THE LIVING WITH SICKLE CELL QUESTIONNAIRE:
PSYCHOMETRIC PROPERTIES OF A NEW DISEASE- SPECIFIC SELF-REPORT MEASURE OF HEALTH-RELATED QUALITY OF LIFE FOR PEDIATRIC SICKLE CELL DISEASE

By

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A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy
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The Living with Sickle Cell Questionnaire: Psychometric Properties of a New Disease-Specific Self-report Measure of Health-related Quality of Life for Pediatric Sickle Cell Disease

Doctor of Philosophy 2018
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Abstract

Health-related quality of life (HRQoL) remains a relatively new area of investigation in pediatric sickle cell disease (SCD). The purpose of this study was to determine the reliability, validity, and sensitivity to change of the Living with Sickle Cell Questionnaire (LSCQ), a new disease-specific HRQoL self-report instrument for children and adolescents with SCD. The LSCQ was constructed using a ‘clinimetric’ approach, which assigned items identified as important by patients to one of four traditional domains of HRQoL: Somatic Sensation, Cognitive/Psychological Functioning, Social Functioning, and Physical Functioning. Self-report versions of the PedsQL, a generic HRQoL questionnaire for children and adolescents, were co-administered in counterbalanced fashion to help establish questionnaire properties.

One hundred children and adolescents with SCD (mean age: 11.7 years) participated in the study at two time points approximately two weeks apart. At the second visit, patients were asked to estimate change in their overall health since the first administration. Parents provided demographic information. High internal consistency (Cronbach’s alpha > .70) was found for
each LSCQ domain at both timepoints. The LSCQ instrument’s sensitivity to patient-reported change in health between testing timepoints was only weakly demonstrated.

Child demographic and disease-related factors predicted LSCQ Total Score and PedsQL About My Feelings and About School scores at Time 2 only. Confirmatory factor analyses performed at Time 1 and Time 2 showed high intercorrelations among items belonging to the same parent domain for the four-factor traditional HRQoL model, but indicated poor model fit at both time points. Follow-up Principal Component analyses for the LSCQ computed at Time 1 and Time 2 yielded four-factor solutions that accounted for 68% and 71% of the variance explained, respectively, but did not confirm the hypothesized four-domain generic HRQoL model. Rather, the four factors organized around themes of treatment, impact of fatigue, and pain and mobility, with some variation at each time point. High item loadings on the first factor suggest that a unidimensional structure might underlie HRQoL as measured by the LSCQ. Hypothesized associations between LSCQ and the PedsQL domains did not emerge as predicted. Findings are discussed in the context of disease-specific HRQoL conceptualization, instrument construction and child response style.
Acknowledgements

I wish to express gratitude to my supervisory committee, chiefly, Dr. Ross Hetherington, in whom I have found a wise and dedicated mentor and friend. He has lent his significant skills as a clinician and researcher to this project along with invaluable support throughout the ups and downs that sometimes accompany graduate study. I thank him wholeheartedly for investing in my learning and professional development.

I also wish to express my deepest thanks to Dr. Patrick McGrath of Dalhousie University who, with Dr. Hetherington, provided me with an introduction to sickle cell disease and quality of life years ago that have lead to so much more. I am grateful to him for having generously lent his expertise to this dissertation project over time. I could not be more grateful to co-supervisor Dr. Ruth Childs of OISE/UT for her belief in the merits of this project and for continuing to lend her support and expertise over years of development. Thank you, Ruth!

Dr. Katreena Scott, Associate Chair of my graduate program and department at OISE/UT, provided enduring support and advocacy during my graduate school journey. I offer her my sincerest thanks for her sound advice and all efforts made my behalf. Dr. Olesya Falenchuk and Dr. Monique Herbert provided expert statistical consultation and assisted me greatly in developing this dissertation story.

Dr. Eunice Jang brought significant expertise and insightful commentary to the thesis, and her participation in my defence was also sincerely appreciated. Dr. Marsha Treadwell of Children’s Hospital Oakland’s Research Institute and External Examiner has been a long admired leader in the clinical and research investigations into biological and psychological aspects of sickle cell disease, and it has been a privilege to have her participation in these final
steps towards completion of the dissertation. I thank Dr. Rick Volpe for his willingness to serve in an alternate capacity at the examination. My thanks also extends to administrators and staff at the University who helped me to see this project through. I owe a special debt of gratitude to Adina Burden and RMV.

I would like to thank dear friends from my graduate program for providing practical and moral support when it was needed most. Dr. Latika Nirula, Anna Macri, and Allia Karim remain close friends from the Master’s program and have been great encouragers of my progress. Fellow program grads Dr. Maureen Jean, Dr. Jenifer Scully, Dr. Tammy Drain, and Dr. Kelley Drummond have remained constant friends and supporters. Dr. Trina Epstein and Dr. Brenda Miles were supporters from the very start. I am grateful for having these special people in my corner and admire the good that they are doing personally and professionally.

I am certainly indebted to the many children, adolescents, parents, clinicians, and volunteers who have so generously welcomed me into their spaces and supported my interests and training through their participation in research, and willingness to share their stories. They have inspired me through their perseverance and resilience. It has been my privilege to know each one and to do my part to raise awareness about sickle cell disease. My thanks to the Sickle Cell Association of Ontario, especially Ms. Lillie Johnson, Advocate; Ms. Lanre Tunji-Ajayi (Sickle Cell Disease Association of Canada); Ms. Doreen Alexander (Sickle Cell Awareness Group of Ontario); Ms. Unita Louis (Children’s Hospital of Eastern Ontario) and the Ottawa Sickle Cell Parent Support Group; hematologists Dr. Melanie Kirby-Allen and Dr. Isaac Odame, and nursing staff Marcia Palmer and Doris Baxter (The Hospital for Sick Children) for their enduring support. We await a cure with hope.
Finally, I would like to express my deepest appreciation to my mother, Olveta Newton, whose unwavering support, faith and belief in me has truly helped to make all things possible. I dedicate this work to my parents, family, and friends for offering unflagging support along the way, and to those in the sickle cell disease community.
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Chapter 1: Introduction

Examination of the nature of sickle cell disease, its course, complications, and treatment is essential starting point if its impact on the developing child’s quality of life is to be understood. The following section is intended to provide an overview of this inherited chronic condition.

Sickle Cell Disease: An Overview

**Prevalence.** Sickle cell disease (SCD) is a group of inherited blood disorders. There are approximately 5000 children and adults in Canada with SCD (Sickle Cell Disease Association of Canada, 2014). In the United States, where longstanding state and national registry records are available, the number of affected individuals is estimated to range from 70,000 to 100,000 persons (National Heart, Lung, and Blood Institute, 2014). Individuals of Black or African descent make up the greatest proportion of affected persons, with a diagnosis of SCD given in 1 of every 500 births; however, individuals of Hispanic or southern European ancestry, Mediterranean, Middle Eastern, and Asian Indian descent are also represented in prevalence estimates (Centers for Disease Control, 2015; Farrell et al., 2010). Indeed, SCD is found worldwide, with concentrations in the Americas, Caribbean, Central and South Asia, the Arabian Gulf, and Africa (Serjeant, 2013). Migration and re-settlement patterns appear to partially account for the gene’s global distribution patterns.

**Pathophysiology and course.** Although long-recognized as a condition with associated morbidity and mortality by African peoples and a familiar aspect of West African cultural descriptions and vocabulary (Konotey-Ahulu, 1973), SCD was first reported in the American scientific literature in 1910 following microscopic observations of distorted, unusual ‘sickle’ shaped red blood cells (Herrick, 1910). By the mid-twentieth century, it was recognized as a ‘molecular disease’ arising from a recessively-inherited autosomal genetic mutation. Sickle cell
disease is thought to be the most common single-gene defect (Charache, Lubin & Reid, 1989; Debaun & Vichinsky, 2007).

Sickle cell disease arises from a point mutation (substitution of the amino acid valine for glutamic acid) on the β-globin chain (Pauling, Itano, Singer, & Wells, 1949). The disease is pleiotropic, affecting multiple organ systems through its processes. The gene for sickle hemoglobin (HbS) may occur in combination with the gene for normal adult hemoglobin (HbAS genotype) to produce a typically asymptomatic phenotype referred to as sickle cell ‘trait’. It may also be expressed as a compound homozygote state (HbSS) or as a compound heterozygote in combination with other hemoglobin variants, such as the thalassemias (for example, HbSC, HbSβ°Thal). Each genotype has a characteristic symptomology and course, but the variability observed in phenotypic or clinical expression of SCD suggests influence of epigenetic factors (Smith-Whitley & Pace, 2007). Sickle cell disease is found worldwide and thought to be most prevalent in areas where malaria is endemic, as having the single HbS gene or sickle cell trait confers some protection against contracting the illness (Serjeant, 2001, 2013).

The sickle cell mutation alters hemoglobin production and changes affinity of the red blood cells for oxygen. Due to reduced solubility of sickle hemoglobin under hypoxic conditions, there is clumping of the hemoglobin into a fibrous form within the red blood cells (Evans & Badman, 2007). Rigid, misshapen red blood cells result and fewer of the discoid, flexible red blood cells produced by healthy individuals with normal hemoglobin are present. Sickled red blood cells are also ‘sticky’ and adhere to blood vessel walls as well as to one another. This impedes blood flow through the various vascular systems of the body, particularly the small vessels (a process termed vaso-occlusion), which compromises integrity of blood vessel walls and reduces optimal supply of blood to the vital organs (Ballas, 1998). Vaso-
occlusive episodes, commonly known as ‘crises’, might occur multiple times a year (five to seven times, on average) and can be of several days’ duration (Lemanek & Ranalli, 2009). Oxygen deprivation of the tissues and organs resulting from vaso-occlusive episodes is a primary cause of the severe and debilitating painful episodes that are hallmarks of SCD (Reid & Rodgers, 2007), as is cumulative end-organ damage affecting structures such as the kidneys and lungs (Serjeant, 2013). Vaso-occlusive episodes can occur in all areas of the body, can affect any of the vital organs, and are a significant cause of Emergency Room visits, admissions to hospital, and missed school or work (Dale, Cochran, Roy, Jernigan, & Buchanan, 2011).

Complications arising from sickle cell disease

**Stroke.** Occlusion of the intracranial vessels due to sickling events places individuals with SCD at risk for debilitating neurological events such as stroke. Overt stroke occurs in 11% to 20% of children with the severest form of SCD by early adolescence (Ohene-Frempong, Weiner, & Sleeper, 1998). Risk of recurrence within three years post-stroke is estimated to be 50% to 70% in the absence of preventative steps. It is estimated that 30% to 40% of children and adolescents with SCD have experienced symptoms of ‘silent’ stroke, with evidence of stroke on neuroimaging studies in the absence of frank neurological signs or symptoms. There is high risk of recurrence of stroke without initiation of chronic blood transfusion therapy as a preventative strategy (Quinn & Buchanan, 2007).

