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Patient Reported Outcomes in Sickle Cell Disease Examined Within a Conceptual Model

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Patient Reported Outcomes in Sickle Cell Disease Examined Within a Conceptual Model

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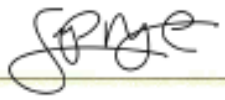
This Clinical Dissertation, written under the direction of the candidate's dissertation committee and approved by the members of the committee, has been presented to and accepted by the faculty of the PsyD Program in Clinical Psychology in partial fulfillment of the requirements for the degree of Doctor of Psychology. The content and research methodologies presented in this work represent the work of the candidate alone.

Student Signature



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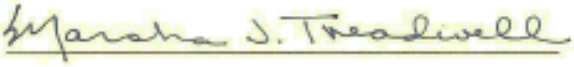

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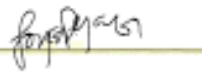

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Chapter I

Abstract

Objective: To examine the relations between patient reported outcomes (PROs) within a conceptual model for adults with sickle cell disease (SCD) ages 18 – 45 years enrolled in the Sickle Cell Disease Implementation Consortium (SCDIC) registry. We hypothesized that patient and SCD related factors and barriers to care would independently contribute to functioning as measured using the PRO domains. Additionally, pain and other SCD related complications are expected to impact the relation between the variables. **Methods**: Participants completed a 48-item survey that included socio-demographics and PRO measures, such as social functioning, pain impact emotional distress, and cognitive functioning. Participants reported on lifetime SCD complications, pain episode frequency, timing and severity, and barriers to medical care. Healthcare utilization was obtained from medical records abstractions. **Results**: Higher pain frequency and severity and history of treatment for depression were associated with higher odds of worse outcomes in almost all PRO domains, controlling for age and gender for the 2,054 participants. Such social determinants of health as lower household income and unemployment, particularly due to disability status, were associated with higher odds of worse outcomes. Reports of fewer individual barriers to care were associated with better outcomes in emotion, social, cognitive and fatigue domains, while reports of fewer self-reported SCD complications/treatments were associated with better outcomes in emotion and sleep impact domains. **Conclusions**: Study results highlight the importance of the biopsychosocial model to enhance understanding of the needs of this complex population, and to design multi-dimensional approaches for providing more effective interventions to improve outcomes.

Keywords: patient reported outcomes, sickle cell disease, implementation science, conceptual model

CHAPTER II

Introduction

Sickle cell disease (SCD) is one of the most prevalent genetic blood disorders in the world (Piel et al., 2013), affecting 100,000 individuals in the United States (Yawn et al., 2014). Hemolytic dysfunction caused by SCD results in hemoglobin (the protein responsible for delivering oxygen) to alter the shape, flexibility, and function of red blood cells to become "sickled," resulting in multi-organ dysfunctions (American Society of Hematology, 2016). The hallmark of SCD is pain caused by interrelated chronic and acute co-occurring health conditions. The pervasive nature of SCD morbidities cuts across multiple domains of functioning. Individuals with SCD must deal with biological (e.g. increase rates of stroke, asthma, and infection), psychological (e.g. increased rates of depression), and social (e.g. increase challenges with employment) issues (Aneke & Okocha, 2017; Haywood 2013; Yawn et al., 2014). As such, it is imperative that research examines the impact of SCD on health-related quality of life (HRQoL), a multidimensional concept that captures the degree to which an individual's well-being and level of functioning, compared to the perceived ideal, is affected by their health (Dampier, 2011; Panepinto & Bonner, 2012; Shih & Simon, 2008).

Historically, SCD was a life-threatening condition for infants and children (Alrayyes et al., 2018); however, due to medical advances in the last fifty yeas such as standardized newborn screening and implementation of penicillin prophylaxis, individuals with SCD live well into adulthood (Lanzkron et al., 2013; Paulukonis et al., 2016; Powars, et al., 2002). Today, the cohort of adults with SCD face chronic health complications such as persistent chronic pain, progressive deterioration of microvasculature causing chronic end-stage vital organ damage, and neurologic issues (Ballas et al., 2010; Ballas, et al., 2012; Vichinsky, 2017). As a result, many

adults with SCD experience poor HRQoL due to limited physical, social, and emotional functioning (Dampier et al., 2011; Tarrt et al., 2015).

Unfortunately, the needs of adults with SCD are not being met due to limited access to comprehensive care centers (Kaur et al., 2020; Lankzron et al., 2018), a shortage of providers knowledgeable in the care and treatment of SCD (Grosse et al., 2009; Smith, et al., 2006), and less funding compared to other chronic illnesses (Farooq & Strouse, 2018). A notable consequence of these systemic issues are the increased rates of healthcare utilization, morbidity, and mortality for transition age adults (ages 18-24) with SCD (Brousseau et al., 2010; Lebensburger et al., 2012; Yusuf et al., 2011). As a result, many adults may be forced to over-utilize emergency departments and inpatient settings to receive treatment due to lack of comprehensive care. It is clear that a large proportion of healthcare costs could be reduced if adults with SCD received consistent outpatient treatment (Blinder et al., 2013). Admissions for SCD related issues account for an estimated 115,000 encounters and $500 million per year, with 75% of those encounters made by adults (Brousseau et al., 2010; Singh et al., 2014).

When adults do engage with the healthcare system, they face systemic barriers to care such as poor provider interactions (Glassberg et al., 2013; Haywood, Lanzkron et al., 2015), stigma and discrimination (Bulgin et al., 2018; Haywood et al., 2014; Nelson & Hackman, 2013) and lack of resources and social support (Hankins et al., 2012). Additionally, barriers to care are compounded by mix of individual and system factors such as transportation limitations, insurance coverage issues, and disruptions to social-role responsibilities (Mayer et al., 2003; Smith et al., 2017; Wolfson et al., 2012).

Poor social and emotional functioning for adults with SCD is associated with a constellation of disease-related factors, patient related factors, and systemic barriers to care

(Aneke & Okocha, 2017; Mann-Jiles & Morris, 2008). Rates of depression range from 18 - 44% across several studies of mental health for adults with the disease (Tartt et al., 2015). Research focused on sociodemographic factors (Asnani et al., 2010; Hasan, et al., 2003), SCD-related neurologic dysfunction (Mackin et al., 2014; Vichinsky et al., 2010) and somatic symptoms (Sogutlu et al., 2018; Toumi et al., 2018) demonstrate the complex interrelationships that negatively impact mental health outcomes for individuals with SCD. Furthermore, many adults with SCD experience poorer lower mental health functioning due to limited social support and resources (Jenerette & Murdaugh, 2008; Telfair et al., 2003; Treadwell et al., 2014).

Self-reported measures of functioning are needed to gain insight into the unique challenges adults with SCD experience (Dampier et al., 2011). Patient-reported outcome measures provide a subjective perspective of one's health status and level of functioning (Aneke & Okocha, 2017), and are reliable and feasible methods for assessing HRQoL across different settings (Bulgin et al., 2019; Esham et al., 2019). Giving voice to adults with SCD is critical in understanding how to best serve this patient population. Moreover, implementation of resources and interventions are likely to be more effective when considering patient's subjective experience of the disease (Basch et al., 2018).

Identification of problem

SCD has deleterious effects across social, emotional, and physical domains of functioning (Dampier et al., 2011). This inherited blood disorder fundamentally disrupts essential biologic functioning resulting in multi-organ failure and high rates of mortality (Yawn et al., 2014). The interrelated nature of SCD complications results in a feedback process that amplifies physical, psychological, and social problems (Anie, 2005; Ballas, 2007; Jenerette et al., 2014; Vichinsky et al., 2010). For example, SCD causes intermittent acute and chronic pain (Brandow

& DeBaun, 2018) which significantly limits functioning which contributes to increased anxiety, low mood, and disrupts role functioning (Edwards et al., 2005; Jonassaint et al., 2016; Levenson et al., 2008).

The burden of sickle cell disease is experienced both at the individual and systemic levels. The cumulative impact of SCD is compounded by barriers to care that significantly contribute to poorer HRQoL compared to the general population (Treadwell et al., 2014). Adults with SCD face health-related complications due to the progression of the disease into adulthood while dealing with pressure to navigate healthcare systems with limited support. There are less comprehensive care centers and fewer knowledgeable providers to treat adults with SCD compared to children. This inequity in access is shown to contribute to lower HRQoL and increases rates of mortality for adults with SCD (Hamideh & Alvarez, 2014; Paulukonis et al., 2016).

A patient-centered approach that encompasses a biopsychosocial model is key to effectively to treating patients with SCD. Research utilizing PROs provide insight into the subjective experience of one's well-being and level of functioning, compared to the perceived ideal, as affected by one's health (Panepinto & Bonner, 2012; Shih & Simon, 2008). The experiences of adults with SCD have been silenced for decades in America (Burnes et al., 2008; Nelson & Hackman, 2013; Thompson, 2013). The holistic stance to health outcomes research that centers the experience of adults with SCD will push for increased support for a historically underfunded chronic health condition (Farooq & Strouse, 2018).

Rationale and alignment with Jesuit mission

There are only a handful of national studies examining a wide range of health-related factors. This dissertation will shed light on the contextual factors such as social economic status,

race, and barriers to care that influence health outcomes for individuals with SCD. Many adults affected by the disease identify as Black or African American, lack economic resources, rely on government-funded insurance (i.e., Medicaid and Medicare), and face discrimination when attempting to seek treatment (Jenerette et al., 2014; Hassell, 2010). We must better understand the nuances of individual, systemic, and disease related factors to best serve this population. Furthermore, there is a paucity of funding allocated for SCD compared to other diseases (Farooq & Strouse, 2018). The lack of funding and attention has led to poorer HRQoL as healthcare systems are unable to effectively meet the needs of adults with SCD. The burden of the disease significantly disrupts activities of daily living and lowers social and emotional functioning (Palermo et al., 2008; Treadwell et al., 2014). Previous research on HRQoL for adults has been done (Dampier, 2011), but an updated exploration on the impact of SCD is needed.

The findings of this dissertation will inform implementation science strategies to promote the adoption of evidence-based care in SCD. We will analyze data from a large national cohort gathered by the Sickle Cell Disease Implementation Consortium (SCDIC) which is funded by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The SCDIC is a multi-site study that was established in 2016 with the aim of improving the overall health and well-being of adolescents and adults ages 15 to 45 years with SCD. The SCDIC is composed of eight academic and clinical centers across the U.S. each enrolling at least 300 adolescents and adults with SCD into a registry. The SCDIC's objectives are to: 1) conduct a community-based needs assessment of the barriers to care for both local and national populations, 2) participate in the development of a SCD Registry, in collaboration with clinical centers and the NHLBI, and 3) design implementation research studies to address identified barriers to care. The SCDIC is committed to using implementation science, the scientific study of

the methods to promote systematic adoption and utilization of research findings into routine care (Bauer, et al., 2015). This research will contribute to the SCDIC's aim to close the "research to practice gap," ultimately improving care for more people with SCD in a shorter period.

This dissertation will yield key insights on ways to improve the quality of life of the whole person, or the *cura personalis*. The focus on the whole person is in alignment with the mission of University of San Francisco. The dissertation project will follow USF's Jesuit spirit by attending to the social, emotional, and physical aspects of health. Individuals who have SCD face chronic health disparities and systemic injustices (Haywood et al., 2014; Nelson & Hackman, 2013). The efforts of the SCDIC more broadly, and this dissertation specifically, are reflections of USF's mission to critically examine factors cause injustice for adults living with SCD and seeks to find solutions to address the problem.

Purpose and aims of dissertation

The purpose of this dissertation is to examine the relations between PROs within a conceptual model for adults with SCD ages 18 – 45 years enrolled in national SCD data registry. Participants completed a 48-item Patient Enrollment Survey that included validated self-reported measures (full or partial measures used) of health and functioning. The first aim was to update the literature regarding HRQoL for adults with SCD. It has been over a decade since the last large, multi-national cohort study of adults using measures of HRQoL to examine the relationship between SCD and PROs (Dampier et al., 2011). Our study will update the field and inform future research and areas for interventions for SCD. The second aim was to understand the relationships between patient-related, disease-related, and systemic factors that influence PROs for adults with SCD. The third aim was to examine the influence of health-behaviors on PROs for adults with SCD.

We hypothesize that patient related and disease related factors along with barriers to care would independently contribute domains of functioning when measured using validated measures for PROs. Additionally, given the pervasive impact of pain and comorbid nature of the disease, we hypothesized that pain and other SCD related complications would account for a significant degree of the relation between the variables when assessing PRO. Lastly, we hypothesized a significant bidirectional influence between health behaviors such as adherence and healthcare utilization on PRO domains.

Project Specific Definitions

Acute Chest Syndrome (ACS): a range of pulmonary issues (chest pain, cough, fever, hypoxia (low oxygen levels), lung infiltrates) due to occlusion of the pulmonary vasculature resulting in life-threatening lung damage

Adult hemoglobin (HbA): the main oxygen transport protein for adults

Avascular necrosis: the deterioration or death of bone tissue due to the lack of blood supply

Cerebral vascular accident (CVA): also known as stroke; death of brain cells due to lack of oxygen

Chronic transfusion: a blood transfusion provides a person with donated blood via intravenous injection; chronic transfusions refer to this process occurring regularly (~1x per month) over a period of time

Fetal hemoglobin (HbF): the main oxygen transport protein in the fetus and persists in the newborn until roughly 2-6 months of age

Health related quality of life (HRQoL): multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning

Hematologic disease: disorders which primarily affect the blood & blood-forming organs

Hemoglobin: oxygen-binding protein, found in erythrocytes, which transports oxygen from the lungs to the tissues

Hemorrhagic stroke: occurs when weakened blood vessels rupture

Ischemic stroke: occurs when a blood vessel supplying blood to the brain is obstructed

Implementation science: is the study of methods to promote the adoption and integration of evidence-based practices, interventions and policies into routine health care and public health settings

Neuropathic pain: pain caused by damage or disease affecting the somatosensory nervous system

Nociceptive pain: The "felt" experience of pain, relating to the perception or sensation of pain

Microvasculature: Microvessels are the system of small blood vessels in the body, responsible for circulation

Patient reported outcomes (PRO): the patient's subjective interpretation and report of their own health status and level of functioning.

