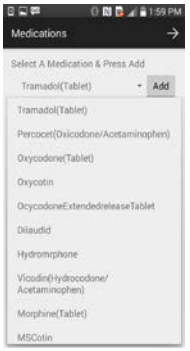
Login Screen



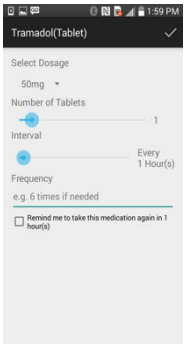
Login Verification



Main Page

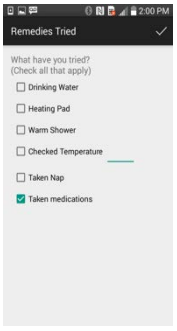


Medication Page

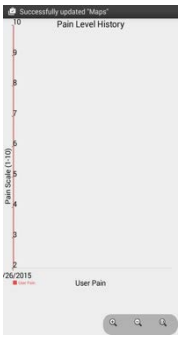


Medication Dosage

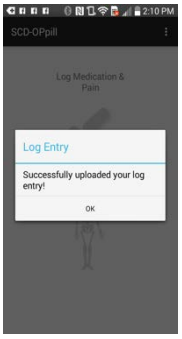
Pain Rating Page



Alt Remedies Tried



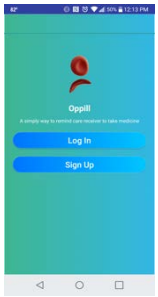
Pain Level History



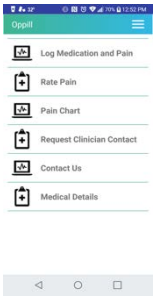
Entry Confirmation

Contact Information

Figure 3: Final Application Screenshots



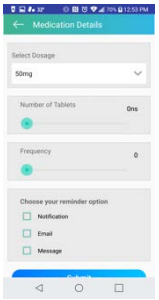
Login Screen



Main Screen

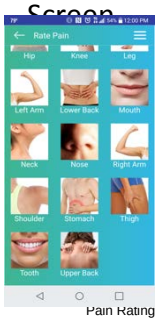
Contextual Menu

Medication List

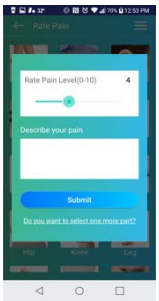


Medication Dosage

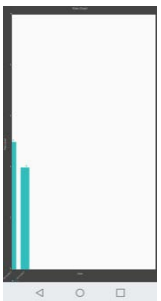
Pain Rating-1



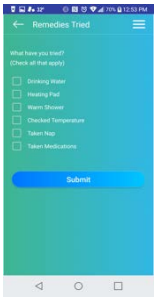
Pain Rating - 2



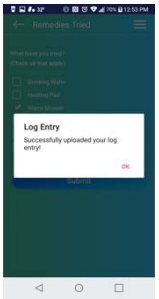
Pain Rating - 3



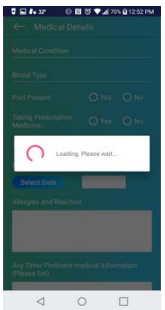
Pain Chart



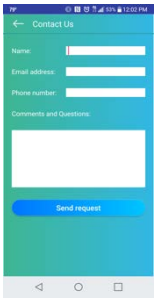
Remedies



Entry Verification

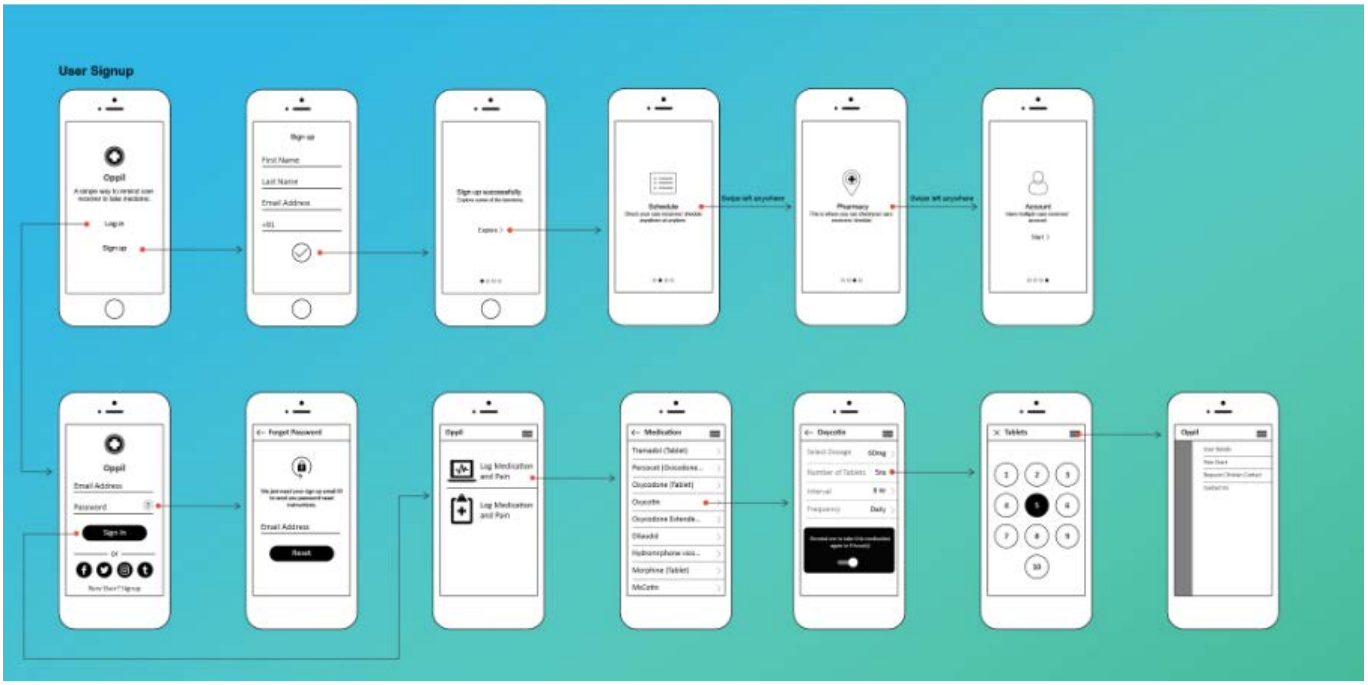


Medical Details



Contact Us Page

Figure 4: OpPill application Wireframe



III. Phase 3: Low Fidelity Testing

Following the development, the app was trialed with adults SCD caregivers to include clinicians, social workers, patient navigators, and pharmacy personnel for feedback regarding the application's appearance, content validity and flow of information. Suggestions were made to improve the application's fluidity, to break down the anatomical body image into body sections for clarity, to make the application more engaging, to improve the application's responsiveness, to improve dull coloring, to add provider information collection functions and personal medications information collection functions. The above noted feedback was verbally collected in an open conversation manner and no formal structure. These recommendations were taken into consideration and implemented in last iteration of the application's development.

IV. Study Participants Phase 4

Patients' ages ranged from 18.77 to 58.83, with a mean of 36.56 years. Overrall 46.4 %(13) participants were males whereas 53.6 %(15) were females. 2 patients were withdrawn the sample due to acute onset of Vaso-Occlusive crisis. A ranking of participant's education showed that 25%(7) had completed an education equivalent to that of a high school graduate or a GED equivalent, 39.3%(11) had completed some college, 14.3%(4) had completed a degree equivalent to that of a 2year college, 7.1%(2) had completed a 4-year degree and 14.3%(4) had completed a master's degree. None of the participants had completed a doctoral or professional education. Income representation was spread from <$10,000 (25%), $10,000 to $19,000(29.2%), $20,000 to $29,000(12.5%), $40,000to $49,000(12.5%), $50,000 to $59,000 (4.2%) to ≥$60,000 (4.2%). Sickle cell patient's genotypes represented in the study were as follows: Hemoglobin SS 26.9%(7), Hemoglobin SC 42.3%(11), Hemoglobin S β0 Thalassemia 11.5%(3), Hemoglobin S β+ Thalassemia 3.8%(2) and 15.4% where not sure of their genotypes at time of the study.