**Acute chest syndrome.** The acute chest syndrome typically arises from complex interactions of factors that may include infection, embolism, or a lung-based infarct/sickling event. It is a very severe, rapidly progressing disease complication that can result in respiratory failure within hours of diagnosis and is thought to be the most frequent cause of death in individuals with SCD (Quinn & Buchanan, 2007; Vichinsky et al., 2000). Complications of SCD
also include chronic anemia resulting from rapid destruction and turnover of sickled red blood cells, post-infection red blood cell loss, and splenic sequestration events. In addition, dehydration, fatigue, nutritional deficiencies, and compromised immunity due to non-function of the spleen are frequently-reported difficulties (Ballas, 1998). During adolescence, nocturnal enuresis (which may not resolve until young adulthood), priapism in males, avascular necrosis of the femoral head (affecting mobility), delays in growth and pubertal development, and leg ulcers may become especially pronounced (Serjeant, 2013). These complications of SCD can affect social perception and self-concept. Bilateral and symmetrical bone pain is particularly problematic for males during adolescence (Baum, Dunn, Maude, & Serjeant, 1987). Although disease severity and course may vary among individuals with SCD, the disease’s effects are lifelong and are typically disruptive to development and well-being across the lifespan (McClellan, Schatz, Sanchez, Roberts, 2008). In recognition of the severe toll of SCD on population health, the disease was formally identified as a public health priority by the U.S Government in 1972. The legislation tabled (Sickle Cell Anemia Control Act, 1972) outlined a strategy for allocation of funding for treatment and further research towards a cure. The Act was also the foundation for establishment of comprehensive treatment centres, which supported multi-site research studies (e.g., the Cooperative Study of Sickle Cell Disease) in addition to providing specialized care (Gaston & Rosse, 1982).

**Treatment**

Bone marrow transplantation is the only currently known cure for SCD. Only a small minority of patients are eligible for this treatment (Ioannone, Ohene-Frempong, Fuchs, Cassella, & Chen, 2005; Panepinto et al, 2007). Gene therapy appears to offer the greatest promise for tailoring and optimization of treatments, and perhaps ultimately, a universal cure (Smith-Whitley & Pace, 2007). Life expectancies for individuals with SCD have increased over the decades to
median ages of 42 years for men and 48 years for women with HbSS disease, largely as a result of initiatives such as newborn screening, introduction of penicillin prophylaxis in babies and young children, and pneumococcal vaccination to reduce early-life mortality due to infection (Platt et al., 1994; Quinn & Buchanan, 2007). Increased availability and improved efficacy of interventions has supported greater survivorship beyond childhood into adulthood. An estimated 90% of individuals with SCD survive beyond childhood in the United States and the United Kingdom (National Heart, Lung, and Blood Institute, 2014). Modern treatments have decreased disability and lost time at school, work, or desired activities due to illness. Treatments such as hydroxyurea or chronic blood transfusion are intended to modify (decrease) the proportion of sickle hemoglobin content for individuals with severe disease and frequent pain or complications. Chelation therapy is required for some patients to treat iron overload in organs arising from chronic blood transfusion regimens. Patients may experience treatments as burdensome. Some treatments produce bothersome side effects and are ineffective, unsuitable for, or unavailable to some patients (for example, bone marrow transplantation).

**Somatic sensation (pain experience) in sickle cell disease**

Severe bodily pain can be chronic, acute, or episodic in presentation in SCD (Lemanek & Ranalli, 2009). Pain is one of the most salient features of SCD for patients, with chronic pain typically underreported and therefore, frequently undertreated (McGann, Nero, & Ware, 2013; Solomon, 2008). Pain episodes are the most common single reason that medical care is sought by patients (McClellan, Schatz, Mark, et al., 2009). These episodes are a primary cause of disability in individuals with SCD, interfering with sleep, mobility, and other aspects of physical functioning (Eaton, Haye, Armstrong, Pegelow, & Marshall, 1995). They often co-occur with or precede serious complications of SCD such as vaso-occlusive episodes, acute chest syndrome, or stroke (Benjamin & Payne, 2007).
Onset of sickle cell pain may occur as early as the first 6 months of life. Frequency of pain generally increases across childhood and adolescence and stabilizes by adulthood (Platt et al., 1994). The homozygous form of SCD (HbSS disease) and variants of the HbSβ Thalassemia genotype are associated with the greatest disease severity (Platt et al., 1991; Serjeant et al., 1994). The HbSC subtype is often associated with pain episodes that are less severe, but it is typically accompanied by characteristic complications, the most frequently occurring of these being avascular necrosis of the hip joint, retinopathy, and splenic sequestration (Koduri, Agbemadzo, & Nathan, 2001).

The large-scale Cooperative Study of Sickle Cell disease, which tracked patients prospectively, found that pain rates were typically low during the first two to three years of life but increased with age. Children with homozygous SCD, or HbSS disease, had experienced a pain episode by a mean age of 4.9 years, while children with HbSC disease had experienced a pain episode by a mean age of 7.1 years (Platt et al., 1991). The study also found that pain rates (number of reported episodes) for children nine years of age and under tended to be lower than those of older children (Platt, et al., 1991). Researchers noted the variable course of SCD. Some patients thought to have milder forms of SCD, such as HbSC, reported a greater number of pain episodes than those believed to have the most severe manifestation of the disease (HbSS disease), with approximately 33% of all pain events attributed to only 5.2% of patients with HbSS disease (Platt et al., 1991). A key pain modifier appears to be fetal hemoglobin, present in the newborn period and first two years of life, and its role in reducing the vaso-occlusive action of HbSS. An increase in fetal hemoglobin levels in the blood is induced by the action of hydroxyurea medication. This medication has been shown to significantly reduce frequency of
pain episodes and to help prevent them in patients with HbSS disease (Bridges et al., 1996; Charache et al., 1995).

Pain events can be experienced anywhere in the body. Dampier and colleagues (2002) noted that the legs, hips and back are the most frequently-reported pain sites. Although fever, dehydration, stress, and fluctuations in extreme cold or hot temperatures may precipitate pain events, the cause of pain onset is not always readily identifiable or predictable (Smith-Whitley & Pace, 2007). At its most severe, sickle cell pain has been described as comparable to cancer pain (Ballas, 1998). Children’s pain episodes have been estimated to occur with a frequency of approximately 1 in 14 days and to last 2.5 days, on average (Fuggle, Shand, Gill, & Davies, 1996).

Pain intensity fluctuates over time. Female sex has been found to be a risk factor for pain, as were emotional and physical stress (Diggs, 1965; Nadel & Portadin, 1977), external conditions that promote sickling events (e.g., low-oxygen/apneic environments), and sudden climatic changes (e.g., extremes of heat or cold; Sergeant & Serjeant, 2001; Swain, Mitchell, & Powers, 2006). The majority of pain events are treated at home using analgesics, heat, and rest (Brown, Connelly, Rittle, & Clouse, 2006; Fuggle et al., 1996); however, painful crises are also a major contributor to emergency room visits and hospital stays for many children and adolescents with SCD (Dale et al., 2011; Eaton et al., 1995). Pain may not resolve by time of discharge from hospital for pain-related difficulties and may continue to affect physical functioning and timing of return to school for several days afterwards (Brandow, Brousseau, & Panepinto, 2008). Prompt management of pain with appropriate pharmacological agents, including opiates such as morphine, is required treatment for the most severe episodes (Platt et al., 1991; Swain et al., 2006).
Psychosocial functioning in pediatric sickle cell disease

The psychological impact of SCD in children and youth is reflected in reports of increased stress risk and adjustment difficulties (Gustafson, Bonner, Hardy, & Thompson Jr., 2006); depression, hopelessness, and anxiety (Anie, 2005; Brown et al., 1993; Scott & Scott, 1999); poor sense of control, reduced self-esteem and self-concept (Burlew, Telfair, Colangelo, & Wright, 2000; Thompson, Gil, Keith, Gustafson, George, & Kinney, 1994), and body image disturbance (Morgan & Jackson, 1986). There is mixed evidence to support externalizing problems (chiefly, oppositional behaviour or conduct problems) in a subset of youth with SCD that are in the clinical range of concern, beyond what is typical of age peers, and impairing of daily functioning (Barbarin, 1999; Hurtig & White, 1986; Kell, Kliewer, Erickson, & Ohene-Frempong, 1998; Thompson et al., 1998). The literature also reports potentially deleterious effects of pediatric SCD on family functioning in terms of increased parenting stress, coping difficulties of children and parents, and well-sibling adaptation challenges (Brown et al. 2000; Thompson, Gustafson, & Gil, 1995). Difficulty with development and maintenance of friendships, particularly after periods of absenteeism from school, and reduced participation in social activities with peers has also been reported in pediatric SCD studies (Barbarin, 1994; Gentry, Varlik, & Dancer, 1998).

Cognitive and academic functioning in pediatric sickle cell disease

Cumulative effects of chronic hypoxia, transient vaso-occlusive events, subtle and overt neurological events such as stroke, and environmental factors, including low socioeconomic status (Sterling, Peterson, & Weekes, 1997), have been linked to decrements in cognitive performance and academic achievement in children and youth with SCD. Findings have included reduced IQ scores (Armstrong et al., 1996; Wang et al., 2001); increased school absenteeism; higher utilization of special education services (Peterson, Palermo, Swift, Beebe, &
Drotar, 2005; Shapiro et al., 1995); below-average academic achievement and higher rates of grade retention (Brown et al., 1993; Schatz, Craft, Koby, & DeBaun, 2000; Swift et al., 1989); more impaired executive functioning and other specific cognitive deficits (Wasserman, Wilimas, Fairclough, Mulhern, & Wang, 1991) compared to typically-developing peers.

**Physical functioning**

The disease process in children and youth with SCD produces delays in physical development that manifest as thin limbs, slim build, lower height and weight than typical, low body fat, and delayed sexual maturation (Serjeant, 2013; Kramer, Rooks, Washington, & Pearson, 1980). These features may therefore differentiate affected individuals from age peers by appearance in marked ways. While the number of studies focusing on physical functioning in pediatric SCD is limited, there is evidence that pain affects upper and lower body movement, participation in everyday activities such as personal care, and comfortable movement through their environment (Zempsky, et al., 2014). The dehydration and fatigue associated with SCD processes also have a direct impact upon physical functioning.

**Summary**

The effects of SCD are pervasive, influencing individual well-being in domains of somatic sensation and physical, cognitive/psychological, and social functioning. Individual differences in disease severity and treatment efficacy and response may modulate the impact of SCD on functioning; however, affected individuals typically experience significant life disruption as a result of their illness. The impact of SCD is experienced beyond the affected individual as well. The largely unpredictable nature of symptoms and potential for disruption of routines of the home may have significant consequences for caregivers and other family members, including healthy siblings. Investigations designed to increase understanding of
chronic disease impact and the influence of disease complications, such as pain, on multiple aspects of functioning with a view to improving treatment and optimizing well-being are therefore of great value.

**Health-related quality of life (HRQoL)**

The following section will review concepts in HRQoL, its measurement, and its usefulness for determining well-being in pediatric chronic disease.