Sepsis: potentially life-threatening condition caused by the body's response to an infection, resulting in multi-organ damage

Sickle cell anemia (SCA): Hemoglobin SS or $S\beta^0$ thalassemia disease, inherited form of anemia, caused by a lack of healthy red blood cells to carry adequate oxygen throughout the body

Sickle cell trait (SCT): A condition in which a person inherits the sickle cell gene mutation from one parent and one normal gene from the other

Silent cerebral infarct (SCI): or "silent stroke," is a brain injury without accompanying outward symptoms of a stroke

Somatization: psychological distress manifested by one or more bodily symptoms

Somatic pain: also known as a form of nociceptive pain. The nerves transmitting somatic pain are in the skin, or muscles and connective tissues

Somatic symptom burden (SSB): the stress caused by a heightened focus on physical symptoms such as pain or fatigue which leads to significant emotional and functional problems

Vasculopathy: any disease affecting blood vessels

Vaso-occlusive events (VOEs): also known as acute pain events, caused by obstruction of blood circulation due to sickled red blood cells resulting in ischemic injury and subsequent pain and other clinical complication

CHAPTER III

Review of the Literature

Overview of sickle cell disease

Sickle cell disease (SCD) is one of the most prevalent inherited blood disorders in the world, impacting an estimated 7 million people globally (Piel et al., 2013; Yawn et al., 2014). SCD affects 330,000 births annually and accounts for 3.4% of deaths in children ages 1 to 5 years across the world (Modell & Darlison, 2008). Individuals who inherit a combination of hemoglobin S, C, E, D Punjab, β thalassemia, or α zero (α0) thalassemia may develop a serious hemoglobin disorder, also known as SCD (Modell & Darlison, 2008). Demographic projections of SCD calculated an estimated one-third increase in newborns with sickle cell anemia (SCA - Hemoglobin SS or $S\beta^0$ thalassemia disease) by the year 2050 (Piel et al., 2013). In the United States, there are 100,000 individuals currently living with the disease, and about 3.5 million people are carriers of the sickle cell trait (SCT) (Yawn et al., 2014). Individuals with SCD in the United States predominantly fall into four genotypes: HbSS (60%), HbSC (30%), and $HbS\beta^0$ and $HbS\beta^+$ thalassemia (10%) (Hassell, 2010). SCD type HbSS and $HbS\beta^0$ thalassemia are often associated with increased disease severity, complications, and higher rates of healthcare utilization (Saraf et al., 2014; Yawn et al., 2014). One out of 365 African American children, and one out of 16,300 Hispanic-American children are born with SCD in the U.S. every year (Centers for Disease Control and Prevention [CDC] 2020). SCD is also common in other global ethnic groups from South America, the Middle East, or South Asia (Brousseau et al., 2010).

SCD is caused by a single point mutation in beta-globin on chromosome 11, producing an abnormal form of hemoglobin, the protein in red blood cells responsible for delivering oxygen throughout the body (Musumadi et al., 2012). The hemoglobin gene mutation in SCD produces

aberrations to the amino acid sequence that limits the production of globin-chains. As a result, hemoglobin S polymerizes upon deoxygenation, causing red blood cells to become "sickled," and die prematurely (Saraf et al., 2014). The sticky, rigid, and "sickled" hemoglobin generate SCD pathologies that disrupt fundamental hematologic functioning resulting in SCD complications including vaso-occlusive events (VOEs), ischemia-reperfusion (repeated obstructions to blood vessels causing tissue damage), hemolytic anemia resulting in chronic anemia, and sepsis (Chakravorty & Williams, 2015; Rees et al., 2010). Over time, SCD complications lead to organ dysfunction and intermittent acute and chronic pain (Yawn et al., 2014).

Multi-organ impact of SCD

SCD is a multi-organ disease with a range of clinical complications throughout the body, which cause co-occurring acute and chronic health conditions (Alrayyes et al., 2018; Brandow & DeBaun, 2018; Yawn et al., 2014). The disease interrupts organ functioning leading to liver dysfunction, pulmonary disease, cerebral atrophy, renal failure, and genitourinary complications such as priapism (Alrayyes et al., 2018). Additionally, SCD pathology impairs neurologic functioning and is associated with central nervous system complications such as silent strokes, overt strokes, seizures, cranial nerve neuropathies, and vascular malformations (Elmariah et al., 2014; Lanzkron et al., 2013; Paulukonis et al., 2016; Vichinsky et al., 2010). The risk of hemorrhagic stroke in patients with SCD is 30 times greater compared with those without the disease (Vichinsky, 2017), and a history of stroke in SCD is correlated with increased risk of comorbidity and increased rate of mortality (DeBaun et al., 2012; Miller et al., 2001; Strouse, et al., 2009; Vichinsky et al., 2010).

There are age-related morbidity patterns in individuals with SCD such as splenic dysfunction and dactylitis during the first five years, cerebral infarctions in children and adolescents, and progressive deterioration of microvasculature causing chronic end-stage organ damage of the kidneys, lungs, brain, bones, and retina during the third and fourth decades of life (Powars et al., 2002). Consequently, people with SCD need treatment for a range of medical conditions throughout their lives. The multiorgan dysfunction for adults with SCD cause higher rates of healthcare utilization compared to people with other chronic diseases such as asthma, pneumonia, congestive heart failure, and diabetes mellitus (Alrayyes et al., 2018; Brousseau, 2010; Elmariah et al., 2014). There are evidence-based disease-modifying therapies for SCD including regular blood transfusions and hydroxyurea therapy which are shown to alleviate many acute and chronic SCD complications (Danielson, 2002; Yawn et al., 2014). Hydroxyurea was FDA approved over 20 years ago and elevates levels of fetal hemoglobin to help reduce the number of acute pain events (Yawn et al., 2014). Unfortunately, side effects to hydroxyurea treatment, lack of knowledge regarding evidence based treatments, and barriers to care can result in poor treatment adherence (Agrawal et al., 2014). Novel techniques to cure SCD such as allogeneic bone marrow transplantation and gene therapy are available, but are accessible to a limited number of patients at this time (Ballas et al., 2010; Yawn et al., 2014).

SCD complications significantly lower quality of life across multiple domains of functioning for adults with SCD (Andong et al., 2017; Dampier et al., 2011; Luzinete Felix de Freeitas et al., 2018). SCD complications such as chronic pain have been shown to lower physical and social functioning (Adegbola, 2015) and are associated with increased prevalence of mental health disorders (Anie et al., 2012; Beverung et al., 2015; Treadwell et al., 2014). Patient-related factors such as lower socioeconomic status and issues with insurance coverage

are also associated poorer health outcomes, high rates of hospital utilization, and increase mortality (Perimbeti et al., 2018; Powers, 2002). Many adults report that having the disease significantly disruptions in their social and occupational functioning (Thomas & Taylor, 2002). In order to maintain proper health, adults with SCD take tremendous efforts associated with health behaviors such as sleep, pain, hydration, monitor physical exertion, medication management, and attend medical appointments (Bulgin et al., 2019; Yawn et al., 2014). The social impact and impact on functioning result in literal costs for adults with SCD. Predictive modeling indicate that adults with SCD have a substantial reduction in quality-adjusted life expectancy and lifetime earnings compared with those without the disease (Lubeck et al., 2019). Despite research highlighting the increased disease burden for adults, particularly as they age (Adegbola et al., 2012; Dampier et al., 2011; Powers et al., 2002), limited attention has been given to holistic assessments of functioning of adults with SCD (Keller et al., 2014).

Patient-reported outcomes in SCD

Assessing HRQoL using PROs measures are necessary to understand the complexity of disease burden on the lives of people with SCD (Aneke & Okocha, 2017). PROs measures capture the subjective experience of health status, without interpretation from a clinician or researcher (Deshpande et al., 2011). Recent studies show that validated measures of PROs are feasible tools to provide an in-depth understanding of patient experiences in clinical settings (Bulgin et al., 2019; Esham et al., 2019). Additionally, PROs provide valuable insight on how treatment impacts functioning which can lead to insights to reduce unnecessary admissions and reduce the overall cost of care (Sarri et al., 2018).

There are few large studies that gather data from multiple sites to understand PROs in adults with SCD. The last large multisite study, Comprehensive Sickle Cell Centers (CSCC)

Collaborative Data Project, was completed in 2008. This study found diminished functioning for adults with SCD across a majority of domains of functioning on the Short Form Health Survey (SF-36) (Dampier et al., 2011).The CSCC study included 1046 participants with a median age of 28, 48% were male, and 73% were SCD genotype SS or Sβ0 thalassemia. The study found that female gender was associated with diminished functioning and vitality scores. Disease related factors such as acute pain events, asthma, and avascular necrosis were each associated with poorer SF-36 scale scores. Additionally, opioid use was associated with lower functioning and chronic antidepressant use associated with poorer reports of bodily pain, vitality, social functioning, emotional role, and mental health scale scores (Dampier et al., 2011).

Pain and health-related quality of life

Pain is a hallmark clinical manifestation of SCD (Musumadi et al., 2012; Piel et al., 2013; Rees et al., 2010) presenting throughout life (Ballas, 2007; Ballas et al., 2010; Kanter & Kruse-Jarres, 2013), and is a central driver of lower HRQoL (Ballas, 2007; Moscou-Jackson et al., 2016; Taylor et al, 2010). SCD pain emerges from four concurrent pathologies: pain syndromes, anemia related sequelae, multi-organ failures, and comorbid conditions (Ballas, 2005; Ballas et al., 2012). The subjective experiences of pain also take multiple forms leading poorer health outcomes. SCD pain produces an array of nociceptive, neuropathic, inflammatory and central pain processes that contribute to poor mental health functioning, somatic issues, and high healthcare utilization rates (Brandow et al., 2015; Campbell et al., 2016; Dampier et al., 2017).

Patient-related characteristics such as such as older age, SCD genotypes (HbSS and HbSß^0 thalassemia), gender identified women, and lower socioeconomic status contribute to poorer health outcomes when linked with pain (Ballas et al., 2010; Killough, 2010; Palermo, et

al., 2015; Wallen et al., 2014; Zempsky et al., 2017). Beginning in adolescence, acute pain episodes are superimposed on a backdrop of emergent chronic pain that persists into adulthood (Ballas et al., 2012; Kaufman et al., 2018; Rees et al., 2010). Increased frequency and intensity of pain is also associated with a decrease in quality of life (Brandow et al., 2010; Taylor et al., 2010; Treadwell et al., 2014), and higher rates of mortality (Ballas & Lusardi, 2005).

SCD pain result in significant interference in daily living (Master et al., 2016) and diminished psychosocial functioning (Aneke & Okocha, 2017; Kaufman et al., 2018; Schlenz et al., 2016). A vaso-occlusive event (VOE), also known as an acute pain episodes, are disruptive, taxing, and chaotic experiences. Acute pain episodes last roughly 4 to 11 days, and many individuals manage pain at home for several days before ultimately seeking medical attention (Aneke & Okocha, 2017; Dampier et al., 2002; Jacob et al., 2005). The disruption of daily living due to VOEs are associated with fear, anxiety, depression, and disconnection from activities of daily life (Ballas 2007; Ballas, Gupta, & Adams-Graves, 2012). The interference caused by SCD pain limits functioning across multiple domains of functioning (Esham et al., 2019; Kaufman et al., 2018).). Lastly, pain interference was associated with increased opioid use, low mood, and decreased levels of engagement (Anie & Steptoe, 2003), while high rates of opioid use for SCD pain have a significant relationship with somatic symptom burden, stress, negative coping, and lower physical and mental HRQoL (Smith et al., 2012).

Patient-reported outcome and measures assessing health related quality of life help stakeholders understand the multifaceted nature of chronic SCD pain (Taylor et al., 2010). Studies show chronic SCD pain decreases overall functioning and HRQoL (Rees et al., 2010; Treadwell et al., 2014; Yawn et al., 2014). Chronic SCD pain is linked to increased morbidity and mortality in both adults and children (Dampier et al., 2017) and is correlated with diminished

attention, low mood, and challenges with learning and memory (Brandow & DeBaun, 2018; Pope et al., 2016). The etiology of chronic pain in SCD varies, yet common disease-related factors include damage to bones and soft tissue, hepatic or splenic enlargement, accumulation of fluid and other internal damage (Apkarian et al., 2009; Ballas, 2005; Dampier et al., 2017). Persistent pain undoubtedly impairs functioning. For adults with SCD, daily pain intensity was associated with lower PROs in the domains of social functioning, pain recall, energy and fatigue (Ballas et al., 2006). The Pain in Sickle Cell Epidemiology Study (PiSCES) found that lower scores on PROs were associated with increased bodily pain, lower social function, and poorer general health compared to adults with asthma (McClish et al., 2005). Additional studies of subjective reports of functioning consistently show the negative impact of chronic pain on overall functioning for adults with SCD (Adegbola, 2011, Gil et al., 2004; Smith et al., 2008).

SCD pain lowers emotional and social functioning in adults with SCD (McClish et al., 2005; Taylor et al, 2010), and scores on PROs remain lower when compared to other chronic conditions (McClish et al., 2005). SCD pain alters perception, attention, mood, motivation, learning and memory (Brandow & DeBaun, 2018; Pope et al., 2016). Increased prevalence of anxiety and depression are linked to experiencing years of SCD pain, and are subjectively experienced as low mood, fatigue, and increased stress (Edwards et al., 2005; Simons et al., 2014). Results from a daily diary study of adults with SCD found 27.6% of participants were depressed and those who were depressed had more pain days (71.1%) than those who were not depressed (49.6%) (Levenson et al., 2008). A two-year cross-sectional study of adults with SCD found worse PRO scores on physical functioning were correlated with somatic comorbidities, anxiety, and depression (Azarkeivan et al, 2009). Additional research using PROs found negative

emotions associated with pain were predictive of psychiatric manifestations including somatization, anxiety, phobic anxiety, and acute psychological symptoms (Edwards et al., 2014).