Table 2: Phase 4 study population demographics

Population Demographics

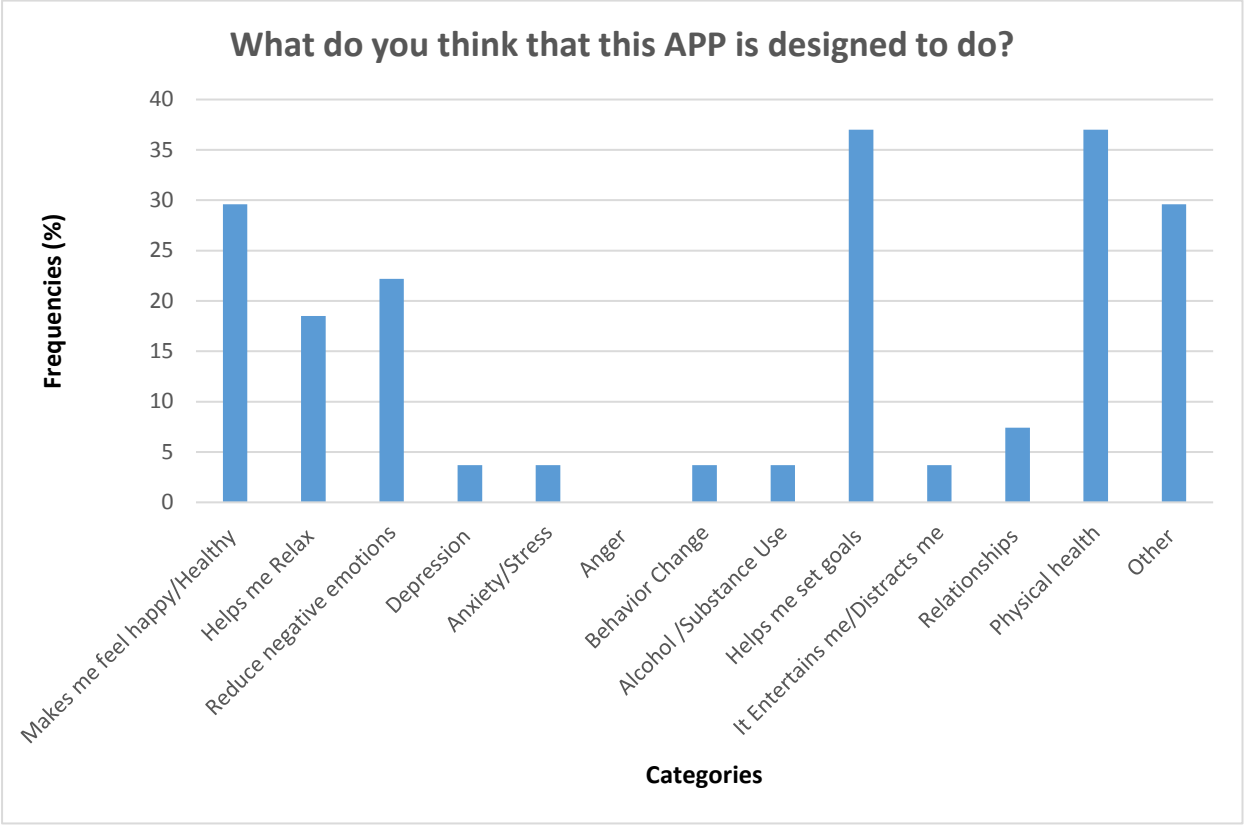
Gender	N	Frequency (%)
Male	13	46.4
Female	15	53.6
Education	**N**	**Frequency (%)**
<HS	0	0
HS/GED	7	25
Some College	11	39.3
2-yr College	4	14.3
4-yr College	2	7.1
Master's	4	14.3
Doctoral	0	0
Professional	0	0
Income	**N**	**Frequency (%)**
<10,000	6	25
10,000-19,000	7	29.2
20,000-29,000	3	12.5
30,000-39,000	0	0
40,000-49,000	3	12.5
50,000-59,000	1	4.2
≥60,000	4	16.7
Genotype	**N**	**Frequency (%)**
Hemoglobin SS	7	26.9
Hemoglobin SC	11	42.3
Hemoglobin S β0 Thalassemia	3	11.5
Hemoglobin S β++ Thalassemia	1	3.8
Don't Know	0	0
Not Sure	4	15.4
Other	0	0

IV. Application Classification

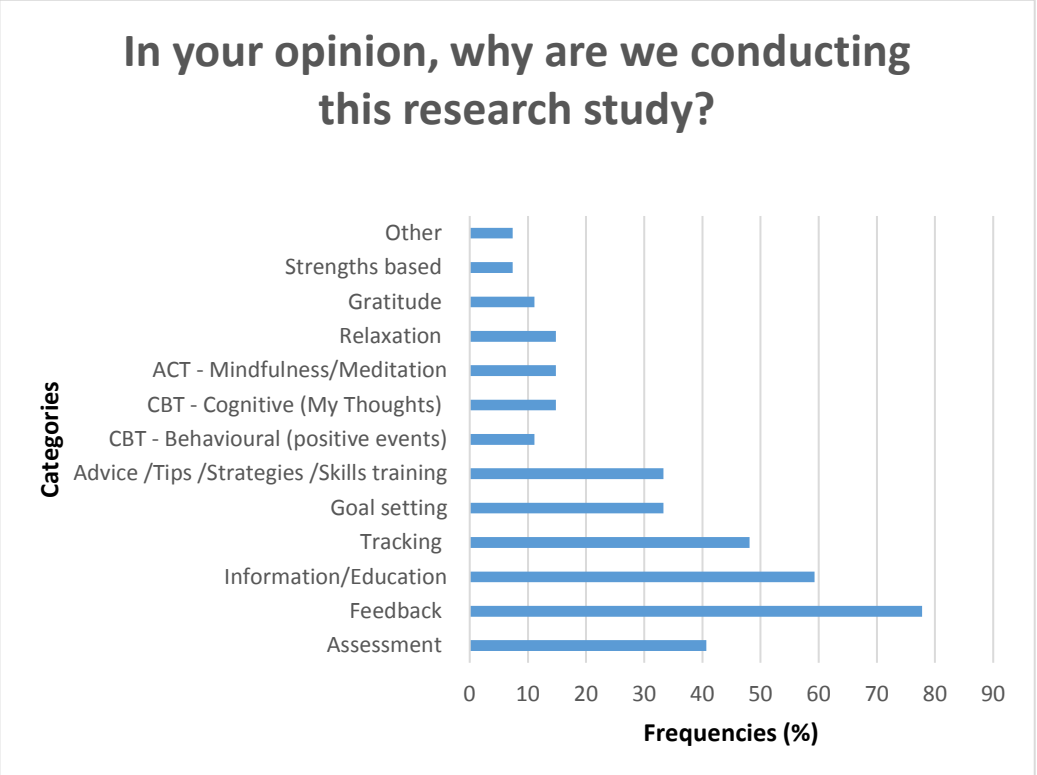
After allowing patients to use the application post consenting, two focus questions were asked to gauge their understanding of what the application was design to do and reason why the study was being conducted. This was kept in the MARS tool to gather information regarding topics that would gain the most traction in the design aspect of the application and the mean of delivery or approach with any future application as it pertains to the reason for conducting the research. Please note that participants could select more than one answer for each question. Results indicated the majority believed the application to have been designed to help them set goals (37%), to improve their physical health (37%), to help them feel happy and healthy (37%) and to reduce negative emotions (22.2%). These are the general themes that fall under the rationale driving this project indicating that our participants had a general understanding of what the application what being built for. We expected there to be a relatively high percent of patients selecting behavior change as one of the reasons for building the application, however the observed results were a mere 3.7%. The complete distribution for this question was summarized in graph 1 below.

We also gauge participants understanding of the reason why the research study was being conducted to evaluate their understanding of the study for which they had just consented to participate in. The vast majority (77.8%) reported that this study was conducted to obtain feedback regarding the application which satisfied our expectations. The next ranking response was education/information which can be explained given that we are aiming to empower patients by getting them involved in their care. The complete distribution was summarized in graph 2 below.

Graph 1: Focus – Understanding the design of the app



Graph 2: Focus – Understanding the reasoning behind the research study



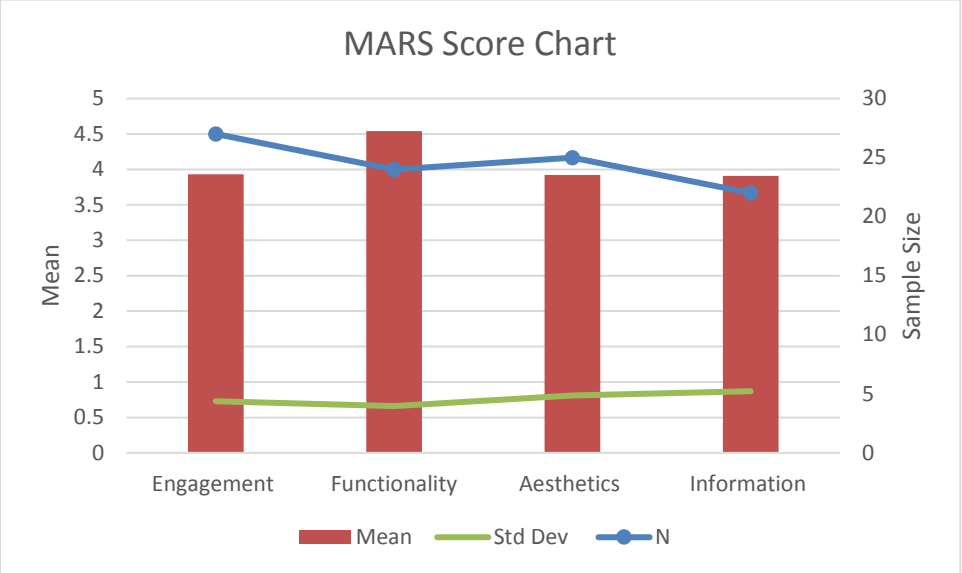
V. MARS tool Scores

The app quality criteria were clustered within the engagement, functionality, aesthetics, information quality, and subjective quality categories, to develop 23 subcategories from which the 23 individual MARS items were developed. Each MARS item used a 5-point scale (1-Inadequate, 2-Poor, 3-Acceptable, 4-Good, 5-Excellent), descriptors for these rating anchors were written for each item and results summarized in table 3 and table 4. A copy of the Mars tool was provided in appendix 3.