**Definition and conceptual framework.** Health-related quality of life concerns the specific impact of health on the individual’s ability to carry out tasks of daily living important to him or her (Juniper, Guyatt, Feeny, Griffith, & Ferrie, 1997; Spieth & Harris, 1996). The World Health Organization’s (WHO) expanded definition of health as “not merely the absence of disease, but the presence of physical, mental, and social well-being” (WHO, 1948) has strongly influenced development and conceptualization of the HRQoL construct. There is no single agreed-upon definition of HRQoL; however, most definitions incorporate information about disease state, physical symptoms, functional status, psychological, and social functioning domains from the WHO definition for comprehensiveness (Levi & Drotar, 1998). Health-related quality of life is a subjective concept, distinct from related terms such as functional status or performance that typically measure the individual’s *demonstrated* ability to perform tasks (capacity) rather than their *perceived* ability to do so. A discrepancy between demonstrated and perceived ability may exist due to physical and psychological factors (Wilson & Cleary, 1995). Health-related quality of life is therefore intended to reflect an individual’s subjective views and expectations regarding their own well-being (Knight, Burwinkle, & Varni, 2003) rather than
external valuations or priorities, such as those of caregivers, family members, or the broader community.

While the components of HRQoL may vary, there is some consensus that evaluation of four broad areas or domains — physical functioning, cognitive/psychological functioning, social interaction and somatic sensation, each contributing to overall quality of life — is appropriate for most studies (Fayers & Mackin, 2000; Schipper & Clinch, 1988; Schipper, Clinch, & Olweny, 1996; Spieth & Harris, 1996).

In addition, school functioning is often included as a dimension in measures related to child HRQoL, such as the PedsQL Generic Core Scales 4.0 (Varni, Seid, & Kurtin, 2001) and the Child Health Questionnaire (Landgraf, Abetz, & Ware, Jr., 1996). Health-related quality of life (HRQoL) is therefore regarded as a multidimensional construct (Wallander, 2001).

Common concepts in Health-related Quality of Life. Health-related quality of life instruments have multiple uses, including determination of disease burden, evaluation of impact and efficacy of treatment interventions, and assessment of health service use (Brandow, Brousseau, Pajewski & Panepinto, 2010; Matthews & May, 2007). These instruments are useful in clinical trials or monitoring at clinic to evaluate treatment efficacy among measures of similar effectiveness (Eiser & Morse, 2001; Testa, Anderson, Nackley, & Hollenberg, 1993; Testa & Simonson, 1996) and to conduct resource allocation planning. They are also valuable tools for enhancing clinician-patient communication (Deyo & Patrick, 1989). Use of questionnaires may bring forward concerns that parents and children might not otherwise raise on their own during clinic visits and routine interviews with staff during those visits (McClellan, Schatz, Sanchez, & Roberts, 2008). These measures are therefore key tools for understanding health experiences from the perspective of the individual affected, particularly where the impact of chronic disease
is concerned (Brandow, Jirovec, & Panepinto, 2010). Regardless of manner of use, the greatest potential value of HRQoL measures as a form of ‘patient reported outcome’ may lie in their potential ability to reveal patient appraisals and perspectives and to capture individual experience of disease burden (Panepinto & Bonner, 2012). Measurement and monitoring also provide opportunities to identify areas of need in childhood and, with the benefit of appropriate, tailored interventions, can increase potential for better HRQoL into adulthood (Dale et al., 2011).

The type of HRQoL measure selected (i.e., health utility, global rating, profile; generic or disease-specific; proxy or self-report) depends upon the goals of assessment. Generic measures offer comprehensiveness of content and facilitate comparisons across patient populations (Spieth & Harris, 1996), but may lack the specificity, responsiveness, and inclusion of all health dimensions of interest for a particular condition (Kane & Radosevich, 2011; Kessler & Mroczek, 1995). Disease-specific measures are typically population-specific measures, include items and domains specific to and most salient for a particular health condition, and may be used to maximize validity, sensitivity and specificity of measurement (Eiser & Morse, 2001; Wright, Rudicel, & Feinstein, 1994). Disease-specific measures are particularly valuable for use in clinical contexts, where they may provide information about responsiveness of specific aspects of disease to treatment intervention (Deyo & Patrick, 1989). A widely-held view is that generic and specific measures should be used jointly to afford the most comprehensive assessment of HRQoL in patients (Aaronson, 1988; Eiser & Morse, 2001; Garratt, Schmidt, Mackintosh, & Fitzpatrick, 2002).

Although HRQoL was first conceptualized in adults, it has received increased attention in studies of pediatric populations. A major review located 94 published HRQoL instruments for
children, over half of these developed for specific health conditions (Solans et al., 2007). Measures of HRQoL are not equivalent for children and adults. Child measures must consider a number of factors, including: developmental goals appropriate for each stage (Rosenbaum, Cadman, & Kirpalani, 1990); differential impact of disease across development and cumulative impact of illness over time (Garrison & McQuiston, 1989); cognitive and academic issues related to illness (Eiser & Jenney, 1996); child cognitions about health and illness, and developmental understanding of these terms (McGhee, 1994); self-concept and ability to reflect upon and report self-states (Cremeens, Eiser, & Blades, 2006; Eiser & Morse, 2001; Flavell, 1999); valued activities and the opportunity to participate in them (Eiser & Jenney, 1996); and impact of disease on family and peer relationships (Eiser & Morse, 2001; Wallander & Varni, 1998). In the past, proxy (caregiver, teacher) reports of HRQoL were typically sought for children under eight years of age due to concerns about their ability to complete such measures; however, discrepancies that may exist between proxy and child self-reports, and strong interest in understanding the impact of disease from a child’s perspective, makes inclusion of self-report data preferable (Eiser & Morse, 2001). Presenting HRQoL measures in child-friendly formats by ensuring that reading level is appropriate, and through inclusion of engaging graphics, intuitive scaling, relatively brief recall periods, reasonable administration length, and computerized presentation, can reduce questionnaire response burden and enhance children’s ability to provide their own self-ratings (Streiner & Norman, 2003).

**Considerations in health-related quality of life measure development.** Approaches to health-related quality of life measure development generally incorporate stages of item generation (literature review, informants, and focus groups as resources), item reduction through statistical methods, and pilot testing of the new instrument. Different approaches to
measure construction may yield different outcome measures or measurement tools (Juniper, Guyatt, & Jaeschke, 1996). Ensuring that the final scale reflects items of clinical importance to patients requires careful selection of methods and taking steps to reduce exclusion or loss of the most relevant items. An influential approach to development of disease-specific health-related quality of life instruments has been the impact method (Juniper et al., 1996), which determines component questionnaire items based on patient-assigned item weighting. Weightings are derived from frequency of a candidate item’s endorsement and importance ratings assigned by patients. Item reduction methods such as factor analysis may exclude clinically important items due to low factor loadings (Juniper et al., 1996). To demonstrate readiness of newly-developed HRQoL measures for clinical use, relevant psychometric properties of reliability (internal consistency, test-retest), validity evidence with regard to representativeness of content and data to construct measured, and sensitivity (ability to detect clinically meaningful change) must be demonstrated (Eiser & Morse, 2001; Lohr, 2002; Solans et al., 2007).

**Measuring psychometric properties of HRQoL instruments.** Establishing the psychometric properties of HRQoL instruments ensures that targeted concepts for study are indeed the ones being measured by the tool (Panepinto & Bonner, 2012). Panepinto and Bonner (2012) note that in HRQoL studies involving pediatric and adult patients with SCD, validity, internal consistency, reliability, and sensitivity or responsiveness to change in HRQoL (over time, or as a result of intervention) are the properties most typically addressed using generic HRQoL instruments, with test-retest reliabilities reported less often. While establishing reliability and validity are essential starting points for ensuring that an HRQoL instrument is psychometrically sound, ensuring instrument sensitivity or responsiveness is important if changes in the disease process or related factors are to be accurately captured (Pal, 1996). A
common source of evidence used to support the validity of use of a given instrument is use of a well-established and widely used ‘gold standard’ HRQoL measure as a reference. Generic and disease-specific measures may not work identically, sometimes revealing differences in underlying domain structure that reflects content (item) differences. When generic instruments such as the PedsQL or the SF-36 are used with patients with SCD, for example, there has been evidence of a different organization or factor structure of items in a disease-specific context than the original structure theorized for the measure in the generic context (Asnani, Lipps, & Reid, 2007; Panepinto, Pajewski, Foerster et al., 2008).

Health-related Quality of Life and pediatric sickle cell disease. Interest in measuring HRQoL in both pediatric and adult SCD has undergone dramatic growth within the past decade in the Canada, the United States, and Europe (Panepinto & Bonner, 2012), perhaps in tandem with improved availability and efficacy of interventions and treatments that can prolong life and lessen impact of disease. Published studies of HRQoL in adults with SCD using qualitative methods or generic assessment measures have identified severely compromised health in individuals with SCD relative to both healthy and other medically ill populations (McClish et al., 2005), significant psychological, social, physical, and occupational burden of disease (Thomas & Taylor, 2002), and interference of aspects of disease management (for example, iron overload therapies following chronic transfusion; Abetz, Baladi, Jones, & Rofail, 2006) on HRQoL. Improvements in health perceptions, pain recall, and social functioning aspects of HRQoL in responders to hydroxyurea treatment were reported in a major multicentre clinical trial (Ballas et al., 2006). Hydroxyurea treatment has been recommended for treatment of children with SCD and frequent episodes of pain but has not been extended to all patients who might benefit due to variation in patient or parent acceptance of the treatment, reported barriers to standard usage by
physicians, including concerns about long-term drug safety in children, and factors such as cost (Brandow, Jirovec, & Panepinto, 2010).

Published studies with a focus on HRQoL in children with SCD have used qualitative, generic, proxy (parent report), and self-report methods of assessment. An overview of studies reporting child and adolescent self-report data are summarized in Appendix A.

Perception of overall health is poorer in children and adolescents with SCD relative to healthy controls (Panepinto et al., 2005). Reports examining overall HRQOL in children and adolescents with SCD note a trend towards worsening of symptoms with increasing age (Dampier et al., 2007). School-age children with SCD report overall HRQoL scores comparable to those of age peers undergoing cancer treatment (Dampier et al., 2007). Effects of sickle cell disease have been shown to influence quality of life in children and adolescents in the four major domains of HRQoL: somatic sensation (pain experience), physical functioning, cognitive/psychological functioning, and social functioning.

**Somatic sensation/pain experience.** Frequent pain (Fuggle et al., 1996; Palermo & Kiska, 2005; Panepinto, O’Mahar, DeBaun, Loberiza, & Scott, 2005; Patel & Pathan, 2005); pain of longer duration than healthy controls (Fuggle et al., 1996; Stegenga, Ward-Smith, Hinds, Routhieaux & Woods, 2004); pain more likely to require treatment with medication than non-SCD pain (Fuggle et al., 1996); pain interfering with sleep (Fuggle et al., 1996; Palermo & Kiska, 2004); and premorbid symptoms predictive of pain episodes (Fuggle et al., 1996) have all been reported in the pediatric SCD literature. The HRQoL of children with moderate to severe SCD has been found comparable to that of children with rheumatologic disorders, frequent migraine and symptomatic fibromyalgia (Dampier et al., 2007). Brandow and colleagues (2010) reported a broad, deleterious impact of acute pain arising from vaso-occlusive episodes on all
aspects of HRQoL. Disease complications such as a history of pneumonia or acute chest syndrome and treatment with chronic transfusion therapy have been associated with reduced HRQoL (Stegenga et al., 2004).