Socio-emotional functioning in SCD

The detrimental impact of SCD on mental health outcomes cuts across biopsychosocial domains. Reported rates of depression and anxiety for adults with SCD are two to three times the national average (Jonassaint et al., 2016). Rates of depression range from 18 - 44% (Tartt et al., 2015) and adults with SCD are at increased risk for suicide (Edwards et al., 2009). Not surprisingly, PRO studies with individual with SCD found poorer mental health scores were associated with lower overall quality of life (Luzinete Felix de Freitas et al., 2018). SCD complications that lowered HRQoL in PRO measures had significant relationships with lower psychological well-being and negative coping (Anie, et al., 2012; Keller et al., 2014). Reasons for poorer mental health outcomes are multifaceted and often co-occur. Several contributing factors include neurological disruption (Vichinsky et al 2010), comorbid somatic issues (Toumi, et al., 2018) and challenges with coping and self-efficacy (Anie, 2005). Patient-reported outcomes measuring mental health in emergency room settings found adults with SCD endorsed feeling depressed (29%) and anxious (20%) (Smith et al., 2017) and self-report measures of functioning showed an inverse relationship between patient self-efficacy and hospital utilization (Cronin et al., 2018).

Neurocognitive issues caused by disease-related sequalae cause problems with functioning throughout the lifespan for people with SCD. Over time, disease-related vasculopathy disrupts blood supply to the brain, reduces gray matter and has been linked to lower cognitive functioning (Mackin et al., 2014; Armstrong et al., 2010; Kato, 2018; Stotesbury et al., 2018). An estimated one third of individuals with SCD will have an identifiable

neurological deficit in their lifetime, and the risk of stroke is three times higher in adults with SCD (Strouse, et al., 2009). Diminished neuropsychological function causes poorer social, emotional, and occupational functioning for individuals with SCD (Gold et al., 2008; Hijmans et al., 2011; Lance et al., 2015). When compared to community samples, adults with SCA had lower global cognitive function, memory, processing speed and executive function (Vichinsky et al., 2010). Similar findings of lower cognitive functioning for adults with SCD have been found in the areas of memory (Mazza et al., 2018) and processing speed (Jorgensen et al., 2017). Unfortunately, a significant proportion of individuals with SCD are likely to have neurocognitive deficits that go undetected due to lack of routine screening and regular assessment (Schatz & McClellan, 2006; Vichinsky et al., 2010).

As this review of the literature attempts to highlight, there are several layers of suffering that people with SCD face. The felt experience, or somatic symptoms of SCD create a burden of disease that causes poorer health outcomes, increases healthcare utilization, and lowers functioning (Ballas et al., 2010; Toumi et al., 2018). Somatic conditions of SCD include a broad range of complications including pulmonary hypertension, leg ulcers, infections, stroke, ocular damage, progressive renal dysfunction, osteonecrosis, acute chest syndrome and asthma (Toumi et al., 2018). Research using PROs found that increased somatic symptom burden was significantly correlated with anxiety and depression as well as a higher number of days in pain and increased healthcare utilization (Sogutlu et al., 2011). Common somatic concerns are issues with sleep and increased fatigue which have been shown to diminish health outcomes, reduce self-efficacy, and reduce quality of life (Adegbolia et al. 2013; Hajibeigi et al., 2009). Fatigue is associated with higher levels of depressed mood and lower levels of functioning (Amerginer et al., 2014), and the variability of scores on PRO measures of insomnia was predictive of acute

pain severity and depression in adults with SCD (Moscou-Jackson et al., 2016). The relationship between depression and sleep was also examined in a cohort study of 328 adults with SCD, which found 71.2% met criteria for a sleep disturbance, and 21% scored in the clinically depressed range on the Beck Depression Inventory II (Wallen et al, 2014).

Many individuals with SCD must carry the burden of their disease with limited social support and resources. The lack of necessary support negatively influences social and emotional functioning for adults with SCD (Crosby et al., 2015). Limited social support, lack of community resources, and challenges to fulfilling role functions have been identified as key factors that lower HRQoL for adults with SCD (Jenerette & Murdaugh, 2008; Telfair et al., 2003; Treadwell, et al., 2014). The complexity of managing SCD disease-related factors such as unpredictable pain events intertwined with systemic challenges such as establishing consistent comprehensive care limit social and occupational functioning (Adegbola, et al, 2012; Hsu et al., 2016). Many adults endorse feeling a lack of agency due to their disease. Increased rates of depressive symptoms were associated with "other people" locus of control domain in a PRO study of adults with SCD (Gibson et al., 2013). Research utilizing PROs found that isolation increased rates of depression for adults with SCD compared to controls (Asnani et al., 2010). Additional research highlights experiences of isolation and reluctance to disclose disease status as a significant social burden (Treadwell et al., 2014). Lastly, the lack of support and resources may diminish an individual's ability to cope effectively. The challenges with coping effectively with SCD results in a deleterious feedback loop of social and emotional issues. Coping with SCD pain and managing healthcare with limited resources is associated with feelings of fear, anxiety and depression for adults with SCD (Hasan et al., 2003; Jacob et al., 2005; Schlenz et al., 2016).

Healthcare Utilization in SCD

Disease-related variables such as acute pain and patient-related variables such as lack of transportation intersect with system barriers to care such as discrimination to contribute to high rates of healthcare utilization for adults with SCD (Mitchell, 2018). Additionally, these factors influence healthcare behaviors such as adherence, which in turn influence utilization rates. The cyclical effect of these factors produce disproportionally high number of admissions and healthcare costs (Brousseau et al, 2010). There is clear evidence that significant number of admissions are potentially preventable with access to comprehensive treatment for people with SCD (Blinder et al., 2013; Nimmer et al., 2015).

Multiple studies illustrate the disease related variables such as such as genotype and pain are strong indicators of utilization rates for adults with SCD. High-risk sickle cell genotypes (HbSS and HbSß^0 thalassemia) are associated with higher reports of pain intensity and rates of healthcare utilization as compared to relatively low-risk groups (HbSC and HbS ß$^+$ thalassemia) (Brousseau, 2010; Schlenz et al., 2016). Recurrent hospital admissions and readmissions give us an insight into the factors that contribute to poorer health outcomes. A 2016 study found that individuals with higher rates of readmissions had more lifetime complications and comorbidities including acute chest syndrome, increased rates of psychiatric comorbidity, and avascular necrosis of hip or shoulder (Carroll 2016). Furthermore, somatic symptom burden of SCD such as pain and depression are associated with increased utilization (Sogutlu, et al., 2011). Healthcare encounters for adults often occur in emergency departments due to unmanaged pain in outpatient settings (Jacob et al., 2005; Rees et al., 2010). Each year, an estimated 200,000 ED visits and 113,000 hospital admissions are related to SCD pain (Yusuf et al., 2010). Notably,

opioid therapy, which is used to treat SCD pain, was associated with greater levels of clinical pain, depression, and increased healthcare utilization (Carroll et al., 2016).

Patient-related variables such as age, distance from treatment center, transportation issues, insurance status, urbanicity, and disease severity are significant factors in healthcare utilization for adults with SCD (Smith et al., 2017; Wolfson, 2012). A life-course perspective (Colen, 2011) is needed to appreciate the influence of early-life experiences, particularly related to economic deprivation and the social disadvantages that shape health outcomes for adults with SCD. Transition age young adults (18-24) account for a disproportionally high utilization rates and increased morbidity and mortality rates compared to any other age group (Paulukonis et al., 2017). The lack of available specialized providers (e.g., hematologists) plays a significant role in an over-reliance on EDs for care for young adults with SCD (Hemker, et al., 2011). Transition age adults with SCD are responsible for the highest rates of utilization for both 30-day and 14-day re-hospitalization compared to other age groups (Brousseau, 2010) as well as the highest healthcare cost (Blinder et al., 2013). Unfortunately, high rates of healthcare utilization are associated with increased SCD complications and the risk of mortality (AlJuburi et al., 2013).

Barriers to care and adherence to treatment

There are evidence-based treatments to manage complications, reduce frequency of VOEs, and manage chronic pain in SCD (Yawn, et al., 2014). Furthermore, research indicates that individuals that are adherent to evidence-based therapies such as blood transfusions or hydroxyurea report better PROs (Luzinete Felix de Freitas et al., 2018; Brandow & Panepinto, 2010). Quality of life measures of social functioning, pain recall, and general health perception were better for adults who were adherent to hydroxyurea compared to those who were not (Ballas, 2006). Despite the efficacy and utility of hydroxyurea to improve health in SCD, it

remains underutilized for adults (Caroll et al., 2013; Lanzkron et al., 2008). Barriers to adherence to hydroxyurea include side effects such as cytopenia, abnormal spermatogenesis, hair loss, and nausea. Provider-level barriers include bias towards patients' capacity to remain adherent, fear of side effects, and lack of knowledge of side-effects of the medication (Brandow & Panepinto, 2010). The provider-level barriers result in lost opportunity for improved health as a study that found that for those who never used hydroxyurea, 50% never received information about the drug, and 85% thought they would not see improvement if they took hydroxyurea (Elander et al., 2011). Barriers to adherence go beyond the patient and provider. System level barriers include poorer treatment of patients from ethnic minority groups and with socioeconomic challenges that affect adherence and ability to attend clinic and laboratory appointments (Brandow & Panepinto, 2010).

The opportunity to engage individuals with SCD to adhere with evidenced-based treatment is often halted by systemic barriers to care. Adults with SCD experience systemic barriers in healthcare settings such as stigma, discrimination, and lower quality of care received (Bediako & Moffit, 2011; Bulgin et al., 2018; Haywood et al., 2014). Adults who enter healthcare settings for acute pain episodes are often met with negative attitudes and biases from providers (Ratanawongsa et al., 2009). Discriminatory practices towards adults with SCD include longer wait times (Haywod et al., 2013), prejudice regarding race and functioning (Royal et al., 2011), and receive inadequate treatment for disease related presentations (e.g., inadequate analgesia for pain management) (Glassberg et al., 2013). Multiple studies demonstrate the negative impact of stigma related to SCD on psychological well-being, physiological outcomes, social connectedness, and care-seeking behaviors (Bulgin et al., 2018). The impact of barriers to care due to discrimination contribute to poorer health and increase suffering. Adults with SCD

reported avoiding or waiting to receive care even when pain was very high because of experiences of discrimination and poor provider interactions such as being labeled a "drug seeker" (Jenerette et al., 2014). These systemic barriers, such as healthcare discrimination, are associated with increased stress and reduced quality of life (Ezenwa et al., 2015; Mathur et al., 2016).

CHAPTER IV

Methods

Model Development

The model examined for this dissertation study was developed from the SCDIC's Conceptual Framework for PROs/HRQoL in SCD, with input from additional experts in the area of PROs in SCD (see Figure 1). Our study identified five predictor variables including SCD-related factors (genotype, disease modifying therapies (hydroxyurea and chronic transfusion therapy). SCD complications (number of self-reported complications, ASCQ-Me Pain Frequency and Severity), Health Behaviors (adherence to hydroxyurea, acute healthcare utilization), Barriers to Care (systemic/access barriers and individual barriers), and Patient-Related Factors (education, income, employment, marital status, lifetime depression, and diabetes). Our seven outcome variables are PRO measures assessing pain, sleep and social functioning impacts, emotional distress, fatigue, and cognitive functioning.

Recruitment Procedures and Enrollment

Data collection into the SCDIC national registry occurred between 2017 and 2018. The cohort of participants in the registry was 2,433 adolescents and adults ages 15 to 45. The data collected for the SCDIC Registry included (1) medical record abstraction (provider completed), (2) laboratory reporting form (clinical/research staff completed with laboratory data pulled from

central medical databases or electronic health records) and (3) Patient Enrollment Survey (patient self-report), including questions regarding pregnancies and conception, with a different form used for men and women. After removing participants with incomplete data (e.g. either a completed medical record abstraction form or Patient Enrollment Survey) and adolescents, the study sample was 2,054 (see Figure 2). All baseline patient surveys were completed under the supervision of study personnel who were available to answer questions as needed. All data collected was entered into the data coordinating center's Research Electronic Data Capture (REDCap) system for management, cleaning, and analysis.

During the recruitment phase of the SCDIC, participants were primarily a convenience sample recruited through SCDIC clinical centers, with some outreach into the community. Eligible participants were identified and recruited into the registry in various ways such as in person (e.g. in clinic, EDs), by phone, or via electronic media (e.g. chat rooms, text). For participants recruited remotely, their consent could be obtained electronically with an online signature collection website. Screening, approaching, consenting and verifying the eligibility of potential study participants was conducted by designated SCDIC research staff.

A participant was considered enrolled when consent was obtained, and inclusion criteria met.

Inclusion Criteria

• Age 15 years up to and including 45 years

• English speaking

• Confirmed SCD diagnosis. Confirmed is defined as supported by documentation in the medical record of a positive test for one of the following: HbSS, HbSC, HbSβ-thalassemia (+ or 0), HbSO, HbSD, HbSG, HbSE, HbSF. If no medical record was available, the enrolling center could conduct its own laboratory test as confirmation.

• Willing and cognitively able to give informed consent and complete the Patient Enrollment Survey

Exclusion Criteria

• Unwilling or unable to give consent/assent or complete the Patient Enrollment Survey

• Sickle cell trait (e.g., HbAS)

• Successful bone marrow transplant

Participants and informed consent

The SCDIC: "Using Implementation Science to Optimize Care of Adolescents and Adults with Sickle Cell Disease" is multi-center study with principal investigators from each of the eight participating sites. The principal investigator for UCSF Benioff Children's Hospital Oakland is Marsha Treadwell, PhD. The local IRB approval was issued through Hematology/Oncology Research Studies at UCSF Benioff Children's Hospital Oakland: IRB# 2017-093.
Informed consent occurred in-person (e.g., in clinic or hospital, at SCD community events, at medical conferences) or via phone. Following consent (and assent where appropriate), participants completed one baseline survey with two versions (depending on sex/gender identification) accessible on tablet or paper. Remote consent through mail or online third-party website was allowed only after the study coordinator walked the participants through the content of the consent form over the phone. Signed informed consent was obtained prior to any data collection, and hard copies of the completed and signed consent were given to participants or parents/guardians. A signed HIPAA Research Authorization was also required of all participants.

The data was collected from participants' medical record abstractions and self-reported responses on the Patient Enrollment Survey. The Patient Enrollment Survey was not deemed to pose greater than minimal risk to participants. It was recognized that questions on the survey

might cause uncomfortable feelings about lifestyle, quality of life, personal or family history of disease, so protocols to manage any distress that arose during completion of the surveys were put into place. Participants received a gift card following survey completion but there were no direct benefits to the participants in the SCDIC Registry. Some participants might benefit from knowing that their contributions to the study is helping advance the state of the science regarding SCD treatment.