Table 3: MARS tool category scores

Variables	N	Mean	Min	Max	Std Dev	CI -	CI +
Engagement	27	3.93	3	5	0.73	3.64	4.22
Functionality	24	4.54	3	5	0.66	4.26	4.82
Aesthetics	25	3.92	3	5	0.81	3.59	4.25
Information	22	3.91	2	5	0.87	3.53	4.29

Graph 3: MARS Score Chart



1) Engagement

Engagement was gauged by assessing the application's ability to be fun, interesting, customizable, interactive (e.g. sends alerts, messages, reminders, feedback, enables sharing), and well-targeted to audience. Although not vigorously found to be entertaining the overwhelming majority found the application to be well targeted, interactive and customizable. Results are summarized and represented in table 4 and graph 4.

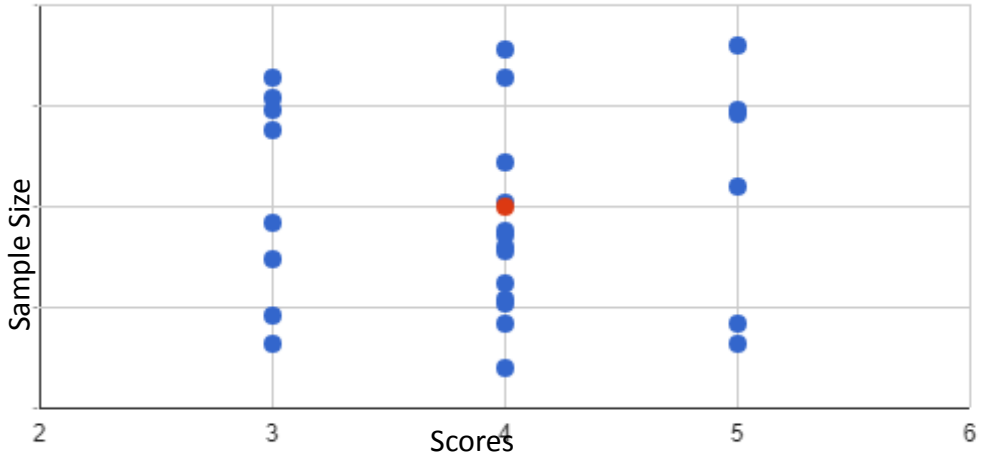
Table 4 – Application Engagement scores

SECTION A **Engagement – fun, interesting, customizable, interactive (e.g. sends alerts, messages, reminders, feedback, enables sharing), well-targeted to audience**		
Entertainment: Is the app fun/entertaining to use	**N**	**Frequency**
Dull, not at all	5	18.5
Mostly Boring	2	7.4
OK, for brief time	11	40.7
Moderately	6	22.2
Highly	3	11.1
Interest: Is the app interesting to use?	**N**	**Frequency**
Dull, not at all	2	7.1
Mostly Boring	2	7.1
OK, for brief time	4	14.3
Moderately	9	32.1
Highly	11	39.3
Customization: Does it provide/retain all necessary settings/preferences for apps features (e.g. sound, content, notifications, etc.)?	**Counts**	**Percent**
Doesn't Allow	0	0
Insufficient	2	7.7
Basic	8	30.8
Numerous Options	7	29.6
Complete Tailoring	9	34.6
Interactivity: Does this app allow user input, provide feedback, contain prompts (reminders, sharing options, notifications, etc.)?	**N**	**Frequency**
None	0	0
Insufficient	0	0
Basic	7	28
Variety	10	40
Very High	8	32
Target group: Is the app content (visual information, language, design) appropriate for sickle cell patients?	**N**	**Frequency**
Completely inappropriate	0	0
Most inappropriate	0	0
Acceptable	3	11.1
Well-targeted	12	44.4
Perfectly targeted	12	44.4
A. Engagement mean score =	3.93	

Table 5: Section A – Mean Engagement Score

Total Count (N)	Missing	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
27	1 (3.6%)	3	3.00	5.00	3.93	0.73	106.00	3.00	3.00	3.00	4.00	4.00	5.00	5.00

Graph 4: plot- MARS mean engagement score



2) FUNCTIONALITY

The application's functionally was assessed by asking patients to report on the app functioning, ease to learn, navigation, flow logic, and gestural design of app. On this topic results indicated that majority of patients found the application to be easy to use and learn, to perform as intended and easy to navigate. Results summarizing patients' report on application functionality were summarized and graphed in table 5 and graph 5.

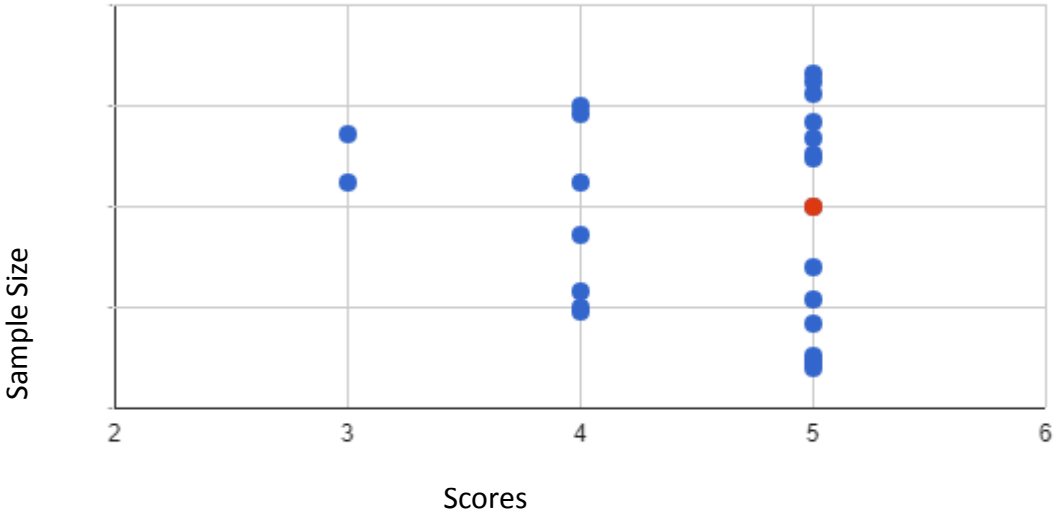
Table 6: Application functionality scores

SECTION B **Functionality – app functioning, easy to learn, navigation, flow logic, and gestural design of app**		
Performance: How accurately/fast do the app features (functions) and components (buttons/menus) work?	**N**	**Frequency**
Broken	0	0
Some functions work	0	0
Works Overall	5	20.8
Mostly Functional	7	29.2
Perfect/timely response	12	50
Ease of use: How easy is it to learn how to use the app; how clear are the menu labels/icons and instructions?	**N**	**Frequency**
No/limited Instructions	0	0
Useable after a lot of time/effort	1	4.2
Useable after some time/effort	1	4.2
Clear Instructions	9	37.5
Simple	13	54.2
Navigation: Is moving between screens logical/accurate/appropriate/ uninterrupted; are all necessary screen links present?	**N**	**Frequency**
Difficult	0	0
Useable after a lot of time/effort	0	0
Useable after some time/effort	2	8.3
Easy to use	5	20.8
Perfectly clear	17	70.8
Gestural design: Are interactions (taps/swipes/pinches/scrolls) consistent and intuitive across all components/screens?	**N**	**Frequency**
Completely Inconsistent	0	0
Often Inconsistent	0	0
OK w/ some inconsistencies	3	12.5
Mostly consistent	9	37.5
Perfectly consistent	12	50
B. Functionality mean score =	4.54	

Table 7: Section B – Mean Functionality Score

Total Count (N)	Missing	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
24	4 (14.3%)	3	3.00	5.00	4.54	0.66	109.00	3.15	4.00	4.00	5.00	5.00	5.00	5.00

Graph 5: plot- MARS mean functionality score



3) Aesthetics

Application aesthetics were assessed by asking patients to rate questions regarding the app's graphic design, overall visual appeal, color scheme, and stylistic consistency. Although 2 people indicated that the application did not look good and one patient reported that the application had a bad design, the majority found the application's layout to be satisfactory, clear or professional. Most people found the application's graphics to be of good quality and to have high visual appeal. Results were summarized in tabled 6 and graph 6.