**Physical functioning.** Children with SCD report lower ratings of physical functioning and increased disability compared to healthy peers (Kater et al., 1999; Palermo, Schwartz, Drotar, & McGowan, 2002; Panepinto, O’Mahar, DeBaun, Rennie, & Scott, 2004; Panepinto, O’Mahar, DeBaun, Rennie, & Scott, 2005; Patel & Pathan, 2005). Factors such as older child age, female sex, and number of disease-related complications present have been associated with physical health limitations in SCD (Palermo et al., 2002). Physical functioning difficulties may persist for several days following discharge from hospital for a pain-related admission (Brandow et al., 2008). Physical HRQoL has been found to be better in children with mild disease than those with severe disease (Panepinto et al., 2004) and higher baseline hemoglobin has been associated with better physical functioning and general fatigue scores (Dampier et al., 2007).

**Cognitive/psychological functioning.** Poor schoolwork and increased school absenteeism are commonly reported in pediatric SCD studies (Fuggle et al., 1996; Palermo et al., 2002; Stegenga et al., 2004). Children with SCD may also experience increased behavioural or mental health difficulties compared to healthy controls (Palermo et al., 2002; Panepinto et al., 2005). Emotionally, affected children and youth tend to endorse a greater number of depressive symptoms and more sadness than typically developing controls (Palermo & Kiska, 2005). Higher numbers of reported behavioural comorbidities are associated with poorer overall child psychosocial health and greater parental emotional impact in QoL measures (Wrotniak, Schall, Bault, Blamer, & Stallings, 2014). As has been found for physical functioning outcome, better
school functioning in children with SCD is associated with higher baseline hemoglobin levels (Dampier et al., 2007).

Social functioning. Psychosocial functioning findings have been mixed for children and youth with SCD. It has been reported as an area of greater difficulty for youth with SCD than for their healthy peers (Palermo et al., 2001; Panepinto et al., 2005), with missed social or recreational activities due to pain (Fuggle et al., 1996) and limitations in peer relationships (Palermo et al., 2001; Stegenga et al., 2004) reported. At school, students may perceive themselves to have less support from teachers relative to their classmates (Patel & Pathan, 2005). At home, the significant support needs of a child with SCD may place particular stress upon parent and family functioning (Palermo et al., 2001). Other studies present a more positive view of psychosocial outcomes for children and youth with SCD, reporting comparable social functioning to peers (Kater et al., 1999; Panepinto et al., 2005) and higher baseline mental health than healthy controls, attributed to children’s positive perceptions of their well-being and availability of social support (Wrotniak et al., 2014).

Measuring overall or total HRQoL. In the absence of an available validated, disease-specific measure of HRQoL for pediatric SCD at the commencement of the present study, research studies using validated generic measures of child and adolescent HRQoL were reviewed. Several generic questionnaires have been used to assess HRQoL in pediatric SCD to date, with The Child Health Questionnaire (CHQ; Landgraf, Abetz, & Ware, 1996) and The Pediatric Quality of Life Inventory (PedsQL; Varni, Seid, & Rode, 1999) emerging as the primary assessment tools cited by studies. At time of writing, only the CHQ (CF87 child-completed and PF28 and PF50 parent-completed versions) and PedsQL Generic Core Scales 4.0 had been validated for use with the SCD population. Among the varied findings emerging from
research with the CHQ, lower scores, corresponding to poorer HRQoL, have been reported by parents for children and youth with SCD on domains pertaining to general health, overall physical health, and parental (emotional and time-related) impact when compared to a normative sample (Barakat, Lutz, Nicolaou, & Lash, 2005; Palermo et al., 2002). Good parent-child agreement on HRQoL was observed for physical functioning, behaviour, health and self-esteem reports (Panepinto et al., 2005). Parents reported higher functioning across CHQ subscales for children and youth with milder disease than for those with more severe disease course (Panepinto, O’Mahar, DeBaun, Rennie, & Scott, 2004), and endorsed significant impact of multiple neurobehavioural comorbidities on psychosocial functioning, in particular (Panepinto et al., 2005). Self-reports of children and youth with SCD revealed that they perceived their mental health to be better than healthy peers did (that is, assigned themselves higher ratings and scores), demonstrated typical behavioural functioning for their age group (Panepinto et al., 2005), and reported at least moderate associations between mood symptoms, sleep and HRQoL (Palermo & Kiska, 2004).

While both instruments have strong psychometric properties, the length of the child self-report and parent report versions of the CHQ make in-clinic use impractical. The PedsQL is a briefer instrument and offers an acute (one-week) retrospective period for study. The Acute version of the PedsQL has been used in several cross-condition HRQoL studies, including those involving pediatric SCD patients.

A disease-specific module for pediatric SCD, the PedsQL Sickle Cell Disease Module (Panepinto, Torres, & Varni, 2012) was published some years after initiation of the present study, and therefore could not be administered to participants as part of the validation protocol. Child, adolescent, and adult self-report versions as well as a parent report version are available.
In addition to Total Score, component domains of the module’s child self-report version include: Pain and Hurt, Pain Impact, Pain Management and Control, Worry I, Worry II, Emotions, Treatment, Communication I, and Communication II (Panepinto et al., 2013).

Interpretation and applicability of findings from previous studies of HRQoL in pediatric sickle cell disease is limited by one or more factors referenced in the literature. In terms of study design, use of cross-sectional study designs (Palermo et al., 2001; Panepinto et al., 2004, 2005), small sample sizes, and samples of narrow age range (Patel & Pathan, 2005; Stegenga et al., 2004) have been cited as limitations.

Methodological limitations related to instrument selection include use of non-standardized measures of HRQoL and measures with incomplete HRQoL domain coverage (Fuggle et al. 1996), as well as measures that discriminate poorly between children and youth with different severities of SCD (Wrotniak et al., 2014). Reliance upon proxy (parent) report to the exclusion of child self-report of HRQoL is also cited as a shortcoming of previous work (Dampier et al., 2007; Palermo et al., 2001). Schlenz and colleagues (2012) have also noted that measures used to assess HRQoL in the SCD population may not capture the impact of pain on physical and psychosocial health in a consistent manner, citing differences in pain measurement methods or differences in measure response to pain-related changes in HRQoL as possible causes.

**Rationale for the present study**

To advance the study of HRQoL in pediatric sickle cell disease and provide a complement to exiting generic measures, a reliable, valid disease-specific measure of child and adolescent HRQoL suitable for self-report and able to detect changes in health is needed.
(Palermo et al., 2001; Panepinto et al., 2005). This research aims to address this concern with a validation study of the *Living with Sickle Cell* computer-based HRQoL instrument.
Chapter 2: Method

Participants

Candidates for the study were identified using The Hospital for Sick Children’s Division of Hematology/Oncology database of registered, active patients. The hospital’s Sickle Cell Clinic is the largest specialized centre in Canada. It is considered a treatment ‘hub’ or central point of contact for all pediatric patients with an SCD diagnosis in the region even if care is occasionally accessed at other hospitals or clinics in the Greater Toronto Area.

Inclusion criteria. Patients eligible for recruitment had an SCD diagnosis (that is, any genotype variant including sickle hemoglobin) and were from families able to communicate effectively in English. Patients with histories of stroke not impairing communication, other disease complications, or receiving preventative treatment interventions, such as transfusion therapy, hydroxyurea treatment, and oral or subcutaneous chelation therapy were also eligible to participate.

Exclusion criteria. Children and adolescents with a history of severe stroke, intellectual disability (Full-Scale IQ < 70) or visual or auditory impairments were excluded from the study. Individuals meeting exclusion criteria were identified in advance with the assistance of clinic staff and not approached to participate. Recruitment was accomplished by mailing an initial letter of introduction co-signed by the researcher, supervisor, and physician head of the program to parents of eligible patients. Telephone follow-up was completed by the researcher and in-person introduction to families was facilitated by clinic staff at the time of a patient’s routine clinic visit or inpatient stay. In addition, local support group organizations agreed to distribute information about the study to their membership through their print and e-mail newsletters and made information flyers available to members at meetings and education conferences. A total of
384 registered patients potentially met eligibility criteria. Data collection was completed over the course of nine months and recruitment terminated at 100 cases for feasibility in consultation with the thesis committee. In all, parents of 100 children and teens (26% of the potential recruitment sample) consented to participate in both data collection time points for the study.

**Sample characteristics.** Mean chronological age of patients at first participation in the study (Time 1) was 11.7 years ($SD = 2.74$). Child participants between the ages of 8 and 12 made up the majority (64%) of the participant group. The sample was evenly distributed between males and females (51% male). All participants self-identified as of African or Afro-Caribbean background. The mean Wechsler Abbreviated Scale of Intelligence (WASI) Full-Scale IQ (standard) score obtained for the participant sample was $89.6$ ($SD = 4.71$; range 78 to 101), which fell within one standard deviation of the normative mean.

The majority of patients had a diagnosis of HbSS disease, with HbSC disease being the next most common diagnosis. Forty-one percent of the sample was made up of youths receiving chronic transfusion therapy at clinic on a routine basis, and 22% were receiving hydroxyurea treatment. Just over one third of participants (37%) were not receiving prescribed or specialized treatment at the time of participation in the study. Medical history including two or more sickle cell disease-related complications (for example, vision, learning, attention, behaviour, silent or overt stroke) was reported for just over half (56%) of the sample. Using disease severity categories described by Scott and colleagues (2005), 21% of participants met criteria for having severe SCD (that is, history of stroke, acute chest syndrome, more than three hospitalizations for vaso-occlusive episodes in the previous three years, or recurrent priapism necessitating hospitalization) and 79% met criteria for mild disease, having none of these complications in
their recent health history. Summarized demographic data for patient participants are presented in Table 1.

Table 1. Demographic Characteristics of Patient Participants in the Study (N = 100 patients)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>%</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>11.70</td>
<td>2.74</td>
<td>8-17</td>
<td>64</td>
</tr>
<tr>
<td>8 to 12 years</td>
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<tr>
<td>13 to 18 years</td>
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<tr>
<td>Severity</td>
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</tr>
<tr>
<td>Mild</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>64</td>
<td></td>
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<tr>
<td>Treatment Group</td>
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<tr>
<td>No additional treatment</td>
<td>37</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chronic transfusion</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea treatment</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total disease complications reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.70</td>
<td>1.13</td>
<td>0-5</td>
<td>44</td>
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<tr>
<td>One or fewer</td>
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<tr>
<td>Two or greater</td>
<td>56</td>
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</table>

**Parent respondents.** Parent respondents’ demographic data are summarized in Table 2. One hundred parents participated in the study. Respondents were primarily female (n = 95) and all were biological parents of the participants. The majority of parents were married, widowed,
or divorced (61% of the sample), and just over one-third (39%) reported single or unmarried marital status. Employment status was reported by all respondents, with 78% of parents indicating that they were employed on a part- or full-time basis. Annual family income was reported by 91% of respondents (nine parents declined to provide this information). Twenty percent of respondents reported an annual family income of $25,000 or higher. Seventy-one percent of respondents reported a family income below $25,000 annually.