Patient Reported Outcomes measures

The SCDIC Registry gathers information through the use of common data elements (CDEs) in SCD developed in such sources as the PhenX Toolkit, ASCQ-Me, and PROMIS (measures described below) to collect standard clinical measures, laboratory values, lifestyle factors, medical history, treatment, and healthcare utilization. The measures capture PROs associated with pain, co-morbidities, quality of life, physical functioning, mental health and barriers to care. The use of CDEs in the SCDIC registry allows for the identification of gaps in research, large data queries and analysis, as well as informs future directions of research locally and nationally.

Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me)

The ASCQ-Me is a PRO measurement system that examines and monitors the physical, mental, and social well-being of adults with SCD. ASCQ-Me development included formative research to generate a comprehensive conceptual model of the ways in which SCD affects the lives of adults in order to develop a SCD-specific quality-of-life measurement system (Keller et al., 2014; Treadwell et al., 2014). The research team conducted an extensive literature review, interviews and focus groups with key stakeholders and field testing for validation (Treadwell et al., 2014). The qualitative research team reached saturation after analysis of additional data until

no further categories could be identified. The final taxonomy was demonstrated to be reliable for the classification of qualitative data at the domain level ($\kappa = 0.623$, $P < 0.0001$) and at the category level ($\kappa = 0.606$, $P < 0.0001$) (Treadwell et al., 2014).

The PRO measures used in this study were the ASCQ-Me Pain, Sleep and Social Functioning Impact. Pain impact was assessed using two items: "How often did you have very severe pain?" and "How often did you have pain so bad that it was hard to finish what you were doing?" over the past week. Sleep impact was also assessed using two items: "How often did you stay up most of the night because you could not fall asleep?" and "How often did you have a lot of trouble falling asleep?" over the past week. Social functioning impact was assessed with two items: "How much did you rely on others to take care of you because of your health?" and "How much did your health make it hard for you do things with your friends?" over the past 30 days. All ASCQ-Me items were rated on a 5-point Likert scale, from Never to Always. Item responses were uploaded to HealthMeasures Scoring Service (https://www.healthmeasures.net/score-and-interpret/calculate-scores) and T-scores were provided in reference to the ASCQ-Me field test population (n = 556). The ASCQ-Me short forms have demonstrated reliability and validity (Keller et al., 2017). The standardized T-score mean is 50 (SD = 10), with higher scores indicating more desirable (better) outcomes.

Patient-Reported Outcomes Measurement Information System (PROMIS)

PROMIS is a system of multiple patient-centered measures that evaluates and monitors physical, mental, and social health for the general population and those with chronic conditions (Cella et al., 2010). PROMIS is appropriate for use with both adults and children. PROMIS measurement development included comprehensive literature reviews of existing measures, focus groups with relevant stakeholders, and thematic analysis followed by item-review process.

The validity and reliability of the PROMIS measures has been demonstrated across a variety of chronic conditions, settings, and populations (Askew et al., 2016; Cook et al., 2016). A 2016 study of a cohort of cancer patients found PROMIS Physical Function short forms showed high internal consistency (Cronbach's $\alpha = 0.92 – 0.96$), convergent validity (Fatigue, Pain Interference, FACT Physical Well-Being all $r \geq 0.68$) and discriminant validity (unrelated domains all $r \leq 0.3$) across survey short forms, age, and race-ethnicity (Jensen et al., 2015)

The PRO measures used in this study were Emotional Distress (depressive symptoms) and Tiredness. Four items from the PROMIS Emotional Distress short form were used to assess depressive symptoms in the last 7 days including: “I felt worthless,” “I felt helpless,” “I felt depressed,” and “I felt hopeless.” One item ("I felt tired") from the PROMIS Fatigue item bank was used to assess tiredness in the past 7 days. PROMIS measures are scored on a 5-point Likert scale. Item responses were uploaded to HealthMeasures Scoring Service, where T-scores were provided in reference to the PROMIS Wave 1 representative population (adults) (Liu et al., 2010). The standardized T-score mean is 50 (SD = 10), with higher scores indicating worse health outcomes.

Quality of Life in Neurological Disorders (Neuro-QoL)

The Neuro-QoL is a set of self-report measure within the HealthMeasures system that assesses quality of life associated with the physical, mental, and social effects experienced by adults and children living with neurological conditions (e.g. stroke, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy and muscular dystrophy). Since individuals with SCD are at increased risk for stroke and silent cerebral infarcts, the SCDIC Registry subcommittee deemed Neuro-QoL an appropriate measurement system to assess HRQoL associated with cognition for the SCDIC Registry participants. The development phase

of Neuro-QoL consisted of an extensive literature review, an on-line Request for Information for feedback from neuroscience scholars, scientists, and clinicians, two phases of in-depth expert interviews, patient and caregiver focus groups, and individual interviews with patients and proxies (N = 63). The Neuro-QoL Cognitive Function measure was designed to assess perceived difficulties in cognitive abilities (e.g., memory, attention, and decision making, or in the application of such abilities to perform everyday tasks (e.g., planning, organizing, calculating, remembering and learning). The measure has been normed on an adult population of n = 1,009 and has demonstrated validity and reliability (Gershon et al., 2012; Lai et al., 2018).

The Neuro-QoL Cognitive Function short form was used to assess cognitive functioning. The measure uses a five item Likert scale (i.e., Never to Very Often / several times a day). Item responses were uploaded to HealthMeasures Scoring Service where T-scores were provided in reference to the PROsetta Stone Wave 2 population (adults) (Liu et al., 2010). The standardized T-score mean is 50 (SD = 10), with higher scores representing better health.

ASCQ-Me Pain Episode Measure – Frequency and Severity

The ASCQ-Me Pain Episode Measure is a five-question measure assessing pain frequency (number of severe pain events in the last 12 months), timing (of most recent event) and severity of the most recent sickle cell pain event (including duration and pain interference). In order to create a "norm-based" interpretation of the scores to represent a comparison to an average score in some reference population, the scores are placed relative to the average scores for the 556 adults with SCD who answered ASCQ-Me questions during the field test. Higher scores indicate worse frequency, timing and severity of SCD pain. ASCQ-Me uses a T-score metric in which 50 is the mean of the reference population and 10 is the standard deviation (SD) of that population. That said, a score of 60 would be one standard deviation worse than average

and a score of 40 would be one-standard deviation better. Internal consistency reliability was between 0.80 and 0.73 for the fixed form and 0.94 to 0.90 for short forms.

Two separate composite scores are calculated to reflect the frequency and the severity of the pain episodes. Due to the differences in the number of questions in each composite, these two scores have different range, which means scores should be standardized through z-score calculations so they are on the same scale and can be compared.

ASCQ-Me Medical History Checklist (MHC) – SCD Complications

The ASCQ-Me MHC (Keller et al., 2017) is a list of conditions or treatments associated with SCD. Participants answer "yes" or "no" to a list of 13 (modified from 9) SCD related conditions (e.g. leg ulcers, hip or shoulder damage, heart failure) or treatments (e.g. medications taken for pain). The MHC is a cumulative measure of yes/no responses to items such as "have you ever had open sores on your feet" or "do you take pain medicine every day for your SCD" along with a list of common complications associated with SCD (e.g. kidney damage, high blood pressure, asthma). High scores on ASCQ-Me MHC indicate poorer health due to greater number of health conditions. Participants separately reported on two comorbidities, diabetes and lifetime treatment for depression, with a follow up question asking if currently in treatment for depression. Participants also indicated "yes" or "no" to current use of hydroxyurea and blood transfusions for SCD. Sickle cell genotype (grouped as sickle cell anemia (Hb SS or S□0 thalassemia; Hb SC; Sβ+ and other variants) was obtained from medical record abstraction.

Measurement of Health Behaviors

Health behaviors were assessed using two variables from the medical record abstraction form: outpatient visit to sickle cell specialist or primary care provider within one year of enrollment ("yes" or "no") and the number of acute care visits for pain in the past year (combined

ED or hospital admissions), categorized as 0, 1 - 2 or >= 3 ED/hospital admissions. The other health behavior was from the Patient Enrollment Survey: currently on hydroxyurea ("yes" or "no"). If yes, participants reported on their adherence in the past seven days, categorized as: not adherent" (0 – 1 day); "partially adherent" (2 – 5 days); and "adherent" (6 – 7 days).

Sickle Cell Disease Barriers to Care Checklist

The SCD Barriers to Care consists of 11 reasons for delays in care or not receiving medical care needed obtained from a longer SCD-specific checklist with demonstrated validity and reliability (Treadwell et al., 2015). Barriers to care were grouped as individual (4) (e.g. … too busy with work or other commitments to take the time; previous bad experiences with the healthcare system) and systemic/access barriers (7) (e.g., … couldn't get an appointment soon enough, provider's office too far away, insurance does not cover, co-pays too high) (Treadwell et al., 2015). The number of individual and systemic/access barriers are summed separately and together, with higher scores indicating more barriers.

Data analysis

The data collection process occurred from 2017 to 2018. Data was analyzed from the SCDIC registry database, including data from medical record abstractions and the Patient Enrollment Surveys. The initial sample size was 2,433 participants ages 15 – 45 years consented and with confirmed SCD diagnosis. We removed the adolescent group (15 to < 18 years), as well as those without either a completed medical record abstraction form or Patient Enrollment Survey for a final sample size for the study of 2,054 adults with SCD (see Figure 2).

Seven patient-reported outcomes (i.e., pain, sleep and social functioning impacts, emotional distress, tiredness, and cognitive function) were included in the analyses. Binary variables were created for all outputs using as cutoffs 1 SD above the mean for PROs where a higher T-score

indicates a worse outcome (PROMIS Emotional Distress and Fatigue scores) and 1 SD below the mean for those where a higher T-score indicates a better outcome as compared to the reference populations (all ASCQ-Me scores and Neuro-QoL Cognitive Function score).

Baseline characteristics and distributions of risk factors are presented as frequencies and percentages for categorical variables, and median and interquartile ranges (IQR) or mean and SD for continuous variables. Bivariate analysis was used to evaluate potentially significant variables for inclusion in multivariable models. Categorical variables were analyzed using chi-square, or Fisher's exact test for sparse tables. Continuous variables were compared using t-test or Mann-Whitney U test, as appropriate. Two-sided p-values $< .05$ were considered to be statistically significant.

Multivariable models were developed for each PRO to identify factors independently associated with worse outcomes. All variables with $p <= .10$ in bivariate analysis were included in a multivariable logistic regression analysis using backward model selection, with an exit criterion of $p < .05$. Variables of theoretical importance (i.e., age and gender) as well as interactions between selected predictors were included in the initial models but none were significant. Odds ratios and corresponding 95% confidence intervals were obtained for variables remaining in the final model. All analyses were conducted in SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

CHAPTER V

Results

Socio-demographics

A total of 2,054 adults with SCD were included in the present analysis. As shown in Table 1, the median age was 28 years, and the predominant age group was 24 – 34 years (43.8%). Over half (56.8%) identified as female, and the majority identified as African

American/Black (95.7%), with 4.5% reporting Hispanic ethnicity. The most common educational attainment was some college (35.2%), followed by high school graduate or equivalent (30.3%), with 24.1% attaining a college or advanced degree. Over a third (37.2%) were employed, 25.2% reported being disabled and the remainder were not working, either due to student status (13.5.%), or "other" (24.1%) including working exclusively in the home or laid off. A significant proportion (74.2%) were never married and over half (54.6%) reported an annual income under $25,000. Similar to other SCD populations, almost 60% had Medicaid or other government sponsored insurance.

Clinical Characteristics, Health Behaviors and Barriers to Care

The majority (72.6%) of participants were diagnosed with sickle cell anemia (SCD genotypes SS or Beta 0 thalassemia) (see Table 2). Of thirteen potential SCD treatments/complications, participants reported a median of 3 treatments/complications on the ASCQ-Me MHC. More than half of the participants (55.9%) reported four or more treatments/complications, 20.6% reported 2 or 3 and 22.6% reported less than two SCD related treatments/complications. Less than three percent reported a diagnosis of diabetes, but 26% reported current or previous treatment for depression. With regard to disease modifying therapies, 48.3% were currently using hydroxyurea and 28.8% were currently receiving regular blood transfusions. Of those currently using hydroxyurea, 64.8% reported they were adherent 6 – 7 days/week with the remainder reporting they were not (0 – 1 days, 9.4%) or were only partially (2 – 5 days, 25.8%) adherent.

The majority of participants (over 80%) reported no barriers to needed healthcare, with 18.2% reporting 1 or more concrete barriers (access/accommodations/insurance) and 18.1% reporting 1 or more individual barriers. Almost all (92.2%) participants had outpatient visits with

their primary care provider or SCD specialist within the past year. More than half (55.2%) had three or more ED or inpatient admissions for acute pain episodes in the past year, however, data on this variable was missing for more than 27% of the cohort.

For ASCQ-Me® Pain Episode Frequency and Severity T-scores, means and standard deviations were similar to the reference sample, with a pain episode frequency mean (SD) of 49.2 (11) and pain severity mean (SD) of 50.8 (9.7).

Patient Reported Outcomes: Multivariable Models

Figure 2 shows means and variability of T-scores for each PRO. On the ASCQ-Me® measures, means and standard deviations were similar to the reference sample. Using the Emotional and Social Functioning Impact measures, participants reported mean (SD) scores of 50.5 (8.8) and 51.2 (9.7) respectively and only a few reported T-scores less than 40, with 12.7% reporting worse emotional impact and 14.8% reporting worse social functioning compared to the population norms. Somewhat higher percentages of participants reported T-scores less than 40 for Pain (mean (SD) of 47.1 (9.0)) and Sleep Impact (mean (SD) of 49.2 (9.7)), with 21.5% reporting worse impact of pain and 16.9% reporting worse sleep impact. For NeuroQol Cognitive Functioning, the mean (SD) was 50.3 (9.1) with 12.9% of the sample reporting impaired cognitive functioning (T-score < 40). For PROMIS Emotional distress, the mean (SD) was 50.9 (9.6), with 20.1% reporting worse emotional distress (T-score > 60). Finally, for PROMIS® Fatigue (tiredness), the mean (SD) was 55.4 (9.5) with 22% reporting worse tiredness (T-score > 60).