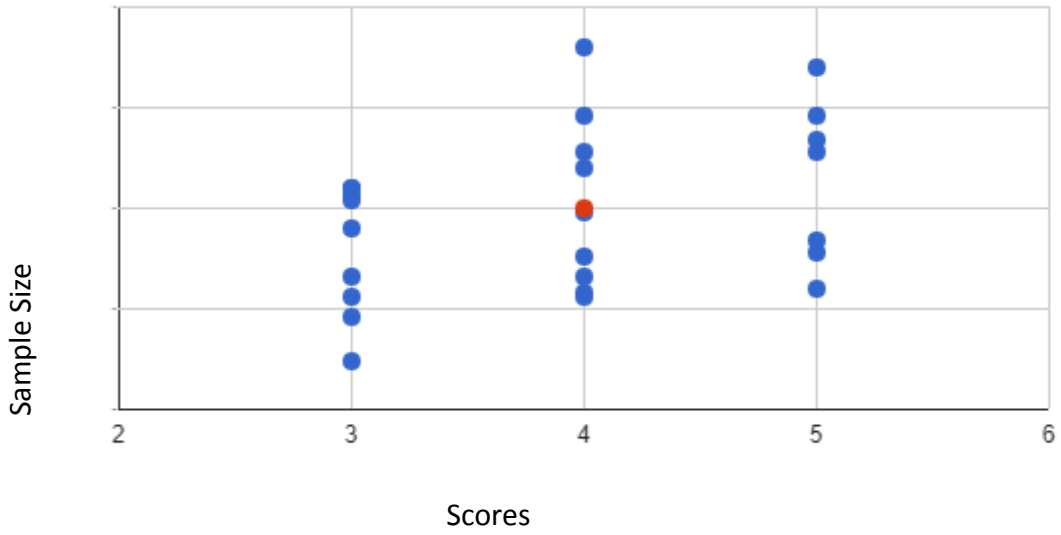
Table 8: Application Aesthetics Scores

SECTION C **Aesthetics – graphic design, overall visual appeal, color scheme, and stylistic consistency**		
Layout: Is arrangement and size of buttons/icons/menus/content on the screen appropriate or zoom able if needed?	**N**	**Frequency**
Very bad design	0	0
Bad Design	1	4
Satisfactory	3	12
Mostly Clear	12	48
Professional	9	36
Graphics: How high is the quality/resolution of graphics used for buttons/icons/menus/content?	**N**	**Frequency**
Very poor	0	0
Low quality	8	8.3
Moderate Quality	5	20.8
High Quality	10	41.7
Very High Quality	7	29.2
Visual appeal: How good does the app look?	**N**	**Frequency**
None	1	4
Little	1	4
Some	9	36
High	8	32
Very High	6	24
C. Aesthetics mean score =	3.92	

Table 9: Section C – mean Aesthetics Score

Total Count (N)	Missing	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
25	3 (10.7%)	3	3.00	5.00	3.92	0.81	98.00	3.00	3.00	3.00	4.00	5.00	5.00	5.00

Graph 6: plot- MARS mean aesthetics score



4) Information Quality

The application's quality of information was rated by participants through questions asking them to rate the content for accuracy, quality, quantity, goals and understanding. Mean scores were calculated and indicated that the majority found the information to be of high quality. Results were summarized and graphed in table 7 and graph 7.

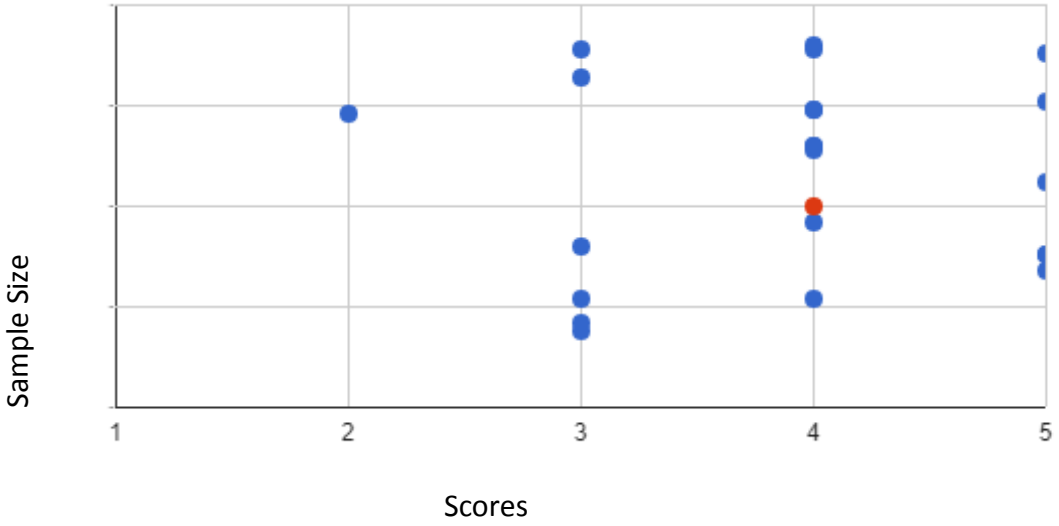
Table 10: Application information quality scores

SECTION D **Information – Contains high quality information (e.g. text, feedback, measures, references) from a credible source. Select N/A if the app component is irrelevant.**		
Accuracy of app description (in app store): Does app contain what is described?	**N**	**Frequency**
Misleading	0	0
Inaccurate	0	0
OK	3	12.5
Accurate	14	58.3
Highly Accurate	7	29.2
Goals: Does app have specific, measurable and achievable goals (specified in app store description or within the app itself)?	**N**	**Frequency**
N/A	2	8.3
App has no chance	0	0
Very little chance	3	12.5
OK	8	33.3
Likely	7	29.2
Highly likely	4	16.7
Quality of information: Is app content correct, well written, and relevant to Sickle Cell disease ?	**N**	**Frequency**
N/A	1	4.2
Irrelevant	0	0
Barely relevant	1	4.2
Moderately relevant	5	20.8
Relevant	7	29.2
Highly relevant	10	41.7
Quantity of information: Is the amount of information in the App complete?	**N**	**Frequency**
N/A	0	0
Minimal	1	4
Insufficient	0	0
OK	7	28
Broad Range	10	40
Comprehensive	7	28
Visual information: Can you understand the images displayed within the App?	**N**	**Frequency**
N/A	0	0
Complelely unclear	0	0
Mostly unclear	0	0
OK	3	12
Mostly clear	7	28
Perfectly clear	15	60
D. Information mean score =	3.91	

Table 11: Section D – Mean Information Score

Total Count (N)	Missing	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
22	6 (21.4%)	4	2.00	5.00	3.91	0.87	86.00	3.00	3.00	3.00	4.00	4.75	5.00	5.00

Graph 7: plot- MARS mean information score



5) Sickle Cell Specific and Awareness – The CORR procedure

In an effort to better understand the feedback provided by the patients, we applied the CORR procedure to evaluate the relationship between demographic information, sickle cell specific responses and the MARS classifications (engagement, functions, aesthetics and information quality) as it relates to the application.

The CORR procedure computes Pearson correlation coefficients, three nonparametric measures of association, and the probabilities associated with these statistics. Prior to analysis, a Simple statistic table is generated alongside with a variable table (see table 8) to account for variables that will be used during the analysis. See table 8 for simple statistics reports. Pearson correlation statistics are computed from observations with non-missing values for each pair of analysis variables. When using the Pearson correlation coefficient, the correlation coefficient can range in value from −1 to +1. The larger the absolute value of the coefficient, the stronger the relationship between the variables. An absolute value of 1 indicates a perfect linear relationship. A correlation close to 0 indicates no linear relationship between the variables. Table 10 displays a summary of the analysis.