Table 2. *Demographic characteristics of parent participants in the study*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>%</th>
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<tbody>
<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Males</td>
<td>95</td>
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<td>95</td>
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<tr>
<td>Females</td>
<td>5</td>
<td></td>
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<td>5</td>
</tr>
<tr>
<td>Age</td>
<td>97</td>
<td>38.59</td>
<td>7.83</td>
<td>21-66</td>
<td>97</td>
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<tr>
<td>Marital status</td>
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<tr>
<td>Married</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>Single</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td>39</td>
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<tr>
<td>Education completed</td>
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<tr>
<td>High School</td>
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<tr>
<td>College or University</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td>46</td>
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<tr>
<td>Employment Status</td>
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<tr>
<td>Employed</td>
<td>78</td>
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<td>78</td>
</tr>
<tr>
<td>Unemployed</td>
<td>22</td>
<td></td>
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<td></td>
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<tr>
<td>Annual Family Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Respondents</td>
<td>91</td>
<td></td>
<td></td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>Less than $25,000</td>
<td>71</td>
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<td>71</td>
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<tr>
<td>$25,000 or greater</td>
<td>20</td>
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</tbody>
</table>
Thirty-four percent of the overall sample reported a family income of at least $40,000 annually, and of this group, a minority (n = 7) reported family incomes in excess of $50,000 annually. Median income for families in Ontario in 2011 was $73,290 (Statistics Canada, 2015). Parent educational attainment data were provided by 97 respondents (three parents declined to provide this data). Forty-six percent had completed high school and 51% had completed college or university. To facilitate analysis, demographic information was collapsed into two categories: parent marital status (married/single), parent educational attainment (high school/college or university), and family income (less than $25,000 annually or greater than or equal to $25,000 annually).

**Instruments**

**Patient and parent history form.** Parents were asked to provide child demographic and medical information (age, sex, level of education, ethnicity, medical comorbidities and neurobehavioural comorbidities) and demographic information about themselves (age, sex, marital status, educational level, relationship to the child, occupation, annual income). Medical chart review was completed separately by the researcher to collect information about child sickle cell genotype, disease status (determination of severity), medical and neurobehavioural comorbidities, current treatments, history of emergency admissions and serious complications (vaso-occlusive episodes, stroke, acute chest syndrome, surgeries). Parents were assisted with completion of the form as required. The Patient and Parent History Form and Chart Review Data Collection Form are presented in Appendix B.

**The Living with Sickle Cell Questionnaire.** The Living with Sickle Cell Questionnaire (LSCQ; Hetherington, McGrath, Olivieri, & Newton, 2000; revised 2010) is the primary measure under study. It is a computer-administered disease specific HRQoL scale for children
and adolescents with SCD that requires approximately 20 minutes to complete. The original form of the LSCQ was 25 items in length and comprised of items generated during focus groups with child and adolescent patients, parents, and medical staff. Assigned weightings (‘importance’ ratings) were used to identify items that would be retained for the measure. (Hetherington et al., 2000) Cognitive interviewing was conducted with a subset of patients ($n = 10$), resulting in clarification of the language for some items and reduction in the number of questionnaire items to a current total of 22 items in four primary domains: Somatic Sensation, Cognitive/Psychological Functioning, Social Functioning, and Physical Functioning. To facilitate self-administration by young users, LSCQ items were read aloud to participants by a recorded female voice on the computer and responses were entered by clicking the computer mouse. All items pertained to experiences with SCD during the previous one-week period. A 7-point Likert-type scale with end anchors ‘None of the time’ and ‘All of the time’ was employed. Items were presented in one of two formats that either asked how often the item was a problem or how much the participant was bothered by the item. Data entered by participants were saved by the program and written directly to a database for later analysis. Five summary scores were generated, one for each of four domains as well as for an overall HRQoL score. Higher domain and overall scores were predicted to be associated with lower burden of disease on functioning, and therefore, better HRQoL. Question text for the current version of the measure is presented in Appendix C.

**The Pediatric Quality of Life Inventory™ – Generic Core Scales 4.0 (PedsQL), Acute Version.** The Acute version of the PedsQL Generic Core Scales 4.0 (PedsQL; Varni et al., 1999) is a standardized one-week retrospective self-report measure of HRQoL for children and adolescents five to 18 years of age. It is a parallel form of the standard PedsQL Generic
Core Scales 4.0, which references a one-month retrospective period, thus permitting comparison between scales and scores (Varni, Burwinkle, Seid, & Skarr, 2003). The PedsQL has been found sensitive to the occurrence and frequency of acute and chronic pain as well as other clinical events in pediatric SCD (Dampier et al., 2007). Normative data are available for healthy children and youth and for children with other chronic conditions for comparative purposes. The PedsQL was included as a ‘gold standard’ measure of HRQoL for this study to help establish construct validity of the LSCQ. The PedsQL Acute form consists of 15 items and yields scores on four subscales: Health and Activities (physical functioning); About My Feelings (emotional functioning); How I Get Along with Others (social functioning); About School (school functioning); and two summary scores, Physical Health and Psychosocial Health, which are composites of the four subscales by domain. The retrospective period is seven days. For each item, a 5-point scale with verbal anchors (0 = Never a problem, 1 = Almost never a problem, 2 = Sometimes a problem, 3 = Often a problem, 4 = Almost always a problem) was used to rate how often an item was a problem during the period of interest. Subscale scores were converted to a 0-100 scale, where higher scores indicate better HRQoL. Items were read aloud to patients as required to assist with completion of the questionnaire. Internal consistency (α) reported for child versions of the PedsQL are 0.88 for the Total Scale Score, 0.80 for the Physical Summary Score and 0.86 for the Psychosocial Summary Score (Varni, Seid, & Kurtin, 2001). Acute (one-week retrospective) form versions for child (8 to 12 years) and adolescent (13 to 18 years) groups were used in the present study.

**Wechsler Abbreviated Scale of Intelligence.** The Wechsler Abbreviated Scale of Intelligence (WASI; The Psychological Corporation, 1999) is an intelligence measure normed for individuals six years, zero months through 89 years, 11 months of age that may be
administered in a two or four subtest format. The abbreviated, two subtest version of the WASI, comprised of Vocabulary and Matrix Reasoning subtests that contribute to a Full-Scale IQ score (FSIQ-2), requires approximately 15 minutes to complete and correlates .83 with the Wechsler Intelligence Scale for Children – Fourth Edition, and .87 with the Wechsler Adult Intelligence Scale – Third Edition. Internal consistency (α) for child and youth samples for Vocabulary (range of .91 to .98) and Matrix Reasoning (range of .88 to .96) are very good (Sattler, 2001). The two-item instrument yields T-scores ($M = 50, SD = 10$) for the subtests and standard scores ($M = 100; SD = 15$) for Full-Scale IQ (Sattler, 2001). An obtained Standard Score ranging from 85 to 115 points is considered to be within the Average range. The two subtest version was used as an estimate of FSIQ to determine whether the FSIQ inclusion criterion was met.

**Global Rating of Change in Health measure.** At the second data collection time point (Time 2), two weeks after the initial data collection (Time 1), and in addition to the LSCQ and PedsQL, a Global Rating of Change in Health measure was administered to determine each participant’s perception of the degree of change in his or her overall health since the Time 1 visit. The 15-point Likert-type scale, developed for use in HRQoL studies of childhood asthma and allergy by Juniper, Guyatt, Willan, and Griffith (1994), ranges from ‘A very great deal worse’ (a score of -7) to ‘A very great deal better’ (a score of +7), with the option to mark intervening numerical anchors. Categorizations outlined by Juniper and colleagues were used in the present study to determine the degree of perceived change in health indicated by each participant. Individuals recording a score of -1, 0 or +1 were considered to have experienced no change in health since the first administration (Time 1). Global ratings of -2, -3, or +2, or +3 were regarded as representing small but important change. Moderate change was indicated by
change scores of -4, -5, or +4, +5, and large change by change scores of +6, +7, or -6, -7. The rating scale is presented in Appendix D.

**Procedure**

All data were collected in accordance with protocols of The Hospital for Sick Children Research Ethics Board and The University of Toronto Office of Research Ethics. Prior to instrument testing, revision of the original 25-item LSCQ was performed. Ten patients (n = 5 children 8 to 12 years, and n = 5 adolescents 13 to 18 years) attending the Sickle Cell clinic for day treatment or as inpatients were recruited for this purpose. These patients participated in individual cognitive interviews with the researcher using the computer-based LSCQ to establish that interpretation of each item was occurring as intended. A list of probes developed by Jobe (2003) and Levine and colleagues (2001) was used to determine patients’ degree of understanding and to gather qualitative feedback about modifications that might improve comprehension of wording and satisfactoriness of item coverage. The cognitive interview script, as presented to participants, appears in Appendix E. Consensus was reached with the thesis committee to reword items to improve their specificity and to eliminate three items to improve clarity and usability of the instrument. The list of item modifications and final item list appear in Appendix F. Following completion of the instrument testing phase (a two-month period), formal recruitment and data collection commenced using the current 22-item form of the LSCQ. Following telephone or in-person contact at clinic with families, written parent consent and child assent or youth consent to participate in the study was obtained. (Assent and consent forms are presented in Appendix G.) The researcher met with each participant privately in the hospital setting to carry out the initial phase of measure completion (Time 1).
Subtests of the WASI were administered using the standardized procedure outlined in the test manual. Following this, either the LSCQ or PedsQL, as determined by counterbalancing, was completed by the patient followed by a short break and administration of the second questionnaire. At the initial visit, parents were asked to fill out the Patient and Parent Information Forms that included family information (i.e., parent age, sex, ethnicity/languages spoken, marital status, education level, occupation, income range, home location (urban or rural)) and child information (i.e., date of birth, current age, sex, ethnicity, languages spoken, current grade, treatments (e.g., transfusion; hydroxyurea). Data were also collected regarding other health conditions, history of stroke, number of hospitalizations in the last two years, and history of learning difficulties. Following completion of questionnaires at Time 1, an appointment was arranged for Time 2 administration of the study measures at a location convenient for families (e.g., local hospital, library, family home).

Time 2 administration took place approximately two weeks following Time 1 administration. At Time 2, the first of the two study measures, the LSCQ or PedsQL, as determined by counterbalancing, was completed by the patient, followed by a short break and administration of the second questionnaire. Following completion of both measures, the Global Rating of Change in Health measure, a 15-point Likert-type scale ranging from ‘A very great deal worse’ (-7) to ‘A very great deal better’ (+7) was administered. Obtained rating of change scores were interpreted as small, moderate, or large per Juniper, Guyatt, and colleagues’ (1994) methods, described previously.

The final stage of data collection (Fall 2011) involved clinical chart review where relevant medical data from the previous 3 years (after Panepinto et al., 2005) were recorded.
Data Analysis

The following analyses were conducted to address research questions for the study.

Descriptive statistics. Demographic data (that is, child age, sex, and disease-related data and parent age, sex, education, and family income data) were gathered using the study’s Data Collection Form and Chart Review Form, and were analyzed to generate descriptive statistics.

Primary research questions and analyses.

Question 1: What are the psychometric properties of the Living with Sickle Cell questionnaire (LSCQ)?

Reliability. The internal consistency of the LSCQ was determined using the Cronbach’s coefficient alpha (α) statistic. Alpha values of 0.6 or greater were considered acceptable for internal consistency of each domain and the overall measure. Item discrimination was determined by examining item-total and item-scale correlations (Pearson r statistic) to confirm that each item was most highly associated (correlated) with its parent domain. Stability of ratings between administration points was examined as part of sensitivity analysis.