Results for univariate models can be found in supplemental materials (Table S1). In the univariate model, age, gender, income, employment status, marital status, treatment for depression, concrete and individual barriers to care, pain frequency and severity, and number of

reported complications were entered in the model according to our selection criteria for the outcome Emotional Impact. In the multivariable model (Table 3), individuals with incomes of $25,000 and under (OR: 1.87; 95% CI 1.20-3.00), those who were divorced or separated/widowed (OR: 1.87; 95% CI 1.06-3.21), ever treated for depression (OR: 2.36 95% CI 1.70-3.29) and with higher pain frequency (OR: 1.06; 95% CI 1.03-1.08) and severity (OR: 1.07; 95% CI 1.04-1.09) had higher odds for worse outcomes on the Emotional Impact measure. Fewer individual barriers to care (OR: 0.46; 95% CI 0.28-0.80) and fewer complications on the MHC (0-2 complications (OR: 0.54; 95% CI 0.32-0.90) compared to 4 or more complications (OR: 0.54; 95% CI 0.38-0.78) were significantly associated with better outcomes with regard to Emotional Impact. These variables remained as independently associated with Emotional Impact when age and gender were forced into the model.

Age, gender, education, income, employment status, diabetes diagnosis, treatment for depression, concrete and individual barriers to care, pain frequency and severity, complications from the MHC and ED and inpatient utilization for pain met criteria for inclusion in the univariate model for Social Functioning Impact. In the adjusted model, individuals with disabled (OR: 3.34 95% CI 2.32-4.87) or student status (OR: 1.48; 95% CI 0.88-2.44) had higher odds for worse social functioning impact as did individuals treated for depression (OR: 1.64; 95% CI 1.23-2.18) and with increasing pain frequency (OR: 1.04; 95% CI 1.03-1.06) and severity (OR: 1.09; 95% CI 1.07-1.11). Fewer individual barriers to care (OR:0.50;95% CI 0.31-0.82) were associated with lower odds of worse social functioning impact. These variables remained as independently associated with social functioning impact when age and gender were in the model.

Age, gender, education, income, employment status, marital status, diagnosis of diabetes, treatment for depression, disease modifying therapies, concrete and individual barriers to care,

pain frequency and severity and ED and inpatient utilization for pain met selection criteria in the univariate model for Pain Impact. In the adjusted model, individuals with disabled and "other" employment status (OR :1.09; 95% CI 0.68-1.72 and OR: 2.07; 95% CI 1.49-2.90) had higher odds of poor outcomes with regard to pain impact as did those who were divorced, separated or widowed (OR: 1.76; 95% CI 1.09-2.81). Odds for worse outcomes on Pain Impact increased with increasing pain frequency (OR: 1.1; 95% CI 1.08-1.12) and severity (OR: 1.10; 95% CI 1.08-1.12). These variables, except for marital status, remained in the model when age and gender were included.

Gender, education, income, employment status, treatment for depression, concrete and individual barriers to care, pain frequency and severity and complications from the MHC met selection criteria in the univariate model for Sleep Impact. In the adjusted model, individuals with incomes of $25,000 and under, as well as incomes of $25,001 - $50,000 (OR :2.03; 95% CI 1.38-3.05 and OR: 2.03; 95% CI 1.30-3.22) had higher odds of poor outcomes with regard to sleep impact as did those ever treated for depression (OR: 2.07; 95% CI 1.55-2.75). Odds for worse outcomes on Sleep Impact increased with increasing pain frequency (OR: 1.03; 95% CI 1.01-1.04) and severity (OR: 1.03; 95% CI 1.01-1.05). Those with fewer concrete barriers to care (OR: 0.60; 95% CI 0.40-0.93) and 0-2 (OR: 0.48; 95% CI 0.30-0.73) or 3-4 (OR: 0.71; 95% CI 0.53-0.96) complications on the MHC had lower odds for poor outcomes. These variables remained in the model when age and gender were included.

For Neuro-QoL® Cognitive Function, in the univariate model, gender, education, income, employment status, treatment for depression, concrete and individual barriers to care, pain frequency and severity, number of reported complications, and acute utilization for pain met criteria for inclusion. In the adjusted model, individuals with high school (OR: 2.0; 95% CI 1.25-

3.29) or less (OR: 1.98; 95% CI 1.07-3.62) education, ever treated for depression (OR: 1.74; 95% CI 1.23-2.45), higher pain frequency (OR: 1.03; 95% CI 1.01-1.05) and less acute utilization (OR: 2.31 for 0 ED or inpatient admissions in the past year; 95% CI 1.47-3.59 and OR: 1.61 for 1-2 of either ED or inpatient admissions in the past year; 95% CI 1.08-2.37) had higher odds for worse cognitive functioning. Those reporting fewer individual barriers to care (OR: 0.34; 95% CI 0.20-0.57) had lower odds for poor cognitive functioning. These variables remained as independently associated with cognitive functioning when age was also in the model.

Age, gender, education, income, employment status, marital status, diabetes diagnosis, treatment for depression, SCD diagnosis, concrete and individual barriers to care, pain frequency and severity, number of reported complications and ED and inpatient utilization for pain met criteria for inclusion in the univariate model for PROMIS Emotional Distress. In the adjusted model, individuals with incomes of $25,000 and under (OR: 1.87; 95% CI 1.32-2.69), ever treated for depression (OR: 3.30 95% CI 2.52-4.34), SCD diagnosis of other variants (OR: 1.89; 95% CI 1.14-3.07) and with higher pain frequency (OR: 1.02; 95% CI 1.01-1.03) and severity (OR: 1.02; 95% CI 1.01-1.04) had higher odds for worse outcomes on the Emotional Distress measure. Those with fewer individual barriers to care (OR: 0.45; 95% CI 0.28-0.73) and 0-2 (OR: 0.56; 95% CI 0.38-0.83) or 3-4 (OR: 0.61; 95% CI 0.46-0.83) complications on the MHC had lower odds for poor outcomes with regard to emotional distress. These variables remained as independently associated with emotional distress when age and gender were in the model.

Finally, in the univariate model for PROMIS Fatigue (tiredness), age, gender, education, employment status, marital status, treatment for depression, SCD diagnosis, disease modifying therapies, concrete and individual barriers to care, pain frequency and severity and number of

reported complications met selection criteria for inclusion. In the adjusted model, individuals ever treated for depression (OR: 1.75; 95% CI 1.37-2.23) and with higher pain frequency (OR: 1.02; 95% CI 1.01-1.03) and severity (OR: 1.02; 95% CI 1.01-1.03) had higher odds for worse reports of tiredness. Those identifying as male (OR: 0.40; 95% CI 0.31-0.51) and with fewer individual barriers to care (OR: 0.41; 95% CI 0.27-0.62) had lower odds for tiredness. These variables remained as independently associated with tiredness when age was also in the model.

Hydroxyurea Adherence and Patient Reported Outcomes

We conducted a sub-analysis of the 979 participants who reported that they were currently prescribed hydroxyurea. Characteristics of individuals currently prescribed hydroxyurea compared with those not prescribed hydroxyurea can be found in supplemental materials (Table S1). More participants on hydroxyurea were in the 18 – 24-year-old age group (34.7%) compared with those not on hydroxyurea (27.9%, $p = .004$). More male participants (55%) were on hydroxyurea compared with female participants (43.7%; $p < .0001$). Employment status differed between those participants on hydroxyurea compared to those not on hydroxyurea ($p < .001$). Fewer participants on hydroxyurea were working (33.6%) compared with those not on hydroxyurea (40.7%) and conversely, more participants on hydroxyurea reported disabled (27.2%) and student status (15.7%) compared with those not on the medication (22.9% and 11.5% respectively). Seventy-seven percent of participants on hydroxyurea reported that had never been married compared with 72% of those not on hydroxyurea ($p < .01$). As would be expected, most participants on hydroxyurea had genotype SS or $S\beta^0$ thalassemia (86%) compared with other genotypes (14%; $p < .0001$).

In univariate models including hydroxyurea adherence and the other socio-demographic, clinical and health behavior variables, hydroxyurea adherence entered in the models according to

our selection criteria only for the PROs ASCQ-Me Sleep Impact and PROMIS Fatigue (tiredness). In the multivariable model, individuals with incomes of $25,000 and under (OR: 2.42; 95% CI 1.43-4.31), ever treated for depression (OR: 2.5 95% CI 1.70-3.70) and with higher pain frequency (OR: 1.03; 95% CI 1.00-1.05) and severity (OR: 1.03; 95% CI 1.00-1.05) had higher odds for worse outcomes on the Sleep Impact measure. Those with a visit to a primary care provider or sickle cell specialist in the past year had lower odds for worse outcomes on sleep impact (OR: 0.33 95% CI 0.15-0.79).

In the multivariable model for tiredness, individuals ever treated for depression (OR: 1.62 95% CI 1.11-2.33), not adherent with hydroxyurea (OR: 2.04 95% CI 1.17-3.49) and with higher pain frequency (OR: 1.02; 95% CI 1.00-1.04) had higher odds for worse outcomes on the Fatigue measure. Those with male gender (OR: 0.39 95% CI 0.27-0.56) and 0 – 1 versus 2 or more access/accommodation/insurance barriers had lower odds for worse outcomes on the Fatigue measure (OR: 0.50 95% CI 0.29-0.85).

CHAPTER VI

Discussion

This dissertation study hypothesized that patient and SCD related factors as well as barriers to care would independently contribute to functioning as measured using PRO domains from the ASCQ-Me®, PROMIS® and NeuroQoL™ measurement systems. We expected that the experience of pain and other SCD related complications would account for a significant degree of the relation between the variables and further considered the bidirectional influence of health behaviors such as adherence and healthcare utilization on the PRO domains. Generally, our findings were consistent with study hypotheses, with higher pain frequency and severity and history of treatment for depression associated with higher odds of worse outcomes in almost all

PRO domains studied, with findings remaining even when controlling for age and gender. Such social determinants of health as lower household income and unemployment, particularly due to disability status, were also associated with higher odds of worse outcomes on some of the PRO domains studied. Our study includes consideration of barriers to care, and we found a protective effect, with reports of fewer individual barriers to care associated with better outcomes in the emotion, social, cognitive and fatigue (tiredness) domains. Reports of fewer self-reported SCD complications/treatments were also protective, with associations with better outcomes in the emotion and sleep impact domains.

Our findings are consistent with previous research (Dampier et al., 2011; Esham et al., 2019; McClish et al., 2017) that has highlighted dimensions of pain experiences associated with worse outcomes on PROs for adults with SCD, as well as depression (Adam et al., 2017; Master et al., 2016). However, our study is the first large, multi-site cohort of adults with SCD who completed contemporary PRO measures that have been developed and validated with state-of-the-science psychometric methods. We thus contribute to the accumulation of information on the precision, applicability and interpretation of PROMIS® and related measurement systems, ASCQ-Me® and NeuroQoL™.

Reports on the PRO measures for our study participants were on average similar to reference samples, although with considerable variability within and across domains. For several domains, about 20% of participants of large-scale PROMIS reference samples have demonstrated moderate to severe symptomatology or functional impairment (Cella et al., 2010; Rothrock et al., 2010). About 20% of participants in the current study reported moderate/severe pain and emotional impact and tiredness. However, the proportion of participants with moderate/severe emotional (12.7%) and social functioning (14.8%) and sleep impact (16.9%) on

ASCQ-Me were less than that seen in the reference population for PROMIS. Given that a higher percentage of participants endorsed moderate/severe emotional distress on the PROMIS measure compared with the ASCQ-Me emotional impact measure suggests that the two measures are indeed assessing different constructs. Interpretation of scores from the disease specific ASCQ-Me measures needs further exploration, although findings from this large sample can provide a baseline for future studies. Studies establishing sensitivity of PRO measurement to distress and functioning for SCD populations, as well as changes in health status are particularly critical.

Approximately 13% of respondents fell below the moderate/severe threshold on the NeuroQOL Cognitive Function short form (Cella et al., 2012). This tool was designed to capture participants' concerns about general cognition and to assess executive function concerns (Prussien et al., 2018; Shimada et al., 2014). The multivariate model was consistent with prior studies in that worse reports of cognitive function were associated with depressive symptoms (Sanger et al., 2016) and with lower levels of education (Saunders et al., 2018). In this study, worse reports of cognitive function were not associated with very high acute care utilization. It is possible that the proportion of participants with cognitive dysfunction in the SCDIC Registry was underrepresented. Prior studies have documented poor correlation in self-report of executive function and performance of executive function assessments, with less recognition of impairment (Eisenberg et al., 2019). Worse executive function is associated with poor medical treatment adherence, and it may also be associated with less insight into these relationships (Gutiérrez-Colina et al., 2016).

Complex relations were also found among measures. Pain severity, frequency of pain, history of depression and lower income were associated with the highest odds for worse emotional, sleep and tiredness impacts, consistent with other studies (Eisenberg et al.,

2019). Pain experiences in combination with patient-related variables such as unemployment (particularly related to disabled status) and marital status (divorced/separated) played a significant role in worse outcomes on such PROs as social functioning and emotional impact. Similar to previous research, other demographic factors (age, gender) were consistently associated with the PRO measures (Dampier et al., 2011; Wallen et al., 2014). We found that SCD genotype per se, where Hgb SS and Sß^0 thalassemia are considered most severe, was not associated with the PRO measures. In fact, in the one instance where genotype was associated with a PRO measure in the present study, it was other SCD variants (SC, Sß$^+$ thalassemia and others) that were associated with worse outcomes on the PROMIS Emotional Distress measure. Aside from genotype, we did consistently find that fewer patient reports of SCD related complications and treatments was associated with better outcomes on the PRO measures. Thus, when considering clinical and research interventions, there is ample evidence that HRQoL in SCD must be viewed as a complex biopsychosocial phenomenon and there is an urgent need for specific focus on the pain experience and depression.