Table 12: The CORR Procedure variable table

The CORR Procedure	
6 With Variables:	recommend_to_scd awareness_1 knowledge_2 attitudes_3 intention_to_change help_seeking
7 Variables:	engagement function aesthetics information age educ_ordinal income_ordinal

Table 13: The CORR Procedure Simple Statistics

Simple Statistics						
Variable	**N**	**Mean**	**Std Dev**	**Median**	**Minimum**	**Maximum**
recommend_to_scd	25	4.44000	0.86987	5.00000	3.00000	5.00000
awareness_1	24	3.87500	1.48361	5.00000	1.00000	5.00000
knowledge_2	24	3.83333	1.52277	5.00000	1.00000	5.00000
attitudes_3	23	3.86957	1.17954	4.00000	1.00000	5.00000
intention_to_change	24	4.00000	1.10335	4.00000	1.00000	5.00000
help_seeking	24	4.12500	1.03472	4.00000	1.00000	5.00000
engagement	28	3.74940	0.89198	3.80000	1.00000	5.00000
function	24	4.42708	0.60108	4.62500	3.00000	5.00000
aesthetics	25	3.90000	0.76073	4.00000	2.50000	5.00000
information	25	3.96000	0.74833	4.00000	2.40000	5.00000
age	28	36.56849	12.17949	36.25479	18.77534	58.83562
educ_ordinal	28	3.46429	1.34666	3.00000	2.00000	6.00000
income_ordinal	24	3.25000	2.23120	2.00000	1.00000	7.00000

Table 14: Spearman Correlation Coefficients – The CORR Procedure

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations							
	engagement	**function**	**aesthetics**	**information**	**age**	**educ_ordinal**	**income_ordinal**
recommend_to_scd	0.54582 0.0048 25	0.71018 0.0001 24	0.58993 0.0019 25	0.61963 0.0010 25	_0.01079 0.9592 25	0.03013 0.8863 25	0.01074 0.9632 21
awareness_1	0.60610 0.0017 24	0.26131 0.2284 23	0.52606 0.0083 24	0.50695 0.0115 24	0.06086 0.7776 24	_0.05341 0.8042 24	_0.12140 0.6102 20
knowledge_2	0.56786 0.0038 24	0.18557 0.3966 23	0.44796 0.0281 24	0.45136 0.0268 24	0.14122 0.5104 24	_0.03578 0.8682 24	_0.16201 0.4950 20
attitudes_3	0.69285 0.0002 23	0.31349 0.1554 22	0.49637 0.0160 23	0.50843 0.0132 23	_0.14116 0.5206 23	_0.04050 0.8544 23	_0.13037 0.5838 20
intention_to_change	0.49635 0.0136 24	0.31724 0.1402 23	0.52093 0.0091 24	0.58114 0.0029 24	0.06158 0.7750 24	0.08693 0.6863 24	_0.17931 0.4494 20
help_seeking	0.36803 0.0768 24	0.20212 0.3550 23	0.36442 0.0800 24	0.37597 0.0702 24	_0.01397 0.9483 24	_0.07404 0.7310 24	_0.24146 0.3051 20

Pearson correlation calculation showed several positive and linear correlation between objective scales (Engagement, Information quality, Functionality, and Aesthetics) and Sickle cell specific questions. Engagement positively and linearly correlated with the willingness to share the application with others (R=054582, P>0.05, p=0.0048), Ability for the application to raise awareness about Sickle Cell Disease (R=0.60610, P>0.05, p=0.0017) , The ability for the application to increase Sickle Cell Knowledge amongst users (R=0.56786, P>0.05, p=0.0038) , the ability for the application to increase attitude towards sickle cell disease care (R=0.69285, P>0.05, p=0.0002), The application's ability to increase motivation to change sickle cell disease care (R=0.49635, P>0.05, p=0.0136) . Positive linear correlations were also found between Aesthetics and the application's ability to raise awareness about sickle cell disease (R=0.52606, P>0.05, p=0.0083), the application's ability to increase SCD knowledge (R=0.44796, P>0.05, p=0.0281), the application's ability to increase attitude to sickle cell disease care (R=0.49637, P>0.05, p=0.0160) , the ability for the application to increase motivation to change sickle cell disease care (R=0.52093, P>0.05, p=0.0091). Positive linear correlations were also observed between the information quality subscale and the application's ability to raise awareness (R=0.50695, P>0.05, p=0.0115), increase sickle cell knowledge (R=0.45136, P>0.05, p=0.0268) , increase attitude towards SCD care (R=0.50843, P>0.05, p=0.0132) , the ability to motivate intention to change SCD care (R=0.58114, P>0.05, p=0.0029). Although there were no statistical significance in the correlation of the application's functionality and most of the sickle cell specific questions, a strong linear correlation was found with patient's willingness to recommend the application (R=0.71018, P>0.05, p=0.0001). This correlation was the highest and most statistically significant observation.

Chapter 6

Discussion & Conclusion

Discussion

Although there are several studies evaluating the use of web-based applications in medicine, there is currently no published literature evaluating the acceptance and feasibility of web-based application for adherence to prescribed opioids in SCD. Therefore, we offer alternative explanations and comparisons of the current results with past research on cancer and non-cancer pain conditions.

In addition, SCD patient care has a greater focus on not just minimizing pain to the level of “enough,” but to allow SCD patients to interact in society and the workplace with independence despite the chronic condition. Many participants emphasized (and advised other patients of) their need to perform (limited) activity and maintain a well-being to minimize the effects of SCD on their lives. Additionally, care for SCD patients may best be optimized with better medication prescribing behavior, better healthcare delivery, and better overall support. These factors are often questioned and distrusted by healthcare teams due to the disparity existing in sickle cell care. The goal of this study was to develop and test the feasibility of a mobile application for adherence to prescribed opioids and capture context-specific data associated with prescription opioid use. This goal was selected with the aim of indirectly bridging the gap of trust between sickle cell patient and provider. Patients with sickle cell disease are often categorized as “drug-seekers” because of the high dosage of opioids they need in order to appease their pain. The recent laws, regulations and attention to opioids prescriptions and opioids behaviors exacerbated this issue amongst provider thus their reluctance to prescribe high dose of opioids. Building a web-based application that allowed for patients to input their pain behavior is one way that the VCUhealth system was able to improve care for sickle cell patients. This software allowed patients to document, their opioids intake behavior and their pain rating and evaluating if the software as a means

of communication was accepted and welcomed in the sickle cell community as a way of building trust and establishing report with the care team. The majority of users in our study possessed an Android device (64%) vs iPhones (36%).

The MARS tool, a reliable, multidimensional measure for trialing, classifying, and rating the quality of mobile health apps was used to evaluate the quality of our application. The evaluation was divided into categories including: Engagement, Functionality, Aesthetics, and Information Quality. Each section was scored according to the MARS tool scoring guide by calculating each one of the above-named scales means and the overall mean app quality total score. The application's functionality rated highest (M=4.54, SD= 0.66) followed by engagement (M=3.93, SD=0.73), aesthetics (M=3.92, SD=0.81), and information quality (M=3.91, SD=0.87). The overall mean app quality total score was M=3.98, SD=0.77. These means are reported on a scale of 1 to 5 with 1 being the poorest quality and 5 being the greatest quality.

These results trendily mirrored those reported in a review and content analysis of engagement, functionality, aesthetics, information quality, and change techniques in the most popular commercial apps for weight management using the MARS tool. Bardus et al reported using the tool to independently assess 23 popular app's features, quality and content. Their reported results were: Engagement (M=3.0, SD=0.9), Functionality (M=3.8, SD=0.9), Aesthetics (M=3.4, SD=1.2) and information Quality (M=2.2, SD=0.7) with a total score (M=3.1, SD=0.8)[56]. An emerging trend with functionality leading in rating scores is observed between our study and their review although our overall performance per category is superior. These results indicate a high internal consistency and speak to the quality of the application that was developed. The application acceptance was analyzed by using the COOR procedure to find relationship between the objective subscales (Engagement, functionality, Aesthetics and Information quality) and subjective sickle cell specific questions. The app quality indicated by MARS scores was positively correlated with number of subjective sickle

cell specific topics. The Highest positive linear correlation was found between the application's functions and the willingness for participants to recommend the application to other sickle cell patients (R=0.71018, P>0.05, p=0.0001). There were no relationships found between age, income and education and any of the sickle cell specific subjective measures indicating no bias due to age, income or level of education in the application's rating using the MARS tool. Although no studies are without limitations, these results highlight the feasibility of a mobile software application as a mean of measure of adherence and context specific information surrounding Sickle Cell patients medication intake behavior and their self-reported pain.