Validity. Confirmation that the items of the LSCQ were representative of the broad range of themes relevant to living with pediatric SCD, was established, in part, through review and incorporation of themes arising from original focus groups with child, adolescent, parent and healthcare practitioners during the development phase of the LSCQ. Validity was further assessed with the cognitive interviewing procedure previously reported in the Procedure section. Criterion validity was determined through examination of associations (Pearson r correlations) between LSCQ domains and those of the PedsQL, Acute version, and situated in the context of previously published results of PedsQL administration to sickle cell patients. In some cases, the
domains of the LSCQ were hypothesized to be correlated with more than one domain of the PedsQL given similar content themes. Positive and significant correlations were predicted between:

- LSCQ Somatic Sensation domain and the ‘Health and Activities’ domain of the PedsQL
- LSCQ Physical Functioning domain and both ‘Health and Activities’ (physical functioning) and ‘About My Feelings’ (emotional functioning) domains of the PedsQL
- LSCQ Cognitive/Psychological and PedsQL ‘About School’ domains
- LSCQ Social Functioning and PedsQL ‘How I Get Along with Others’ (social functioning) domains.

Predicted relationships between LSCQ and PedsQL domains are illustrated in Figure 1. The lines illustrate predicted associations between domains of the LSCQ (on the left) and the PedsQL (on the right) questionnaires based on similarities in domain theme and item content between measures.
Sensitivity. To determine the LSCQ’s utility for detection of underlying and clinically important changes in health status over time, LSCQ values obtained at Time 1 and Time 2 were compared. Two subject groupings were created, one made up of patients indicating no perceived change in health status between testing points (that is, those who endorsed values in the range of -1, 0, or +1 on the Global Rating of Change measure) and a second group who endorsed a change in health status between testing points (signified by change scores in the ranges -7 to -2 or +2 to +7 on the Global Rating of Change measure). In addition, computation of Cohen’s Effect Size, $d$, was planned for Time 1 to Time 2 change scores (paired sample t-test). Associations between rating of change scores and LSCQ domain ratings for Time 1 and Time 2 were plotted to identify relationships between these variables.
**Question 2:** Do child and parent factors predict domain-level and overall HRQoL when using the disease-specific instrument (LSCQ) in the same manner that has been found for generic HRQoL instruments?

In follow-up to examining correlations between child/parent factors and the LSCQ domains at both time points, stepwise linear regression was conducted to explore child and parent characteristics identified in the literature as important influencers of disease-specific HRQoL. Child variables included were sex, age group (child or adolescent), disease severity, and presence and number of medical and neurobehavioural comorbidities. Parent variables included were sex, age, marital status, and socioeconomic status, including highest education level attained and employment status at the time of study participation.

**Question 3:** Are common SCD patient group differences in HRQoL identified in studies using generic instruments also observed with use of the disease-specific instrument (LSCQ)?

The analysis of variance procedure was used to determine whether hypothesized group mean differences described in the literature (for example, those described in Panepinto et al., 2008) were found on the LSCQ for the stated comparisons (that is, age group, sex, disease severity, treatment category).

**Question 4:** How does the structure of HRQoL domains derived from factor analysis of disease-specific data compare to the four classical domains used to construct the LSCQ? Are the classical domains preserved in a disease-specific context for this sample of pediatric SCD patients?

An indirect goal of the present study involved comparing questionnaire construction methods, those being the clinimetric approach to development of the LSCQ items according to
generic HRQoL domains, and factor analysis-determined domains and item groupings of the PedsQL. As items of the disease-specific (LSCQ) measure under study were assigned to generic HRQoL domains at the time of scale development as part of the clinimetric approach to scale development (after Juniper, Guyatt, and Jaeschke, 1996), examination of the data’s adherence to this proposed structure was analyzed with a multivariate approach. Factor analysis was performed separately on the LSCQ Time 1 and Time 2 data, as equivalence of the datasets could not be assumed. Although the sample size of 100 cases fell below some recommended ratios of variables-to-observations for factor analysis (e.g., 10 to 15 subjects per variable; Field, 2000; 50 observations at minimum and 5 times as many observations as variables; Habing, 2003; Loo, 1983), Field (2000) indicated that magnitude of factor loadings is as important a consideration as absolute sample size. Given the theory-driven basis for the four domain HRQoL structure, confirmatory factor analysis was deemed appropriate for testing affiliation of LSCQ items assigned to these factors (Jackson, Gillaspy, & Purc-Stephenson, 2009). Confirmatory factor analyses (CFAs) were performed using Stata software, version 13, on a domain-by-domain basis to investigate the goodness-of-fit of LSCQ items to their assigned (generic) parent domains of HRQoL separately at Time 1 and Time 2. Appropriate data and model evaluation (that is, fit indices of chi-square, root mean square error of approximation (RMSEA; target value < 0.05), and comparative fit index (CFI; target value in the range of .90 and .95 for good fit, and >0.95 for excellent fit)) were determined per the recommended confirmatory factor analysis practices outlined by Jackson and colleagues (2009). Where an acceptable model fit was not found for the LSCQ at Time 1 and Time 2, suggesting a latent variable arrangement other than that predicted theoretically (Streiner & Norman, 2003), principal components analysis was performed at Time 1 and Time 2 to explore the possible underlying structure of the variables. Principal components analyses were conducted with request to extract all components with eigenvalues
greater than 1 and oblique rotations performed if multiple components were extracted. Oblique rotation was requested to account for possible correlations between the components. SPSS v.22 software was used to perform principal components analyses. Confirmatory factor analyses (CFAs) were performed using Stata software, version 13, on a domain-by-domain basis to investigate the goodness-of-fit of LSCQ items to their assigned (generic) parent domains of HRQoL. Principal Components Analysis was performed using SPSS v. 22 and an extraction method of Promax oblique rotation used to investigate whether orthogonal or oblique relationships among variables could be assumed. The first model of the Principal Components analyses performed for each timepoint was conducted by restricting the procedure to a 4-component solution, as predetermined by theoretical considerations during measure construction.
Chapter 3: Results

Descriptive Statistics

Domain-level and overall scores for LSCQ and PedsQL measures at Time 1 and Time 2 are presented in Table 3. Descriptive statistics for the LSCQ items are provided in Appendix H. At item level, mean values were moderately and positively skewed, indicating that respondents tended to endorse values at the upper end of the scale (corresponding to frequent occurrence or bothersomeness of that particular item’s content) more frequently. Significant correlations were observed only across the items within the same domains.

Table 3. Descriptive statistics for LSCQ and PedsQL domains at Time 1 and Time 2 (N= 100)

<table>
<thead>
<tr>
<th>Instrument/Domain</th>
<th>Time 1</th>
<th></th>
<th>Time 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>LSCQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive/Psychological</td>
<td>15.06</td>
<td>4.69</td>
<td>14.13-15.99</td>
<td>15.27</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>18.72</td>
<td>6.19</td>
<td>17.49-19.95</td>
<td>18.64</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>17.10</td>
<td>5.62</td>
<td>15.99-18.21</td>
<td>17.11</td>
</tr>
<tr>
<td>Total Score</td>
<td>66.40</td>
<td>18.52</td>
<td>62.73-70.07</td>
<td>66.32</td>
</tr>
<tr>
<td><strong>PedsQL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health and Activities</td>
<td>77.01</td>
<td>4.29</td>
<td>69.00-88.00</td>
<td>80.36</td>
</tr>
<tr>
<td>About My Feelings</td>
<td>77.67</td>
<td>11.87</td>
<td>50.00-100.00</td>
<td>78.64</td>
</tr>
<tr>
<td>How I Got Along with Others</td>
<td>80.79</td>
<td>6.11</td>
<td>50.00-88.00</td>
<td>77.78</td>
</tr>
<tr>
<td>About School</td>
<td>72.36</td>
<td>12.19</td>
<td>50.00-88.00</td>
<td>74.12</td>
</tr>
<tr>
<td>Physical Summary Score</td>
<td>77.01</td>
<td>4.29</td>
<td>69.00-88.00</td>
<td>80.36</td>
</tr>
<tr>
<td>Psychosocial Summary Score</td>
<td>76.60</td>
<td>6.99</td>
<td>57.00-86.33</td>
<td>75.82</td>
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<tr>
<td>Total Score</td>
<td>76.81</td>
<td>4.82</td>
<td>66.33-85.17</td>
<td>66.32</td>
</tr>
</tbody>
</table>
Question 1: What are the psychometric properties of the Living with Sickle Cell questionnaire (LSCQ)?

Reliability

*Internal consistency*. The internal consistency of the LSCQ’s clinimetrically-derived domains was investigated. Cronbach’s alpha coefficients for each domain at both of the timepoints that the LSCQ instrument was administered are displayed in Table 4. All coefficients of internal consistency were found to exceed the .70 level, indicating that reliable total scores were computed for each domain. Item-total correlations between each LSCQ item and its parent domain were of, or approached, at least moderate strength (i.e., Pearson $r \geq .40$) for the majority of items at Time 1 and at Time 2, with two exceptions: for the “How much did feeling sad or down bother you?” item (parent domain: Cognitive/Psychological Functioning), the Time 1 Pearson $r$ value was .39, and for the item, How much were you bothered by pain?” (parent domain: Somatic Sensation), the Time 1 Pearson $r$ value was .34). Item-scale and item-total correlational data from both timepoints are presented in Appendix I.

Table 4. *Cronbach’s Alpha values for the LSCQ measure at Time 1 and Time 2*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Time 1</th>
<th>Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic Sensation</td>
<td>0.77</td>
<td>0.73</td>
</tr>
<tr>
<td>Cognitive/Psychological</td>
<td>0.78</td>
<td>0.77</td>
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<tr>
<td>Social Functioning</td>
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<td>0.89</td>
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<tr>
<td>Physical Functioning</td>
<td>0.88</td>
<td>0.90</td>
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</table>
Validity

*Time 1.* Correlation values between LSCQ and PedsQL scales at Time 1 are presented in Table 5. At Time 1, all LSCQ domain scores and the total score were strongly and significantly correlated with one another, with Pearson product moment correlations ranging from .59 to .92 ($p = <.001$). PedsQL domains were highly correlated with one another, with the exception of non-significant correlations found between the About School domain score and About My Feelings domain score, and between the About School domain score and How I Get Along with Others domain score. The Health and Activities domain score was positively and significantly correlated with the About My Feelings domain score, the About School domain score, the Physical Health Summary score (equivalent/duplicate scale to Health and Activities scale), Psychosocial Summary Score, and Total Score. The About My Feelings domain score was positively and significant correlated with all PedsQL domain scores except the About School score.