While disparities in quality of life and quality of care are well-recognized in SCD, particularly for adults, the impact of barriers to care has not been widely studied. We used a modified version of the first disease specific measure of barriers to care in SCD and demonstrated that the majority of participants in the SCDIC registry reported no barriers to needed care, and fewer barriers to care were associated with better outcomes on all PRO measures except pain impact. In a recent study of 303 adults with SCD, the most reported barriers to receiving care were discrimination by and mistrust in healthcare professionals, as well as healthcare costs (Rizio et al., 2020). In another recent study, reports of delaying ED care were inter-related with higher stigma experiences, more frequent pain episodes, lower health care

satisfaction, and yet more frequent ED visits (Abdallah et al., 2020). The over 400 adolescents and adults with SCD who participated in the multi-site SCDIC needs assessment similarly reported discrimination and mistrust in the acute healthcare system as barriers (Kanter et al., 2020). The SCDIC has launched an intervention to improve ED care by enhancing co-management between ED and SCD specialists and empowering adults with SCD with improved access to their individualized pain plans in the ED (Luo et al., 2020). Much still needs to be understood and addressed regarding the impact of barriers to care, particularly stigma and discrimination, on HRQoL in SCD.

Higher healthcare utilization is often a reflection of the increased burden of SCD-related complications, which can be associated with worse health outcomes, including morbidity and mortality. While the majority of our sample had outpatient primary or SCD specialty care visits in the past year, over half still had what would be considered high acute utilization, with more than three combined ED visits and inpatient stays in the past year. Contrary to hypothesis, higher healthcare utilization was not associated with worse outcomes in any PRO domain, while lower healthcare utilization was in fact associated with worse outcomes in the cognitive functioning domain. Previous studies have reported various other factors associated with increased healthcare utilization, including female gender (Fosdal & Wojner-Alexandrov, 2007), living away from the hospital (Nietert et al., 1999), and having co-morbidities (Raphael et al., 2012), depression (Jonassaint, Jones, et al., 2016), or other psychiatric illness, such as anxiety and mood disorder (Myrvik et al., 2012). Using PROMIS measures, a recent study focused on youth with SCD in the U.S. reported an association between increased healthcare utilization and worse HRQoL domain scores, particularly depression, social isolation, pain, fatigue and physical function mobility (Badawy et al., 2018). Similar associations were demonstrated in a recent

systematic review of the literature (Jonassaint, Jones, et al., 2016) and in other studies using SF-36 measure in Nigeria (Adeyemo et al., 2015) and Saudi Arabia (Abdel-Monhem Amr et al., 2011; Ahmed et al., 2016).

In addition to healthcare utilization, we were interested in the relation between adherence behavior and PRO domain scores. Previous studies reported better HRQoL outcomes among children and adults with SCD who were receiving hydroxyurea, regardless of adherence level, compared to those who were not (Ballas et al., 2006; Thornburg et al., 2011). In our sub-sample of 979 individuals with SCD currently prescribed hydroxyurea, non-adherence in combination with history of depression and higher pain frequency were associated only with worse outcomes for tiredness, which is consistent with recently published data (Badawy et al., 2017a). Badawy and colleagues reported an association between lower hydroxyurea adherence, using subjective and objective measures, and worse HRQoL outcomes, particularly fatigue, depression and social isolation (Badawy et al., 2017a). Hydroxyurea adherence is multifactorial in nature, and it is a dynamic behavior that likely varies across patients and within the same patient over time. Our sub-sample of participants prescribed hydroxyurea was younger, male, never married and unemployed with disabled or student status, compared with those not on the hydroxyurea. Male gender and fewer barriers to care were associated with better outcomes for tiredness for the subsample. In an in-depth analysis of qualitative interviews from the SCDIC needs assessment, a majority of the 90 participants (70%) with SCD described unintentional barriers to hydroxyurea adherence, including misunderstanding of medical instructions, the burden of complex treatment regimens, never being offered the drug, and the low quality and weak patient-provider relationship and communication (Hodges et al., 2020). Similarly, among youth with SCD, patient-reported negative perceptions of hydroxyurea and more frequent barriers were associated

with lower hydroxyurea adherence rates as well as worse HRQoL outcomes (Badawy et al., 2018; Badawy, et al., 2017).

Limitations

Despite our gathering data from participants with SCD from multiple sites across the U.S., the generalizability of the sample may still represent a limitation, given that the majority were recruited through sickle cell centers and had in fact seen a sickle cell specialist or primary care provider in the previous year. Due to the vast shortage of adult sickle cell specialists in the U.S., it is known that most adults with SCD simply do not have access to needed preventive care and the impact of disparities in access to care on HRQoL can only be determined when more patients who are "unaffiliated" with SCD care are recruited into research. The cross-sectional nature of the study precludes any conclusions about causal relations between study variables and the PROs. In order to reduce participant burden, we did not include all items for every PRO measure, thereby limiting full comparison with studies using the complete PRO measures. However, PROMIS measures have been constructed to maintain precision even when only single, or a few items are used. Our registry data collection included both self-report and information extracted from medical records, however for completeness of data, we only used self-reports of SCD complications experienced, and these reports may or may not correspond with actual complications endured by participants. When we did use data from the medical record, such as in relation to healthcare utilization, we were subject to missing data on the order of greater than 25% of our sample. There is also a possibility that during data collection, participants might have misunderstood the items listed on the medical health history checklist or responded based on incorrect recollection. Study limitations notwithstanding, our research contributes to the literature in its examination of interrelations between modern PRO measures

and SCD related and other variables within a conceptual model and utilizing a large, geographically diverse sample.

Study implications:

Reliable and valid PRO measurement is essential to the design of clinical trials and other research, so much so, that the National Institutes of Health invested in a high-profile Common Fund effort to develop PROMIS measures and related ASCQ-Me and NeuroQoL measurement systems (Sarri et al., 2018; Yount et al., 2019). Results from the present study can provide a baseline for longitudinal investigations that can establish sensitivity to change of the PRO measures and that can advance our understanding of how SCD and its treatments impact outcomes for patients.

From a clinical standpoint, the current research provides data supporting that PRO measures can provide meaningful information for providers and patients in areas of focus to improve HRQoL. The study also highlights how critical it is to view lives, care and treatments for individuals with SCD within a biopsychosocial model. For example, our sample evidenced a high prevalence of history of depression, and substantial impact of pain experiences and social determinants of health, yet protective influence of fewer barriers to care and disease complications. Multi-dimensional interventions that include case management as well as expert medical care could improve PROs. In one study, case managers were considered to be the only healthcare team member who has a broad knowledge of the patients' experience of pain, state of health, behavioral health needs, and how psychosocial factors may affect both inpatient and outpatient health care use and outcomes (Brennan-Cook et al., 2018).

It is important for providers, especially sickle cell specialists, to understand their patients' perspectives about their expected health outcomes after treatments. Patients might be reluctant to

disclose their dissatisfaction if their expectations were not met. Patients might also feel misunderstood or unheard by their providers. Previous studies have demonstrated that patients' mistrust in healthcare professionals can lead to lower treatment adherence and adversely impact health outcomes due to delays in care (Oyedeji & Strouse, 2020). Collecting PROs during clinical encounters, on the other hand, may enhance provider-patient communication and promote effective symptom management. It is important to attend to these issues to close the gap in health equity for SCD care.

Directions for future research:

We were unable to focus on a number of potential contributing factors to outcomes with regard to PROs, such as other mental health symptoms, e.g., anxiety in addition to depression; actual experience of stigma and discrimination as barriers to care; coping and self-efficacy. Prospective longitudinal studies are warranted to assess and better understand the dynamic relation between hydroxyurea adherence and HRQoL outcomes over time, including the long-term effect of one on the other. Longitudinal studies will also allow for the examination of changes in PROs over time, will advance our understanding of the impacts of SCD and its treatments, as well as of the impact of therapies to improve PROs. Future research including PRO measures can refine models for intervention to improve overall care of those living with SCD.

Conclusion:

The present study provides important new information regarding inter-relations between SCD complications, disease modifying therapies, social determinants of health and barriers to care for adults with SCD. Our findings emphasize the importance of the biopsychosocial model

to enhance our understanding of the needs of this complex population, and to design multi-dimensional approaches for providing more effective interventions to improve outcomes.

Tables & Figures

Table 1. Participant Socio-Demographics

Characteristic	N = 2054
Age	
Mean (SD) years	29.1 (7.2)
Median (IQR)	28 (23-35)
	n (%)
18 to 24 years	641 (31.2)
25 to 34 years	900 (43.8)
35 to 45 years	513 (25.0)
Gender Identity	
Male	888 (43.2)
Female	1166 (56.8)
Race/Ethnicity	
Black/African American	1918 (95.7)
Multi-racial	67 (3.3)
Other Race (American Indian/Alaska Native, Asian, White)	20 (0.9)
Hispanic ethnicity	91 (4.5)
Highest Education	
Some high school or less	209 (10.4)
High School (Graduate, GED or equivalent)	612 (30.3)
Some college	711 (35.2)
College graduate or advanced degree	487 (24.1)
Employment	
Working now	748 (37.2)
Disabled	507 (25.2)
Student	272 (13.5)
Other (unemployed, retired)	485 (24.1)
Marital Status	
Married or living together	313 (16.2)
Never married	1499 (77.6)
Not married (divorced/separated, widowed)	120 (6.2)

Annual Household Income	
$25,000 or less	998 (54.6)
$25,000 - $50,000	403 (22.1)
$50,001 or more	426 (23.3)
Insurance	
Medicaid, CHIP, other government-sponsored	1216 (59.2)[a]
Private	567 (27.6)
Medicare	468 (22.8)
None	83 (4.0)
Other	16 (0.8)

[a]Percentages add up to greater than 100% as more than one option could be selected

Table 2. Clinical Characteristics, Barriers to Care and Health Behaviors

Characteristic	N = 2054
	n (%)
Sickle cell disease diagnosis	
Hb SS or Sβ^0 thalassemia	1490 (72.6)
Hb SC	432 (21.1)
Hb Sβ+ thalassemia and other variants	130 (6.3)
ASCQ-Me Medical History Checklist	
Mean (SD)	3.1 (2)
Median (IQR)	3 (2-4)
Range (minimum – maximum)	0 – 12
	n (%)
Diabetes	
Yes	53 (2.6)
No	1953 (97.4)
Ever treated for depression	
Yes, current	181 (9.2)
Yes, previous	330 (16.8)
No	1455 (74.0)
Hydroxyurea use and adherence	
Yes, current use	
Adherent (6 – 7 of 7 days)	628 (31.3)
Partially adherent (2 – 5 of 7 days)	250 (12.5)
Not adherent (0 – 1 of 7 days)	91 (4.5)
No, not currently using	1035 (51.7)
Regular blood transfusions for SCD	
Yes	587 (28.8)
No	1449 (71.2)
Barriers to Care	
Access/Accommodations/Insurance	
No barriers	1681 (81.8)
1 – 2 barriers	302 (14.7)
3 or more barriers	71 (3.3)
Individual barriers	
No barriers	1683 (81.9)
1 – 2 barriers	323 (15.7)
3 or more barriers	48 (2.3)

From Medical Record Abstractions:	
Outpatient visit to hematologist or primary care provider within past 12 months	
Yes	1893 (92.2)
No	92 (4.5)
Unknown	69 (3.4)
Emergency department (ED) and inpatient admissions for pain within past 12 months	
No ED or inpatient admissions	279 (18.7)
1 – 2 ED or inpatient admissions	388 (26.0)
3 or more ED or inpatient admissions	823 (55.2)

Patients with missing data are not included in calculations of percentages unless otherwise specified

Table 3. Significant Multivariate Relations Between Patient-Reported Outcomes and Demographic and Clinical Characteristics

Model	Predictor	Overall type III p-value	OR (95% CI)
ASCQ-Me® Emotional Impact	Income	.02	
	$25,000 and under		1.87 (1.20-3.00)**
	$25,001 - $50,000		1.45 (0.85-2.52)
	$50,001+		Ref
	Marital status	.03	
	Married/Living as married		1.44 (0.93-2.20)
	Divorced/Separated/Widow		1.87 (1.06-3.21)*
	Never married		Ref
	Ever treated for depression	<.0001	2.36 (1.70-3.29)**
	# Individual barriers to care	.004	
	0-1 versus 2 or more		0.46 (0.27-0.80)**
	ASCQ-Me® Pain Frequency	<.0001	1.06 (1.03-1.08)**
	ASCQ-Me® Pain Severity	<.0001	1.07 (1.04-1.09)**
	ASCQ-Me® SCD-MHC	.002	
	Low (0-2)		0.54 (0.32-0.90)*
	Medium (3-4)		0.54 (0.38-0.78)**
	High (>4)		Ref
ASCQ-Me® Social Functioning Impact	Employment	<.001	
	Disabled		3.34 (2.32-4.87)**
	Student		1.48 (0.88-2.44)
	Other		2.33 (1.58-3.46)**
	Working		Ref
	Ever treated for depression	.0007	1.64 (1.23-2.18)**
	# Individual barriers to care	.005	
	0-1 versus 2 or more		0.50 (0.31-0.82)**
	ASCQ-Me® Pain Frequency	<.0001	1.04 (1.03-1.06)**
	ASCQ-Me® Pain Severity	<.0001	1.09 (1.07-1.11)**
ASCQ-Me® Pain Impact	Employment	<.0001	
	Disabled		2.4 (1.75-3.31)**
	Student		1.09 (0.68-1.72)
	Other		2.07 (1.49-2.90)**
	Working		Ref

	Marital status	.049	
	Married/Living as married		1.20 (0.86-1.66)
	Divorced/Separated/Widow		1.76 (1.09-2.81)*
	Never married		Ref
	ASCQ-Me® Pain Frequency	<.0001	1.10 (1.08-1.12)**
	ASCQ-Me® Pain Severity	<.0001	1.10 (1.08-1.12)**
ASCQ-Me® Sleep Impact	Income	.0014	
	$25,000 and under		2.03 (1.38-3.05)**
	$25,001 - $50,000		2.03 (1.30-3.22)**
	$50,001+		Ref
	Ever treated for depression	<.0001	2.07 (1.55-2.75)**
	# Concrete barriers to care	.02	
	0-1 versus 2 or more		0.60 (0.40-0.93)*
	ASCQ-Me® Pain Frequency	.001	1.25 (1.01-1.04)**
	ASCQ-Me® Pain Severity	.0008	1.03 (1.01-1.05)**
	ASCQ-Me® SCD-MHC	.002	
	Low (0-2)		0.48 (0.30-0.73)**
	Medium (3-4)		0.71 (0.52-0.96)*
	High (>4)		Ref
Neuro-QoL™ Cognitive Functioning		.03	
	Education		
	<High School		1.98 (1.07-3.62)*
	High school		2.00 (1.25-3.29)**
	Some college		1.45 (0.91-2.36)
	College/Advanced		Ref
	Ever treated for depression	.002	1.74 (1.23-2.45)**
	# Individual barriers to care	<.0001	
	0-1 versus 2 or more		0.34 (0.20-0.57)**
	ASCQ-Me® Pain Frequency	.006	1.03 (1.01-1.05)**
	Acute utilization (ED or Inpatient visits) past 12 months	.0007	
	0 for both		2.31 (1.47-3.59)**
	1-2 of either		1.61 (1.08-2.37)*
	3+ of either		Ref
PROMIS® Emotional Distress	Income	.0012	
	$25,000 and under		1.87 (1.32-2.69)**
	$25,001 - $50,000		1.32 (0.86-2.02)
	$50,001+		Ref
	Ever treated for depression	<.0001	3.30 (2.52-4.34)**