Conclusion

The current technology driven world ruled by apps, interconnectivity and communications begs for the need of more disease-oriented web-based applications. Although large number of medication reminder apps are available in the app stores, the majority of them aim to cover a broad spectrum of disease and lack the specific focus on one disease which often only gives a snapshot or birds eye view into a patient' medication intake behavior. The goal of this project was to develop and test the acceptability of an application developed for a specific group or type of patients to help improve adherence to their opioids intake. Results showed that the application worked well and was well received in the targeted population. Engagement scores were also elevated indicating that patients increasingly want to become more engaged in their own health care, and with patient specific applications such as the we designed and used for this project, we give our patients the ability to positively impact their behaviors, improve their adherence, bridge the gap of trust between patient and provider and impact their overall health. These findings however could be biased according to the Hawthorne effect. The Hawthorne effect refers to the inclination of some people to work harder and perform better when they are being observed as part of an experiment. When transposed in a clinical research environment, this indicates that positive results could be due to the simple fact that participants are aware that they are being observed. The Hawthorne effect was evaluated in a randomized controlled trial were researchers aimed to compare minimal follow-up to intensive follow-up in participants in a placebo controlled trial of Ginkgo biloba for treating mild-moderate dementia and found that more intensive follow-up of individuals resulted in a better outcome than minimal follow-up, as measured by their cognitive functioning[57]. The bias generated by the Hawthorne effect pushes us to consider longitudinal evaluation with minimal intervention in future work when evaluating medial health applications. Our Study focused on evaluating the application's quality, future work should consider adding a

verification mechanism to validate the self-reported entries. Potential verification mechanisms could be items such as the newly FDA approved digital pill — a medication embedded within and ingestible sensor that could provide objective verification of medication adherence.

Appendix

Appendix 1: Interview Guide

Semi-Structure Interview Guide

Project Title: Understanding Adherence to Prescribed Opioids in Sickle Cell Disease
Arrival
Welcoming patient and having some informal chat in order to put them in their ease and make them feel comfortable. **Opening Questions:** How are you today? How is [school] [Work]?
"Please tell us your first and last name."
The following statement is to be read to the participants before each interview.
"Thank you so much for agreeing to participate in this study. What we would like to do today is talk about issues connected with sickle cell disease pain. We will be discussing how you manage your pain, drawing on your experiences. We want to learn from you to help other people in the future. We have a number of areas we would like to cover, including how patients use their medicine and other ways of pain control. At any time if you think of any comments or experiences, we would very much like to hear them, even if that's not what we are talking about right then. We want to understand the different ways people cope with their pain."

Introduction

Medication adherence: "As I mentioned before, the first thing we will ask you is a series of questions about your experience with pain and how it made you feel. Then we will ask you a series of questions about how patients take their prescribed pain medicines. I am interested in things that people do that affect their ways of taking their pain medicines. The purpose of the study is not to judge whether your ways of taking pain medicine are good or bad. The purposes of the study are to just learn exactly how pain affects you and what you do about it. That includes what medicines you take, and how you take them, regardless of how they are prescribed. Please try and answer each question with as much detail as possible."

Sickle Cell Anemia and Pain (generally)

1) **Beginning the interview:** I'd like to start out this interview by hearing a little bit about your experiences with Sickle Cell Disease. Can you tell me how you usually experience your disease?

   Probe:
   a) *How has your sickle cell disease pain affected your personal life? Think about when you are in pain–during that time, how are your family, life style, daily activities affected?*

2) Please tell me all the medical problems that cause you pain.

   Explore:
   a) *Follow-up questions (f/u): Of all the problems you have that are causing you pain, which one is the worst?*

3) What medicines are you currently taking for your pain? (Please tell me all you can remember, regular or occasional, prescription or over the counter).

Explore:

   a. *(f/u): How well do these medicines work for you?*

In the following questions, I would like to know about how you use your strong pain medicine like Morphine, MS Contin, Tramadol, Tylenol III, Codeine, Darvocet, propoxyphene, Percocet, OxyContin, oxycodone, Vicodin, Lortab, hydrocodone, Dilaudid,

hydromorphone, or Pain patches (Fentantl), prescribed by a doctors. But from now on I will just say pain medicine for strong pain medicine. Let's talk now about that.

Adherence to Prescribed Opioid: To Identify Actual Behavior of Use

4) It sounds like you are taking (select appropriate phrase according to above) [both] [short-acting] [and] [long-acting] to manage your pain. Thinking back over the last 30 days, how did you use your pain medicine?

Probes:

a. Do you usually use as needed and/or scheduled pain medicine every day?

b. How often do you take them? How many pills do you take each time? How many times are you supposed to take pills each day?

Explore:

a. Typically, how long do you wait to take your next dose of pain medication? What factors influence your decision?
b. How long does it take you to get comfortable after taking your medication?
c. Do you ever take your medicine in a different order or dosage than prescribed by your doctor? Why? What factors influence your decision?
d. Have you ever stopped using your medicine for any reason? Can you tell me a little bit about that?

Reasons for Underuse, Overuse, Erratic, and Quitting

5) The following questions below depend on answer to this question # 4) [For Adherent what was it that made you want to keep taking your pain medicine as prescribed?] [For Non-adherent: Why did you decide that you wanted to quit using your pain medicine?] [For Erratic User: You mention that you sometimes use more and sometime use less of your pain medications that your doctor than prescribed of your strong pain medicines; what is the reason? What made you use it that way?]

6) I know that many doctors prefer to treat sickle cell pain with a combination of as-needed and scheduled pain medicine or a number of different medicines at the same time. How do you know which kinds of medicine to use? How did you decide to take them?

7) Besides using your pain medicine to help with pain, what other methods do you use, such as home remedies?

Explore:

a. (f/u) If you use more than one method, how do you choose which one to use when? How do you combine methods?

8) Thinking about a typical day (with pain or without pain), tell me how you usually take your prescriptions during that 24 hour period.

Probes*:*

a. When do you usually take your pills?

b. Are there any times of day (or night) when you take more or less of your medications?Why?

c. How would your medication usage vary on an atypical (unusual) day? What does an atypical day look like for you? Why would you change the way you use your medicine?

9) Do you agree with the amount of pain medicine your doctor prescribes for your sickle cell pain?

Probes:

a. *Do you think that your doctor has you on the right medicines?*
b. *What changes would you make to your drug regimen if it were up to you?*

10) Regimen Complexity Do you take your pain medication the way that your doctor originally prescribed it? Have you ever had any problems understanding how to take your medications? (If so) Tell more me about it.

General Factors Affect Adherence (Motivations and Difficulties) Over the Time or Episodically

Transition: Next, I would like to ask you some questions about your experiences with pain medicine

11) Motivations or Factors for Use: What factor influence, encourage, or motivate you to use your pain medicine (scheduled pain medicine or as-needed pain medicine)?

12) Barriers, Challenges or Difficulties of Adherence to Pain Medicine at Home: Sometimes SCD adults find it difficult to take medicines as the doctor has ordered. What are some things that make it difficult to continue taking your pain medicines as prescribed? Why?

Explore:

a. *(f/u) Describe a time when you experienced difficulty taking your scheduled or as-needed pain medicine. How did these challenges affect your ways of using pain medicine?*

13) Family or Friends Concern of Opioid Use: Think of your environment. By environment I mean the physical and social world around you. How does your environment affect the way you take your medicine?

Probe:

a. *How do your family and friends affect how you take (or don't take) your pain medicine? Share with us about how people in your life play a role in taking your medicine?*
b. *(f/u) How does society affect how you take your pain medicine? Do you feel you must be "responsible" to yourself or to others?*
c. *How does the weather affect how you take your pain medicine? If you can, share with us what kinds of weather change the way you take your pain medicine.*

14) Reasons for Underuse: There are many reasons why SCD patients use less pain medicine than prescribed, don't use pain medicine for a time, or choose not to use it. Thinking about the last three months, please tell me a story of a time when you took less of your medicine than you usually take or took less than you thought you needed?

Explore:

a. *(f/u) What were the reasons for each of the times that you needed/wanted to use pain medicine, but didn't use? Describe those reasons in detail.*

15) Reasons for Overuse: There are many reasons why SCD patients use more pain medicine than prescribed or there are times when they don't need or want to use pain medicine, but they choose to use it anyway. Thinking about the last three months, please tell me a story of a time when you took more of your medicine than you usually take or took more than you thought you needed?

Explore:

a. *(f/u) What were the reasons for each of the times that you didn't need/want to use pain medicine, but used more or used it anyway? Describe those reasons in detail.*

Using Opioid for Symptoms/Reasons Other than Pain

16) Some SCD patients may use pain medicine for reasons other than pain. Thinking about the last three months, please tell me a story of a time you used your pain medicine for reasons or symptoms other than pain. How would you describe these reasons?

17) Forget or Missing Doses: People have a lot of different feelings about how medicines work and what the results are if they miss a dose. Thinking about the last three months, please tell me a story of a time you missed a dose or several doses of pain medicine.

Explore:

a. *(f/u) How did you feel you when you missed a pill or several pills?*
b. *(f/u) How important is it to you to take your medicines as prescribed? Please explain.*
c. *(f/u) What do you do when you realize you miss/forget to take a dose of your prescribed medicines? Take more, take less? Describe.*

Reasons for Episodic and Temporary Change in Adherence

Using Opioid while in Pain when Feeling Worse than Usual

18) Think back to when you were **feeling worse** pain than usual or when you having crises. What, if anything, did you do differently to get rid of your pain?