Predicted cross-measure associations presented in Figure 1 were not found between the LSCQ and PedsQL at Time 1. The LSCQ Somatic Sensation Summary score was positively but not significantly correlated with the PedsQL Health and Activities score/Physical Summary score. The LSCQ Cognitive/Psychological domain score was positively but weakly correlated with the PedsQL About My Feelings domain score and negatively correlated with the PedsQL About School domain score. Neither of these correlations was statistically significant. Finally, the LSCQ’s Social Functioning domain score was negatively correlated with the PedsQL How I Get Along with Others domain score.
Table 5. Correlations between the LSCQ and PedsQL domains at Time 1

<table>
<thead>
<tr>
<th></th>
<th>SS</th>
<th>CP</th>
<th>SF</th>
<th>PF</th>
<th>LTOT</th>
<th>HA</th>
<th>AF</th>
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<th>AS</th>
<th>PH</th>
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<th>PTOT</th>
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<tbody>
<tr>
<td>SS</td>
<td>0.75*</td>
<td>0.60*</td>
<td>0.60*</td>
<td>0.83*</td>
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<td>0.00</td>
<td>-0.01</td>
<td>-0.04</td>
<td>0.10</td>
<td>-0.06</td>
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<tr>
<td>CP</td>
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<td>0.73*</td>
<td>0.92*</td>
<td>0.11</td>
<td>0.09</td>
<td>0.01</td>
<td>-0.12</td>
<td>0.11</td>
<td>0.00</td>
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<tr>
<td>SF</td>
<td>0.66*</td>
<td>0.88*</td>
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<tr>
<td>PF</td>
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<td>0.09</td>
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<td>LTOT</td>
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<tr>
<td>AF</td>
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<td>0.39*</td>
<td>0.71*</td>
<td>0.68*</td>
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<td>0.01</td>
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<td>0.39*</td>
<td>0.81*</td>
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<tr>
<td>AS</td>
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<td></td>
<td>0.48*</td>
<td>0.65*</td>
<td>0.51*</td>
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<tr>
<td>PH</td>
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</tbody>
</table>

Note. **LSCQ domains:** SS = Somatic Sensation; CP = Cognitive/Psychological; SF = Social Functioning; PF = Physical Functioning; LTOT = LSCQ Total Score

**PedsQL domains:** HA = Health and Activities; AF = About My Feelings; GA = How I Get Along with Others; AS = About School; PH = Physical Summary Score; PS = Psychosocial Summary Score; PTOT = PedsQL Total Score (Time 1)

*Correlation significant at .05 level (2-tailed); ** Correlation significant at .01 level (2-tailed)

**Time 2.** Correlation values between LSCQ and PedsQL scales at Time 2 are presented in Table 6. At Time 2, a similar pattern of strong within-measure associations was noted for domains of the LSCQ and domains of the PedsQL. Correlations between LSCQ domain scores were strongly positive and ranged from .45 to .76 (p = .000). For the PedsQL, all domain and summary scores were positively and significantly correlated with one another (range: -.10 to 1.00) and correlated at the p = .01 level or below, with the exception of associations between the About School and About My Feelings domain scores. A negative but significant correlation was found between the LSCQ Social Functioning domain score and the PedsQL About My Feelings domain score (r = -.22, p = .032). Hypothesized associations between the LSCQ and PedsQL domains illustrated in Figure 1 were not demonstrated at Time 2, and correlations were weak and non-significant across the domains of each scale. The LSCQ Somatic Sensation and LSCQ Physical Functioning domain scores did not correlate significantly with the PedsQL Health and
Activities Scale. The LSCQ Cognitive/Psychological domain was not highly correlated with the PedsQL About My Feelings score or with the PedsQL About School domain. Finally, the LSCQ Social Functioning domain score was not found to be significantly correlated with the How I Get Along with Others domain of the PedsQL ($r = -0.068$, $p = .50$).

Table 6. Correlations LSCQ and PedsQL domains at Time 2

<table>
<thead>
<tr>
<th></th>
<th>SS</th>
<th>CP</th>
<th>SF</th>
<th>PF</th>
<th>LTOT</th>
<th>HA</th>
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<th>GA</th>
<th>AS</th>
<th>PH</th>
<th>PS</th>
<th>PTOT</th>
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</thead>
<tbody>
<tr>
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<td>.56*</td>
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<td>CP</td>
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<td>.69*</td>
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<td>.40*</td>
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<td>.92*</td>
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</table>

Note. LSCQ domains: SS = Somatic Sensation; CP = Cognitive/Psychological; SF = Social Functioning; PF = Physical Functioning; LTOT = LSCQ Total Score

PedsQL domains: HA = Health and Activities; AF = About My Feelings; GA = How I Get Along with Others; AS = About School; PH = Physical Summary Score; PS = Psychosocial Summary Score; PTOT = PedsQL Total Score (Time 2)

*Correlation significant at .05 level (2-tailed); ** Correlation significant at .01 level (2-tailed)

Sensitivity to change

To explore the LSCQ’s sensitivity to reported change, prior to the study’s second administration point, patients were asked to rate the degree to which they felt their health status had changed since the first visit using the 15-point Global Rating of Change in Health Scale. Negative values reflected perceived decline in rated health and positive values reflected perceived improvement in health between timepoints (after Juniper et al., 1994). This information was further used to divide the patients into two groups: 1) a group that experienced
and reported change; and 2) a group where minor change could be considered as a fluctuation due to normal variation. A number of groupings were created to examine what ranges or amounts of endorsed change on the rating of change scale might best correspond to change observed in the LSCQ scores at Time 1 and Time 2 as part of investigating the instrument’s sensitivity to change. Global rating of change scores were centrally clustered, ranging from -4 (‘Moderately worse’) to +3 (‘Somewhat better’), and endpoints of the scale were not selected by respondents. When a score of ‘zero’ was used to represent no perceived change in health between timepoints and ratings above and below zero considered to represent improved or worsened health, respectively, 40% of children and youth endorsed no change, 22% endorsed some worsening in their health, and 38% endorsed improved health between Time 1 and Time 2.

In order to examine reported change more finely, three grouping variables for Rating of Change were then created and compared: 1) when a score of zero was considered as ‘no change’; 2) when a change of one point on either side of the zero midpoint (that is, a rating of change score range of -1 to +1 range) was considered as ‘no change’ (as in Juniper et al., 1994); and 3) when change of up to two points in either direction (that is, a Rating of Change score range of -2 to +2) was considered as ‘no change.’ The percentage of participants located within the ‘change’ and ‘no change’ groups based on each of these classifications is displayed in Table 7.

Table 7. Participant groupings by Global Rating of Change Score range (Change versus No Change in Health)

<table>
<thead>
<tr>
<th>Definition of Stability</th>
<th>No change group (%)</th>
<th>Change group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = no change</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>0 or +/-1 = no change</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>0 to +/-2 = no change</td>
<td>92</td>
<td>8</td>
</tr>
</tbody>
</table>
The first two categories, representing no change at the ‘0’ midpoint of the scale, and +/- 1 point range, respectively, were used to investigate the sensitivity of the measure to change. The third grouping indicated, representing change using ratings outside of the +/- 2 range, was not used in further analyses as originally proposed given the very small percentage of participants represented in one of the cells (Change group). Scatter plots, presented in Figure 2 and Figure 3, were used to investigate whether change or no change, as observed in LSCQ domain scores between Time 1 and Time 2, was consistent with reports of change in health or no change in health, respectively, endorsed by participants using the Global Rating of Change scale. As the datapoints for the change group did not align with the graphed diagonal as anticipated, no discernable correspondence could be established between change scores observed for Time 1 and Time 2 LSCQ domain scores and the Global Rating of Change score that had been assigned by participants.

Effect sizes were then computed on the mean LSCQ domain and total score difference between Time 1 and Time 2. Data patterns for the group endorsing ‘no change’ in overall health when defined as a Global Rating of Change score ranging from -1 to +1 were compared to data patterns for ‘no change’ in overall health status when defined by a wider Global Rating of Change score band between -2 and +2. Results are presented in Table 8 and interpreted cautiously for the Global Rating of Change score band ranging from -2 to +2 given the small number classified as showing change. Paired samples t-tests computed on Time 1 to Time 2 LSCQ domain and total score mean differences were not significant for either the group endorsing a change in health between timepoints or the group endorsing no change in health between timepoints; however, significant differences were found between Time 1 and Time 2 mean PedsQL domain scores for these groups. For the ‘change’ group, PedsQL Health and
Activities/Physical Summary mean domain scores differed significantly between Time 1 and Time 2, $t(31) = -4.62, p = .00$, with a large effect size (Cohen’s $d = .82$) and significant differences were also found for the About School scores between Time 1 and Time 2, $t(31) = -2.58, p = .02$, and for Total Score between timepoints, $t(1, 31) = -2.91, p = .01$, with a moderate effect size (Cohen’s $d = 0.46$). For the ‘no change’ group, significant Time 1 and Time 2 mean score differences were found for PedsQL Health and Activities/Physical Summary Score domains, $t(67) = 3.52, p = .001$, with a moderate effect size (Cohen’s $d = 0.43$); How I Get Along with Others domain, $t(67) = 3.52, p = .001$, with a moderate effect size (Cohen’s $d = 0.43$); Psychosocial Summary score, $t(67) = 2.24, p = .03$, with a small effect size (Cohen’s $d = 0.27$) and Total Score, $t(1, 67) = -2.22, p = .03$, with a small effect size (Cohen’s $d = 0.27$).
Figure 2. Associations between Global Rating of Change score (when a score of zero represents ‘No change’) and mean LSCQ score differences observed between Time 1 and Time 2
Figure 3. Associations between Global Rating of Change score (when scores from -2 to +2 represent ‘No change’) and mean LSCQ score differences observed between Time 1 and Time 2.
Table 8. Difference scores for LSCQ and PedsQL domains and effect sizes for groups identifying Change or No Change in health between Time 1 and Time 2

<table>
<thead>
<tr>
<th>Domain</th>
<th>Change Group</th>
<th></th>
<th>No Change Group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean T1-T2</td>
<td>Effect Size</td>
<td>Mean T1-T2</td>
<td>Effect Size</td>
</tr>
<tr>
<td></td>
<td>Difference D</td>
<td></td>
<td>Difference d</td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>1.22</td>
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<td>-2.50</td>
<td>-.06</td>
</tr>
<tr>
<td>CP</td>
<td>.69</td>
<td>.16</td>
<td>-.63</td>
<td>-.13</td>
</tr>
<tr>
<td>SF</td>
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<tr>
<td>PF</td>
<td>.09</td>
<td>.02</td>
<td>-.06</td>
<td>-.01</td>
</tr>
<tr>
<td>LTOT</td>
<td>4.97</td>
<td>.30</td>
<td>-2.22</td>
<td>-.12</td>
</tr>
<tr>
<td>HA</td>
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<td>-.81</td>
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<td>.37</td>
</tr>
<tr>
<td>AF</td>
<td>-2.00</td>
<td>-.15</td>
<td>-.49</td>
<td>-.05</td>
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<td>GA</td>
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<td>.37</td>
<td>3.16</td>
<td>.38</td>
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<tr>
<td>AS</td>
<td>-4.94</td>
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<td>-.02</td>
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<td>-3.24</td>
<td>-.69</td>
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<tr>
<td>PS</td>
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<td>-.86</td>
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<td>.18</td>
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<td>PTOT</td>
<td>-2.05</td>
<td>-.38</td>
<td>-.92</td>
<td>-.17</td>
</tr>
</tbody>
</table>

Note: LSCQ domains: SS = Somatic Sensation; CP = Cognitive/Psychological; SF = Social Functioning; PF = Physical Functioning; LTOT = LSCQ Total Score

PedsQL domains: HA = Health and Activities; AF = About My Feelings; GA = How I Get Along with Others; AS = About School; PH = Physical Summary Score; PS = Psychosocial Summary Score; PTOT = PedsQL Total Score

The LSCQ mean domain difference scores were small to medium in magnitude (per Cohen, 1988) for the ‘change’ group (Somatic Sensation and Total Score domains) and small for the ‘no change’ group. The magnitude of effect sizes for mean differences in the ‘change’ group for the PedsQL ranged from small to large, while effect sizes for the ‘no change’ group’ ranged from small to medium.