	SCD dx	.03	
	SS/Sβ^0 Thalassemia		Ref
	SC		1.22 (0.88-1.69)
	Other variants		1.89 (1.14-3.07)*
	# Individual barriers to care	.001	
	0-1 versus 2 or more		0.45 (0.28-0.73)**
	ASCQ-Me® Pain Frequency	.01	1.02 (1.01-1.03)*
	ASCQ-Me® Pain Severity	.01	1.02 (1.01-1.04)*
	ASCQ-Me® SCD-MHC	.001	
	Low (0-2)		0.56 (0.38-0.83)**
	Medium (3-4)		0.62 (0.46-0.83)**
	High (>4)		Ref
PROMIS® Fatigue/Tiredness	Gender Identity Male	<.0001	0.40 (0.31-0.51)**
	Ever treated for depression	<.0001	1.75 (1.37-2.23)**
	# Individual barriers to care	<.0001	
	0-1 versus 2 or more		0.41 (0.27-0.62)**
	ASCQ-Me® Pain Frequency	.003	1.02 (1.01-1.03)**
	ASCQ-Me® Pain Severity	.004	1.02 (1.01-1.03)**

#: number of
ASCQ-Me®: Adult Sickle Cell Quality of Life Measurement Information System
ASCQ-Me® SCD MHC: Adult Sickle Cell Quality of Life Measurement Information System Sickle Cell Disease Medical History Checklist
Neuro-QoL™: Quality of Life in Neurological Disorders
PROMIS®: Patient Reported Outcomes Measurement Information System
*p < .05
**p < .01

Table S1. Significant Multivariate Relations Between Patient-Reported Outcomes and Demographic and Clinical Characteristics (Supplemental Table)

	Emotional Impact (n = 1530; EI<40 = 200)			Social Functioning Impact (n=1924, SF<40 n = 281)			Pain Impact (n=1885, PI<40 n = 410)			Sleep Impact (n=1598, SI<40 n = 270)		
Variables	**<40**	**>40**	**p-value**	**<40**	**>40**	**p-value**	**<40**	**>40**	**p-value**	**<40**	**>40**	**p-value**
Age												
18-24	58 (22.7%)	574 (32.7%)	**0.0006**	77 (25.7)	559 (32.3)	**0.06**	102 (23.3%)	535 (33.6%)	**<0.0001**	102 (30)	532 (31.8)	**0.2**
25-34	127 (49.8%)	748 (42.6%)		146 (48.7)	740 (42.7)		201 (46.0%)	681 (42.8%)		162 (47.6)	713 (42.6)	
35+	70 (27.5%)	434 (24.7%)		77 (25.7)	432 (25)		134 (30.7%)	376 (23.6%)		76 (22.4)	428 (25.6)	
Gender Identity Male	78 (30.6%)	788 (44.9%)	**<0.0001**	100 (33.3)	777 (44.9)	**0.0002**	167 (38.2%)	709 (44.5%)	**0.02**	126 (37.1)	742 (44.4)	**0.01**
Education												
<High School	28 (11.1)	176 (10.1)	**0.6**	34 (11.5)	173 (10.1)	**0.04**	57 (13.4)	150 (9.5)	**0.02**	44 (13.1)	161 (9.7)	**0.08**
High school	81 (32)	526 (30.3)		106 (35.8)	504 (29.5)		135 (31.8)	469 (29.9)		100 (29.8)	506 (30.6)	
Some college	92 (36.4)	606 (34.9)		101 (34.1)	604 (35.3)		151 (35.5)	552 (35.1)		125 (37.2)	570 (34.5)	
Ref: College/Avd.	52 (20.6)	426 (24.6)		55 (18.6)	429 (25.1)		82 (19.3)	400 (25.5)		67 (19.9)	415 (25.1)	
Income												
$25,000 and under	160 (68.1)	820 (52.4)	**<0.0001**	185 (68.3)	807 (52.2)	**<.0001**	257 (66.2)	725 (51.2)	**<0.0001**	202 (65.4)	777 (52.1)	**<0.0001**
$25,001 - $50,000	40 (17)	358 (22.9)		43 (15.9)	358 (23.2)		70 (18)	329 (23.2)		65 (21)	332 (22.3)	
Ref: $50,001+	35 (14.9)	386 (24.7)		43 (15.9)	381 (24.6)		61 (15.7)	363 (25.6)		42 (13.6)	381 (25.6)	
Employment												

Ref: Working	60 (23.7)	680 (39.4)	**<0.0001**	51 (17.2)	694 (40.8)	**<0.0001**	91 (21.4)	652 (41.7)	**<0.0001**	92 (27.5)	647 (39.3)	**<0.0001**
Disabled	99 (39.1)	396 (22.9)		132 (44.4)	370 (21.7)		171 (40.1)	325 (20.8)		105 (31.3)	392 (23.8)	
Student	28 (11.1)	243 (14.1)		30 (10.1)	241 (14.2)		36 (8.5)	235 (15)		36 (10.7)	243 (14.2)	
Other	66 (26.1)	409 (23.7)		84 (28.3)	397 (23.3)		128 (30)	351 (22.5)		102 (30.4)	373 (22.7)	
Marital status												
Married/Living as married	42(16.8)	268(16.2)	**0.046**	43(14.8)	265(16.3)	**0.3**	73(17.5)	239(16.0)	**0.07**	44(13.5)	267(16.9)	**0.3**
Divorced/Separated/Widow	24(9.6)	93(5.6)		24(8.2)	96(5.9)		35(8.4)	83(5.6)		23(7.1)	94(6.0)	
Ref: Never married	184(73.6)	1290(78.1)		224(77.0)	1268(77.8)		310(74.2)	1171(78.4)		258(79.4)	1217(77.1)	
Diabetes "No"	237 (95.6)	1,678 (97.6)	**0.06**	281 (95.6)	1,652 (97.6)	**0.05**	412 (96.0)	1518 (78.4)	**0.053**	327 (97.6)	1,589 (97.3)	**0.8**
Ever treated for depression "No"	124 (51.2)	1,308 (77.2)	**<0.0001**	168 (59.4)	1,278 (76.4)	**<0.0001**	273 (66.6)	1163 (75.9)	**0.0001**	184 (57.3)	1,246 (77.1)	**<0.0001**
SCD dx												
Ref: SS/Sβ^0	183 (72)	1,277 (72.7)	**0.7**	220 (73.3)	1,253 (72.4)	**0.7**	318 (72.8)	1,152 (72.4)	**0.8**	244 (72)	1,216 (72.7)	**0.9**
Thalassemia												
SC	52 (20.5)	371 (21.1)		59 (19.7)	369 (21.3)		89 (20.4)	340 (21.4)		72 (21.2)	354 (21.2)	
Disease Modifying Therapies "yes"	176 (70.1)	1103 (63.8%)	**0.05**	188 (64.2)	1,102 (64.7)	**0.9**	290 (68.6)	999 (63.5)	**0.05**	225 (67.6)	1,053 (64)	**0.2**
Access/Accommodations/Insurance barriers to care												

Ref: 0-1	213 (83.5%)	1630 (92.8%)	**<0.0001**	259 (86.3)	1,598 (92.3)	**0.0006**	384 (87.9)	1,472 (92.5)	**0.002**	290 (85.3)	1,555 (92.9)	**0.002**
2 or more	42 (16.5%)	126 (7.2%)		41 (13.7)	133 (7.7)		53 (12.1)	120 (7.5)		50 (14.7)	118 (7.1)	
# of individual barriers to care												
Ref: 0-1	221 (86.7%)	1676 (95.4%)	**<0.0001**	269 (89.7)	1,645 (95)	**0.0002**	402 (92)	1,509 (94.8)	**0.03**	309 (90.9)	1,589 (95)	**0.003**
2 or more	34 (13.3%)	80 (4.6%)		31 (10.3)	86 (5)		35 (8)	83 (5.2)		31 (9.1)	84 (5)	
ASCQ-Me Pain episodes frequency score												
Mean(SD)	54.6 (8.2)	48.4 (11.2)	**<0.0001**	54.3 (8.3)	48.4 (11.2)	**<0.0001**	55.7 (7.8)	47.4 (11.1)	**<0.0001**	52.5 (9.3)	48.4 (11.2)	**<0.0001**
Median	55.7	51.8		55.7	51.8		59.6	51.8		55.7	51.8	
ASCQ-Me Pain episodes severity score												
Mean (SD)	55.1 (7.3)	50.2 (9.8)	**<0.0001**	55.9 (7.3)	50 (9.7)	**<0.0001**	55.8 (6.5)	49.5 (9.9)	**<0.0001**	53.2 (8.8)	50.3 (9.8)	**<0.0001**
Median	57	52.3		57	52.3		57	50		54.6	52.3	
Expanded ASCQ-Me SCD-MHC score - 13 items*												
Low (0-2)	29 (12.6)	392 (24.1)	**<0.0001**	27 (9.7)	397 (24.9)	**<0.0001**	51 (13)	371 (25.2)	**<0.0001**	40 (12.8)	382 (24.7)	**<0.0001**
Medium (3-4)	59 (25.5)	660 (40.6)		107 (38.4)	617 (38.8)		126 (32.1)	597 (40.5)		107 (34.2)	613 (29.7)	
High (>4)	143 (61.9)	573 (35.3)		145 (52)	578 (36.3)		215 (54.8)	507 (34.4)		166 (53)	549 (35.6)	

Table S1 (continued). Significant Multivariate Relations Between Patient-Reported Outcomes and Demographic and Clinical Characteristics (Supplemental Table)

	Neuro-QOL Cognitive Functioning (n=2040, CF<40 = 264)			**PROMIS Emotional Distress (n = 2014; ED>60 = 405)**			**PROMIS Fatigue (n=2004, FI > 60 = 440)**		
Variables	<40 (worse)	>=40 (better)	**p-value**	>60 (worse)	<= 60 (better)	**p-value**	>60 (worse)	<= 60 (better)	**p-value**
Age									
18-24	86 (32.6)	551 (31)	**0.4**	107 (26.4)	526 (32.7)	**0.04**	117 (26.6)	513 (32.8)	**0.04**
25-34	106 (40.2)	789 (44.4)		183 (45.2)	693 (43.1)		202 (45.9)	670 (42.8)	
35+	72 (27.3)	436 (24.5)		115 (28.4)	390 (24.2)		121 (27.5)	381 (24.4)	
Gender Identity Male	91 (34.5)	794 (44.7)	**0**	152 (37.5)	716 (44.5)	**0.01**	107 (24.3)	756 (48.3)	**<0.0001**
Education									
<High School	32 (12.3)	176 (10)	**0.09**	49 (12.3)	155 (9.7)	**0.03**	39 (9)	165 (10.7)	**0.003**
High school	86 (33.1)	526 (30)		113 (28.3)	494 (31.1)		107 (24.6)	498 (32.2)	
Some college	95 (36.5)	615 (35)		157 (39.3)	542 (34.1)		163 (37.5)	530 (34.3)	
Ref: College/Advanced	47 (18.1)	438 (25)		80 (20.1)	399 (25.1)		126 (29)	352 (22.8)	
Income									
$25,000 and under	158 (65.8)	838 (52.9)	**0**	251 (67.5)	730 (51)	**<0.0001**	222 (56.3)	752 (53.8)	**0.4**
$25,001 - $50,000	48 (20)	355 (22.4)		67 (18)	331 (23.1)		77 (19.5)	320 (22.9)	
Ref: $50,001+	34 (14.2)	392 (24.7)		54 (14.5)	369 (25.8)		95 (24.1)	326 (23.3)	
Employment									
Ref: Working	69 (26.4)	678 (38.8)	**0**	110 (27.6)	631 (39.8)	**<0.0001**	150 (34.6)	588 (38.2)	**0.1**
Disabled	88 (33.7)	418 (23.9)		143 (35.8)	353 (22.3)		118 (27.2)	376 (24.4)	
Student	39 (14.9)	233 (13.3)		44 (11)	227 (14.3)		51 (11.8)	220 (14.3)	
Other	65 (24.9)	417 (23.9)		102 (25.6)	373 (23.5)		115 (26.5)	356 (23.1)	
Marital status									
Married/Living as married	32(13.0)	281(16.7)	**0.2**	60(15.6)	251(16.5)	**0.1**	83(19.4)	223(15.2)	**0.06**
Divorced/Separated/Widow	12(4.9)	108(6.4)		33(8.6)	85(5.6)		30(7.0)	86(5.9)	