Explore:

a. *Why do you think yo**u chose to us**e your pain medicine in this way, in this situation?*
b. *(f/u) What did you do when the pain was not relieved (you **were sti**ll feeling pain) after you took your pain medicines? Did you use your pain medicine differently then? Did you use more or less than prescribed?*
c. *(f/u) What made you decide to use the medicine in such a way?*
d. *(f/u) Did the location of pain affect your way of using pain medicine?*

Using Opioid while in Pain when Feeling Good

19) When you are feeling good, how do you use your medicine?

20) Think back when you are/were feeling better after you took your pain medicines, how did you use your medicine then?

Probes:

a. *Did you ever stop taking your scheduled or as-needed medicines when you were feeling good? If so, tell more about that.*

21) Describe a time for me when you were having no/little SCD pain (or you felt better) but still chose to take more pain medicine?

Explore:

a. *(f/u) Why do you think you chose to use your pain medicine in this way, in the situation you explained to me?*

Psychosocial Factors

Using Opioid while in Pain and Having Social Activities, Special Events, Circumstances, or Situation

22) How do you use your pain medicine before, after, or during some special social event, activity or special situation?

Explore:

a. *(f/u) To what extent are you able to use your medicine as prescribed during this time? Do you change your routine?*

Using Opioid while in Pain and Having Stress or Other Psychological Components

23) How does stress in your life relate to your pain? Which usually comes first, the stress or the pain?

Explore:

a. *(f/u) How do you cope with the stress when you are in pain?*
b. *(f/u) Do you change your routine (I mean the way in which you take your medicine) when you are in stress and in pain?*
c. *(f/u) Do you change how you use your pain medicine when you are under stress?*

Ending the Interview

24) Recommendations: Based on your experience, what information do you think is important for other patients and healthcare providers to know about pain medicine?

Probes:

a. *What advice would you give a person who is considering maintaining his/ her pain medicine as prescribed or improving his /her way of taking pain medicine?*

To wrap up: We have come to the end of the interview. You explained before how you use your pain medicine and the reasons for using them. In light of what we have just been discussing (medicine use and reasons for use), I'd like to ask you if you have any additional, final comments, or anything that you think we should have talked about but didn't? This concludes ends the interview. As we conclude, I would like to thank you for your assistance with this research project. You have been most helpful in responding to the questions. Thank you for taking part in this interview and for responding to the questions so thoroughly. I appreciate your time, interest, and openness. How do you feel about the interview we have just had? May I call you if I need to clarify or add to any information you have provided? Is there anything that you would like to ask me? I am happy to answer any questions that you may have.

Appendix 2: MARS Application rating scale

Patient feedback survey

Adapted from the Mobile Application Rating Scale (MARS)

Patient ID:

The Classification section is used to collect descriptive and technical information about the app.

App Name: **OPpil** _____

Platform: ☐ iPhone ☐ iPad ☐ Android

Brief description: _____

Focus: What do you think that this APP is designed to do?
(select all that apply)

- ☐ Makes me feel happy/Healthy
- ☐ Helps me Relax
- ☐ Reduce negative emotions
- ☐ Depression
- ☐ Anxiety/Stress
- ☐ Anger
- ☐ Behavior Change
- ☐ Alcohol /Substance Use
- ☐ Helps me set goals
- ☐ It Entertains me/Distracts me
- ☐ Relationships
- ☐ Physical health
- ☐ Other _____

In your opinion, why are we conducting this research study?
(all that apply)

- ☐ Assessment
- ☐ Feedback
- ☐ Information/Education
- ☐ Tracking
- ☐ Goal setting
- ☐ Advice /Tips /Strategies /Skills training
- ☐ CBT - Behavioural (positive events)
- ☐ CBT – Cognitive (My Thoughts) ☐ ACT - Acceptance commitment therapy ☐ Mindfulness/Meditation
- ☐ Relaxation
- ☐ Gratitude
- ☐ Strengths based
- ☐ Other _____

Affiliations: To the best of your knowledge, this research is associated with which one of these?

□□ Unknown □□ Commercial □□ Government □□ NGO
□□ University

Please select the age group in which you belong

□□ Children (under 12) □□ Adolescents (13-17) □□ Young Adults (18-25) □□ Adults
□□ General

Technical aspects of app (all that apply)

□□ Allows sharing (Facebook, Twitter, etc.)
□□ Has an app community
□□ Allows password-protection
□□ Requires login
□□ Sends reminders
□□ Needs internet to function

App Quality Ratings

The Rating scale assesses app quality on four dimensions. All items are rated on a 5-point scale from "1.Inadequate" to "5.Excellent". Circle the number that most accurately represents the quality of the app component you are rating. Please use the choices provided for each response category.

SECTION A

Engagement – fun, interesting, customizable, interactive (e.g. sends alerts, messages, reminders, feedback, enables sharing), well-targeted to audience

1. **Entertainment: Is the app fun/entertaining to use?**

   1 Dull, not fun or entertaining at all

   2 Mostly boring

   3 OK, fun enough to entertain user for a brief time (< 5 minutes)

   4 Moderately fun and entertaining, would entertain user for some time (5-10 minutes total)

   5 Highly entertaining and fun, would stimulate repeat use

2. **Interest: Is the app interesting to use?**

   1 Not interesting at all

   2 Mostly uninteresting

   3 OK, neither interesting nor uninteresting; would engage user for a brief time (< 5 minutes)

   4 Moderately interesting; would engage user for some time (5-10 minutes total)

   5 Very interesting, would engage user in repeat use

3. **Customization: Does it provide/retain all necessary settings/preferences for apps features (e.g. sound, content, notifications, etc.)?**

   1 Does not allow any customization or requires setting to be input every time

   2 Allows insufficient customization limiting functions

   3 Allows basic customization to function adequately

   4 Allows numerous options for customization

   5 Allows complete tailoring to the individual's characteristics/preferences, retains all settings

4. **Interactivity: Does this app allow user input, provide feedback, contain prompts (reminders, sharing options, notifications, etc.)?**

   1 No interactive features and/or no response to user interaction

2 Insufficient interactivity, or feedback, or user input options, limiting functions

3 Basic interactive features to function adequately

4 Offers a variety of interactive features/feedback/user input options

5 Very high level of responsiveness through interactive features/feedback/user input options

5. **Target group: Is the app content (visual information, language, design) appropriate for sickle cell patients?**

1 Completely inappropriate/unclear/confusing

2 Mostly inappropriate/unclear/confusing

3 Acceptable but not targeted. May be inappropriate/unclear/confusing

4 Well-targeted, with negligible issues

5 Perfectly targeted, no issues found

A. Engagement mean score = ____

SECTION B

Functionality – app functioning, easy to learn, navigation, flow logic, and gestural design of app

6. Performance: How accurately/fast do the app features (functions) and components (buttons/menus) work?

1 App is broken; no/insufficient/inaccurate response (e.g. crashes/bugs/broken features, etc.)

2 Some functions work, but lagging or contains major technical problems

3 App works overall. Some technical problems need fixing/Slow at times

4 Mostly functional with minor/negligible problems

5 Perfect/timely response; no technical bugs found/contains a 'loading time left' indicator

7. Ease of use: How easy is it to learn how to use the app; how clear are the menu labels/icons and instructions?

1 No/limited instructions; menu labels/icons are confusing; complicated

2 Useable after a lot of time/effort

3 Useable after some time/effort

4 Easy to learn how to use the app (or has clear instructions)

5 Able to use app immediately; intuitive; simple

8. Navigation: Is moving between screens logical/accurate/appropriate/ uninterrupted; are all necessary screen links present?

1 Different sections within the app seem logically disconnected and random/confusing/navigation is difficult

2 Usable after a lot of time/effort

3 Usable after some time/effort

4 Easy to use or missing a negligible link

5 Perfectly logical, easy, clear and intuitive screen flow throughout, or offers shortcuts

9. Gestural design: Are interactions (taps/swipes/pinches/scrolls) consistent and intuitive across all components/screens?

1 Completely inconsistent/confusing

2 Often inconsistent/confusing

3 OK with some inconsistencies/confusing elements

4 Mostly consistent/intuitive with negligible problems

5 Perfectly consistent and intuitive

B. Functionality mean score = ___

SECTION C

Aesthetics – graphic design, overall visual appeal, color scheme, and stylistic consistency

10. Layout: Is arrangement and size of buttons/icons/menus/content on the screen appropriate or zoom able if needed?

1 Very bad design, cluttered, some options impossible to select/locate/see/read device display not optimized

2 Bad design, random, unclear, some options difficult to select/locate/see/read

3 Satisfactory, few problems with selecting/locating/seeing/reading items or with minor screen- size problems

4 Mostly clear, able to select/locate/see/read items

5 Professional, simple, clear, orderly, logically organized, device display optimized. Every design component has a purpose

11. Graphics: How high is the quality/resolution of graphics used for buttons/icons/menus/content?

1 Graphics appear amateur, very poor visual design - disproportionate, completely stylistically inconsistent

2 Low quality/low resolution graphics; low quality visual design – disproportionate, stylistically inconsistent

3 Moderate quality graphics and visual design (generally consistent in style)

4 High quality/resolution graphics and visual design – mostly proportionate, stylistically consistent

5 Very high quality/resolution graphics and visual design - proportionate, stylistically consistent throughout

12. Visual appeal: How good does the app look?

1 No visual appeal, unpleasant to look at, poorly designed, clashing/mismatched colors

2 Little visual appeal – poorly designed, bad use of color, visually boring

3 Some visual appeal – average, neither pleasant, nor unpleasant

4 High level of visual appeal – seamless graphics – consistent and professionally designed

5 As above + very attractive, memorable, stands out; use of color enhances app features/menus

C. Aesthetics mean score = _____

SECTION D

Information – Contains high quality information (e.g. text, feedback, measures, references)
from a credible source. Select N/A if the app component is irrelevant.

13. Accuracy of app description (in app store): Does app contain what is described?

1 Misleading. App does not contain the described components/functions. Or has no description

2 Inaccurate. App contains very few of the described components/functions

3 OK. App contains some of the described components/functions

4 Accurate. App contains most of the described components/functions

5 Highly accurate description of the app components/functions

14. Goals: Does app have specific, measurable and achievable goals (specified in app store description or within the app itself)?

N/A Description does not list goals, or app goals are irrelevant to research goal (e.g. using a game for educational purposes)

1 App has no chance of achieving its stated goals

2 Description lists some goals, but app has very little chance of achieving them

3 OK. App has clear goals, which may be achievable.

4 App has clearly specified goals, which are measurable and achievable

5 App has specific and measurable goals, which are highly likely to be achieved

15. Quality of information: Is app content correct, well written, and relevant to Sickle Cell disease ?

N/A There is no information within the app

1 Irrelevant**/**inappropriate/incoherent/incorrect

2 Poor. Barely relevant/appropriate/coherent**/**may be incorrect

3 Moderately relevant/appropriate/coherent**/**and appears correct

4 Relevant**/**appropriate/coherent/correct

5 Highly relevant, appropriate, coherent, and correct

16. Quantity of information: Is the amount of information in the App complete?

N/A There is no information within the app
1 Minimal or overwhelming
2 Insufficient or possibly overwhelming
3 OK but not comprehensive or concise
4 Offers a broad range of information, has some gaps or unnecessary detail; or has no links to more information and resources
5 Comprehensive and concise; contains links to more information and resources

17. Visual information: Can you understand the images displayed within the App?

N/A There is no visual information within the app (e.g. it only contains audio, or text)
1 Completely unclear/confusing/wrong or necessary but missing
2 Mostly unclear/confusing/wrong
3 OK but often unclear/confusing/wrong
4 Mostly clear/logical/correct with negligible issues
5 Perfectly clear/logical/correct

D. Information mean score = _____ *

* Exclude questions rated as “N/A” from the mean score calculation.

App subjective quality

SECTION E

20. Would you recommend this app to people with sickle cell disease?

1	**Not at all**	I would not recommend this app to
2		There are very few people I would
3	**Maybe**	There are several people whom I would
4		There are many people I would
5	**Definitel**	I would recommend this app to everyone

21. How many times do you think you would use this app in the next 12 months if it was relevant to you?

1 **None**
2 1-2
3 3-10
4 10-50
5 >50

22. Would you pay for this app?

1 No
3 Maybe
5 Yes

23. What is your overall star rating of the app?

1	⋆⋆	One of the worst apps I've used
2	⋆⋆⋆⋆	
3	⋆⋆⋆⋆⋆⋆	Average
4	⋆⋆⋆⋆⋆⋆⋆⋆	
5	⋆⋆⋆⋆⋆⋆⋆⋆⋆⋆	One of the best apps I've used

Scoring

App quality scores for

SECTION

A: Engagement Mean Score = _____

B: Functionality Mean Score = _____

C: Aesthetics Mean Score = _____

D: Information Mean Score = _____

App quality mean Score = _____

App subjective quality Score = _____

App-specific

These added items can be adjusted and used to assess the perceived impact of the app on the user's knowledge, attitudes, intentions to change as well as the likelihood of actual change in the target health behavior.

SECTION F

1. Awareness: This app is likely to increase awareness of the importance of addressing Sickle Cell disease

Strongly				Strongly
1	2	3	4	5

2. Knowledge: This app is likely to increase knowledge/understanding of Sickle cell disease

Strongly				Strongly
1	2	3	4	5

3. Attitudes: This app is likely to change attitudes toward improving Sickle cell disease

Strongly				Strongly
1	2	3	4	5

4. Intention to change: This app is likely to increase intentions/motivation to address Sickle cell disease

Strongly				Strongly
1	2	3	4	5

5. Help seeking: Use of this app is likely to encourage further help seeking for sickle cell disease

Strongly				Strongly
1	2	3	4	5

6. Behavior change: Use of this app is likely increase/decrease sickle cell disease

Strongly				Strongly
1	2	3	4	5

Appendix 4: IRB Approval Letter

Office of Research and Innovati
Office of Research Subjects Protect
BioTechnology Research P
800 East Leigh Street, Suite 3
Box 9805
Richmond, Virginia 23298-05

(804) 828-08
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TO: Thokozeni Lipato
Catherine Law
Thokozeni Lipato
CC: Wally Smith
Daniel Sop

FROM: VCU IRB Panel A

RE: Thokozeni Lipato ; IRB HM20005141 Enhancing Adherence to Prescribed Opioids Using A Mobile-Based App: A Pilot Study in Non-Cancer Pain

On 2/16/2017, the referenced research study was ***approved*** by expedited review according to 45 CFR 46.110 by VCU IRB Panel A. This study is approved under Expedited categories **1, 7**.

The information found in the electronic version of this study's smart form and uploaded documents now represents the currently approved study, documents, informed consent process, and HIPAA pathway (if applicable). You may access this information by clicking the Study Number above.

This approval expires on *1/31/2018*. Federal Regulations/VCU Policy and Procedures require continuing review prior to continuation of approval past that date. Continuing Review notices will be sent to you prior to the scheduled review.

If you have any questions, please contact the Office of Research Subjects Protection (ORSP) or the IRB reviewer(s) assigned to this study.

The reviewer(s) assigned to your study will be listed in the History tab and on the study workspace. Click on their name to see their contact information.

Attachment – Conditions of Approval

Conditions of Approval:

In order to comply with federal regulations, industry standards, and the terms of this approval, the investigator must (as applicable):

1. Conduct the research as described in and required by the Protocol.

2. Obtain informed consent from all subjects without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate (unless Waiver of Consent is specifically approved or research is exempt).

3. Document informed consent using only the most recently dated consent form bearing the VCU IRB "APPROVED" stamp (unless Waiver of Consent is specifically approved).

4. Provide non-English speaking patients with a translation of the approved Consent Form in the research participant's first language. The Panel must approve the translated version.

5. Obtain prior approval from VCU IRB before implementing any changes whatsoever in the approved protocol or consent form, unless such changes are necessary to protect the safety of human research participants (e.g., permanent/temporary change of PI, addition of performance/collaborative sites, request to include newly incarcerated participants or participants that are wards of the state, addition/deletion of participant groups, etc.). Any departure from these approved documents must be reported to the VCU IRB immediately as an Unanticipated Problem (see #7).

6. Monitor all problems (anticipated and unanticipated) associated with risk to research participants or others.

7. Report Unanticipated Problems (UPs), including protocol deviations, following the VCU IRB requirements and timelines detailed in VCU IRB WPP VII-6:

8. Obtain prior approval from the VCU IRB before use of any advertisement or other material for recruitment of research participants.

9. Promptly report and/or respond to all inquiries by the VCU IRB concerning the conduct of the approved research when so requested.

10. All protocols that administer acute medical treatment to human research participants must have an emergency preparedness plan. Please refer to VCU guidance on http://www.research.vcu.edu/human_research/guidance.htm.

11. The VCU IRBs operate under the regulatory authorities as described within:
    a. U.S. Department of Health and Human Services Title 45 CFR 46, Subparts A, B, C, and D (for all research, regardless of source of funding) and related guidance documents.
    b. U.S. Food and Drug Administration Chapter I of Title 21 CFR 50 and 56 (for FDA regulated research only) and related guidance documents.
    c. Commonwealth of Virginia Code of Virginia 32.1 Chapter 5.1 Human Research (for all research).

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