Ref: Never married	203(82.2)	1292(76.9)		292(75.8)	1182(77.9)		314(73.5)	1158(78.9)	
Diabetes "No"	247 (96.5)	1,695 (97.5)	**0.4**	379 (95.9)	1,538 (97.7)	**0.06**	416 (96.3)	1,493 (97.6)	**0.12**
Ever treated for depression "No"	148 (59)	1,305 (76.2)	**<.0001**	193 (50)	1,241(79.9)	**<0.0001**	256 (61.1)	1,171 (77.4)	**<.0001**
SCD dx									
Ref: SS/Sβ^0	194 (73.5)	1,288 (72.6)	**0.6**	287 (70.9)	1,173 (72.9)	**0.1**	297 (67.5)	1,155 (73.9)	**0.02**
Thalassemia									
SC	57 (21.6)	372 (21)		83 (20.5)	342 (21.3)		113 (25.7)	310 (19.8)	
Disease Modifying Therapies "yes"	175 (68.4)	1,124 (64.2)	**0.2**	260 (65.3)	1,020 (64.4)	**0.7**	258 (59.9)	1,015 (65.8)	**0.02**
# of Access/Accommodations/Insurance barriers to care									
Ref: 0-1	222 (84.1)	1,643 (92.5)	**<0.0001**	347 (85.7)	1,498 (93.1)	**<0.0001**	377 (85.7)	1,461 (93.4)	**<0.0001**
2 or more	42 (15.9)	133 (7.5)		58 (14.3)	111 (6.9)		63 (14.3)	103 (6.6)	
# of individual barriers to care									
Ref: 0-1	232 (87.9)	1,691 (95.2)	**0.05**	361 (89.1)	1,538 (95.6)	**<0.0001**	389 (88.4)	1,501 (96)	**<.0001**
2 or more	32 (12.1)	85 (4.8)		44 (10.9)	71 (4.4)		51 (11.6)	63 (4)	
ASCQ-Me Pain episodes frequency score									
Mean(SD)	51.7 (9.8)	48.9 (11.2)	**<0.0001**	52.8 (9.8)	48.3 (11.2)	**<.0001**	51.7 (10.2)	48.5 (11.2)	**<0.0001**
Median	51.8	51.8		55.7	51.8		55.7	51.8	
ASCQ-Me Pain episodes severity score									
Mean (SD)	51.6 (8.9)	50.7 (9.7)	**0.2**	52.5 (8.4)	50.4 (9.9)	**<0.0001**	52.7 (8.5)	50.2 (9.9)	**<.0001**
Median	52.3	52.3		54.6	52.3		54.6	52.3	
Expanded ASCQ-Me SCD-MHC score - 13 items*									

Low (0-2)	33 (13.8)	392 (23.9)	**<0.0001**	53 (14.4.)	369 (24.8)	**<0.0001**	82 (20.1)	337 (23.4)	**0.008**
Medium (3-4)	86 (35.8)	642 (39.1)		114 (30.9)	606 (40.7)		142 (34.8)	577 (40)	
High (>4)	121 (50.4)	606 (37)		202 (54.7)	514 (34.5)		184 (45.1)	527 (36.6)	

Figure 1. Conceptual Model

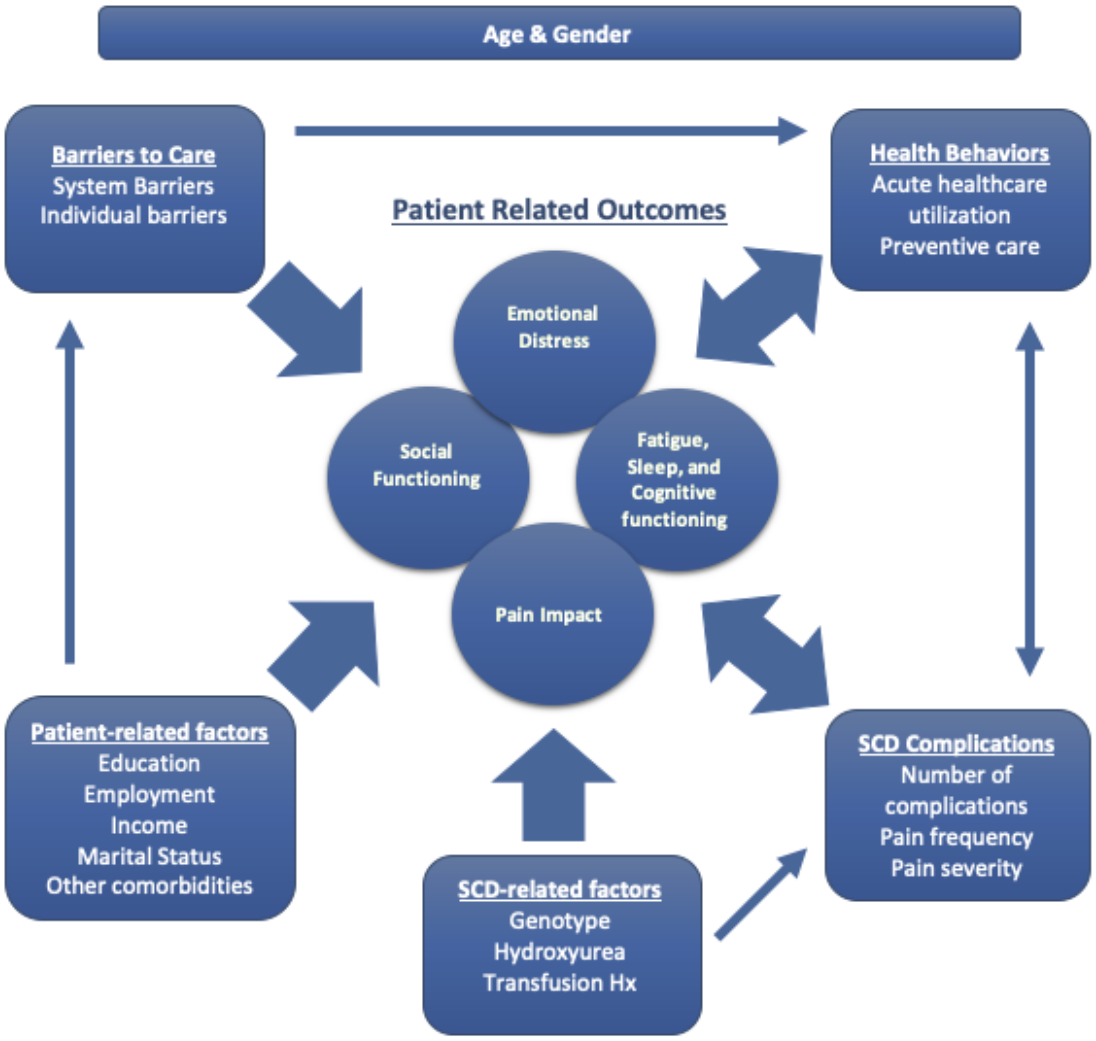

Figure 1. Conceptual model for inter-relations of patient reported outcomes (PROs) in sickle cell disease (SCD). The model includes the inter-relations of four PRO groups (emotional distress, social functioning, pain impact, and fatigue, sleep and cognitive functioning) with health behaviors (acute healthcare utilization and preventive care), SCD complications (number of complications and pain frequency/severity), SCD related factors (genotype, hydroxyurea, chronic transfusion history), patient related factors (education, employment, income, marital status, diabetes and depression) and barriers to care (systemic and individual). All inter-relations are adjusted for age and gender identity.

Figure 2. SCDIC Flow Diagram

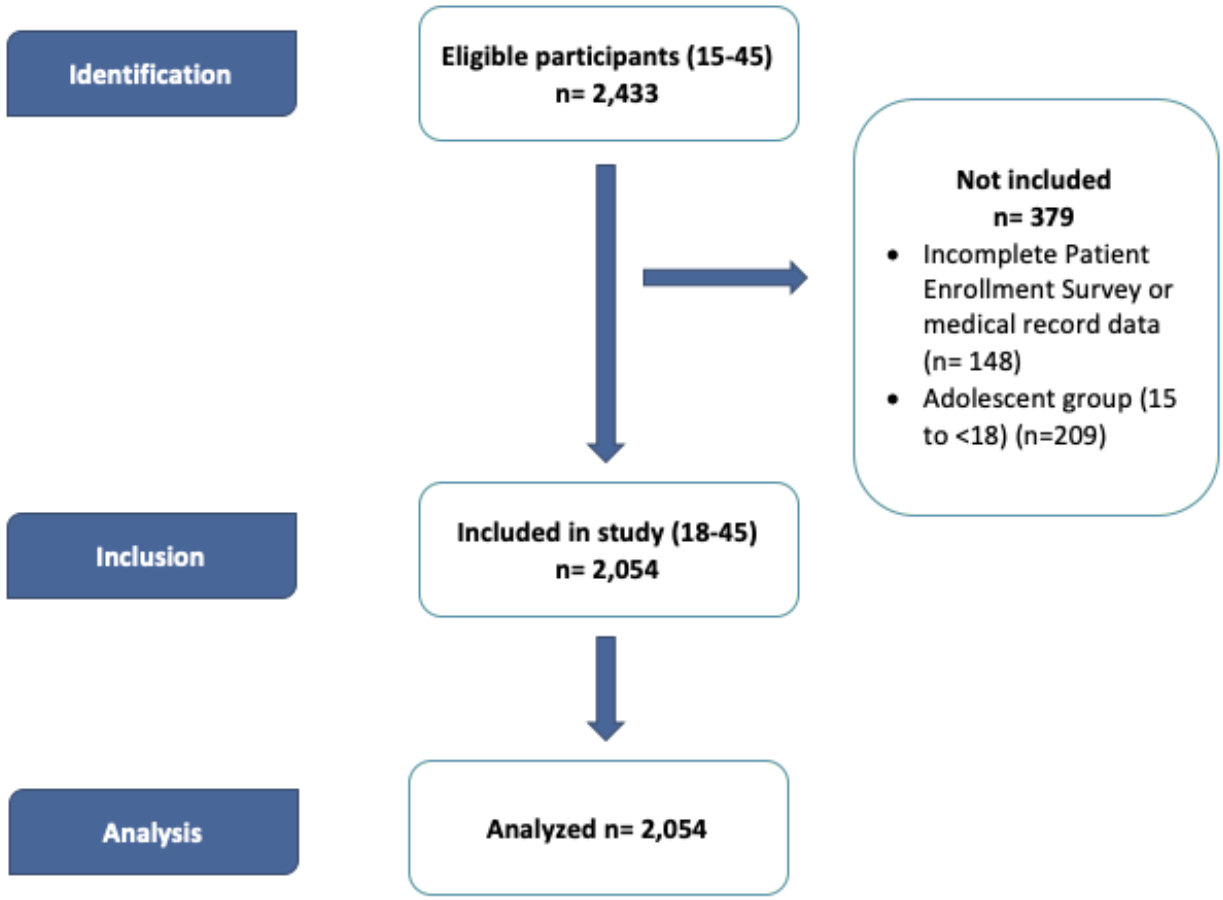

Figure 2 illustrates the process by which our research team came to our to include 2,045 adults 18-45 from the SCDIC participant pool. As noted above, we removed adolescents (< age of 18) and participants with incomplete data from our study.

Figure 3. Distribution and variability in T Scores for Patient Reported Outcomes

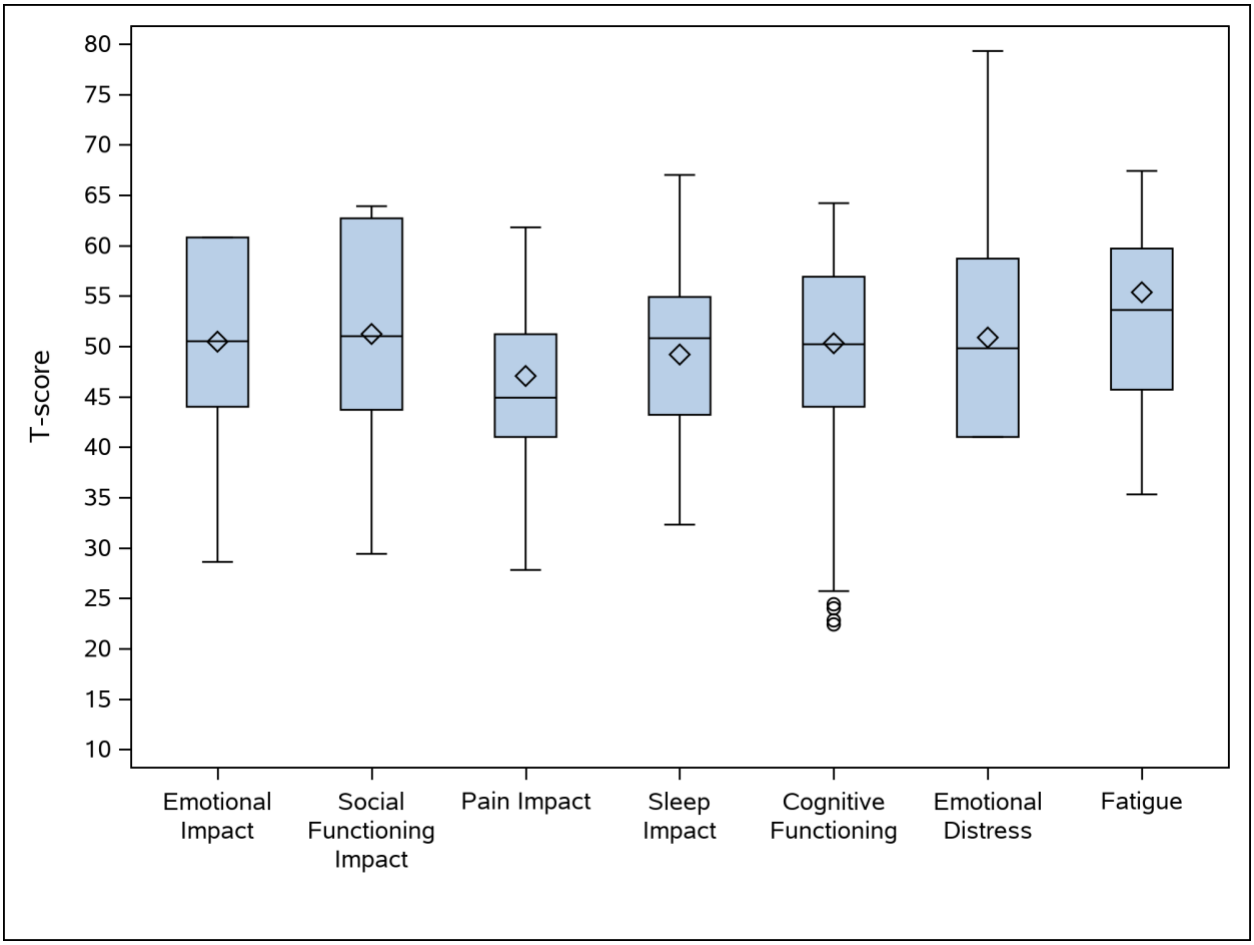

Figure 3 reflects the distribution of T-scores for the seven patient reported outcomes (PROs). For ASCQ-Me® Emotional, Social Functioning, Pain and Sleep Impact and for Neuro-QoL Cognitive Functioning, higher scores indicate better functioning. For PROMIS® Emotional Distress and Fatigue/Tiredness, higher scores indicate worse functioning.

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