Question 2: How does the structure of HRQoL domains derived from factor analysis of disease-specific items compare to the four-domain (classical) structure used to construct the LSCQ? Are the classical domains preserved in a disease-specific context for this sample of pediatric SCD patients?

Model fit solutions were returned from confirmatory factor analyses following three to five iterations. At Time 1 and Time 2, high correlations ($r > .4$) were observed among items
belonging to the same parent domain, consistent with the high Cronbach’s alpha levels previously reported. Model Fit Indices, however, returned values indicative of poor to moderate fit based on RMSEA and CFI findings, and apparently contradictory assessments of model fit depending upon the indexes considered. The statistical program could not converge upon a solution for a proposed model for the LSCQ Somatic Sensation domain at Time 2. All chi-square values for the models returned were significant and had more than three degrees of freedom, further indicators of unstable modelling across domains for each timepoint.

A Principal Components analysis (PCA) approach was then undertaken to determine the nature of the LSCQ’s internal structure at Time 1 and Time 2 independent of hypothesized arrangements of the items, as used in the CFA approach. Although the resultant solution explained a large amount of variance (about 68% at Time 1 and 71% at Time 2), the component structure did not closely align with the structure predicted by theory, as most items heavily loaded on the same principal component. This finding suggested existence of a unidimensional underlying structure. To investigate this possibility, a PCA restricted to one component was conducted at each timepoint. At Time 1, a single component solution accounted for 45.26% of the variance in the data with individual component loadings varying between .48 and .79, a result also suggestive of a strong internal structure for a single domain. Results are presented in Table 9. At Time 2, the amount of variance explained by a single component was 42.93%, with individual component loadings ranging between .43 and .83. These results suggest that the LSCQ instrument’s Total Score could reasonably be used as a measure of overall health-related quality of life in the SCD youth population; however, there may still be practical value in computing scores for individual (traditional) HRQoL domains in order to gain specific information about each functional area.
Table 9. Principal component analysis results for a single component solution for the LSCQ at Time 1

<table>
<thead>
<tr>
<th>Item</th>
<th>Component Loading</th>
<th>Item</th>
<th>Component Loading</th>
<th>Item</th>
<th>Component Loading</th>
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<tbody>
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<td>Q2</td>
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<td>.711</td>
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<td>.642</td>
<td>Q14</td>
<td>.751</td>
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<td>Q7</td>
<td>.735</td>
<td>Q15</td>
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<tr>
<td>Q8</td>
<td>.584</td>
<td>Q16</td>
<td>.772</td>
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</table>

Follow-up PCAs were conducted separately at Time 1 and Time 2 for each of the original LSCQ domains to investigate coherence of the items within each domain and component loadings are presented in Table 10. These results, together with the domain indices of internal consistency reported previously, would appear to support use of individual LSCQ domain scores as indicators of QoL in specific health-related areas.
Table 10. *Component loadings of items on their parent domain at Time 1 and Time 2 derived from Principal Components Analysis*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Component loadings</th>
<th>Time 1</th>
<th>Time 2</th>
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<tr>
<td><strong>Somatic Sensation (% variance)</strong></td>
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<tr>
<td>Q1</td>
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<td>Q5</td>
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<td><strong>Cognitive/Psychological (% variance)</strong></td>
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<td>Q6</td>
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<td>Q7</td>
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<td><strong>Social Functioning (% variance)</strong></td>
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<td>Q11</td>
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<td>Q16</td>
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<td>.77</td>
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<td><strong>Physical Functioning (% variance)</strong></td>
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<td>Q18</td>
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<td>Q21</td>
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</tr>
<tr>
<td>Q22</td>
<td>.80</td>
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<td>.82</td>
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</table>

Domain and total scores were computed for each LSCQ timepoint and the relationships among scores were examined using Pearson correlations. Item-scale and item-total score correlations for Time 1 and Time 2 are presented in Appendix I. The results suggest strong associations between the LSCQ domain scores at Time 1 and more moderate associations at Time 2. These correlational patterns further suggest utility of a single score as an indicator of overall HRQoL.
As a final step, Principal Components Analysis was conducted on Time 1 and Time 2 LSCQ data without restricting the number of domains in advance. The factor structure and factor loadings of items on domains derived from Principal Components Analysis at Time 1 and Time 2 are presented in Appendix J. Four-item solutions were extracted at Time 1 and Time 2. At each timepoint, the 22 items appear to organize into different thematic groupings than observed for classical, generic domains originally used to construct the LSCQ. At Time 1, the four areas appear to group thematically as:

I) Social/Physical impact of disease (pain, fatigue, mood) – 12 items;  
II) Pain and Physical Functioning (without fatigue) – 5 items;  
III) Pain, fatigue, and School – 3 items; and  
IV) Treatment – 2 items (*note: too few to define a factor)*

At Time 2, the four areas appear to group thematically as

I) Social Impact of illness (Pain, Fatigue, and Treatment) – 7 items  
II) Mobility and Physical Functioning – 6 items;  
III) Interference of illness and treatment, or illness/treatment impact, and mood – 4 items;  
IV) Pain, Fatigue, and Cognitive/Mood Impact — 5 items.

A schematic of domain factor structure derived for the LSCQ at Time 1 through Principal Components Analysis appears in the top part of Figure 4, and illustrates the impact or influence of pain on three of four domains of HRQoL derived from the analysis as well as the collective contribution of all four domains to overall HRQoL (Total Score). The bottom part of Figure 4 presents a schematic of the domain factor structure derived for the LSCQ at Time 2
through Principal Components Analysis, and illustrates the impact or influence of both pain and fatigue on two of four domains of HRQoL derived from Principal Components Analysis as well as the collective contribution of all four domains to overall HRQoL (Total Score) at this timepoint.

*Figure 4.* Schematics of proposed LSCQ domain structure derived from Principal Components Analysis at Time 1 and Time 2
Question 3: Are common SCD patient group differences in HRQoL identified in studies using generic instruments also observed with use of the disease-specific instrument (LSCQ)?

Associations among child and parent characteristics

No significant associations were found for child characteristics of sex, genotype, severity, and disease complication categories. In families providing education data, boys were more likely to come from homes with higher parent educational attainment (i.e., education beyond high school) than girls ($r = .30, p = .003$).

Relations between child demographic characteristics on the LSCQ

Participant LSCQ scores at Time 1 and Time 2 were examined for any group differences that might exist based on child characteristics of sex, genotype, severity, and disease complications, and parent characteristics of education, employment status, and family income. Comparison of LSCQ domain mean scores and child demographic characteristics at Time 1 found no significant differences with regard to sex, age group, genotype (dichotomous variable of SS genotype compared to non-SS genotype), or disease severity (dichotomous variable of mild disease versus non-mild (moderate and severe disease). Significant differences were found for the LSCQ Somatic Sensation score at Time 1 based on the number of disease-related complications reported for the child. Participants reporting two or more disease-related complications had higher mean LSCQ Somatic Sensation scores ($M = 16.38, SD = 5.04$) than those with one or fewer disease complications ($M = 14.43, SD = 4.09; F(1, 98) = 4.31, p = .04$), with a small effect size ($\eta^2 = 0.04$). In terms of child treatment status, LSCQ Social Functioning score was significantly lower for children receiving additional treatments ($M = 17.79, SD = 5.46$) than for those not receiving additional treatments ($M = 20.30, SD = 7.09); $F(1, 98) = 3.925, p = .05$, with a small effect size ($\eta^2 = 0.04$). There were no significant differences observed on
LSCQ domains at Time 1 when examined in terms of parent education, parent employment or family income categories.

At Time 2, there were no significant differences found among LSCQ scores based on child characteristics of sex, age group, number of disease-related complications, genotype grouping, or severity grouping. A significant difference was found based on treatment group, with participants receiving additional treatment for SCD reporting higher LSCQ Physical Functioning mean scores ($M = 18.10, SD = 6.26$) than those not receiving additional treatments ($M = 15.43, SD = 4.19; F (1, 98) = 5.29, p = .02$, with a small effect size ($\eta^2 = 0.05$)). There were no significant differences observed when LSCQ Time 2 domain and total scores were examined in terms of parent education, parent employment or family income.

Analyses of variance were performed to examine group differences documented in the literature, such as sex, age group, genotype, disease severity, disease complication category, and SCD treatment category that might exist for the LSCQ and PedsQL based on the current sample. Group mean scores on the LSCQ and PedsQL at Time 1 and Time 2 are presented in Table 11.

**Group differences in Questionnaire scores based on Child characteristics at Time 1 and Time 2.** Time 1 – LSCQ. As previously noted, there were no sex, age-group, or disease severity-based differences found when LSCQ domain and total scores were compared based on these groupings at Time 1. Higher mean Somatic Sensation domain scores (associated with better HRQoL) were found for individuals reporting two or more SCD-related complications
Table 11. Means and standard deviations for LSCQ and PedsQL domain and Total Scores by child characteristic/group

<table>
<thead>
<tr>
<th>LSCQ domain</th>
<th>Sex</th>
<th>Age Group</th>
<th>Genotype</th>
<th>Severity</th>
<th>SCD Complications</th>
<th>SCD Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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PedsQL domain

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Note: LSCQ domains: SS = Somatic Sensation; CP = Cognitive/Psychological; SF = Social Functioning; PF = Physical Functioning; Total=LSCQ Total Score

PedsQL domains: HA = Health and Activities; AF = About My Feelings; GA = How I Get Along with Others; AS = About School; PH = Physical Summary Score; PS = Psychosocial Summary Score; Total = PedsQL Total Score

*Pair mean difference significant at p<.05 level
than for those reporting one or fewer SCD-related complications, $F(1, 98) = 4.31, p = .04$, with a small effect size ($\eta^2 = 0.04$). Individuals who were not receiving additional treatments for SCD had significantly higher scores on the Social Functioning domain of the LSCQ at Time 1 than those not receiving additional SCD treatments, $F(1, 98) = 3.93, p = .05$, with a small effect size ($\eta^2 = 0.04$).

**Time 1 – PedsQL.** There were no significant differences found in PedsQL mean score for sex, age-group, disease severity, and number of disease-related complications groupings at Time 1. Significant differences in mean score were found between SCD genotype grouping, with individuals with HbSS disease reporting higher mean scores on the Health and Activities/Physical Summary domain, $F(1, 98) = 3.94, p = .050$, with a small effect size ($\eta^2 = 0.04$); About School domain, $F(1, 98) = 5.67, p = 0.02$, with a small effect size ($\eta^2 = 0.05$); Psychosocial Summary domain, $F(1, 98) = 7.14, p = .01$, with a small effect size ($\eta^2 = 0.07$); and Total Score, $F(1, 98) = 8.13, p = .01$, with a small effect size ($\eta^2 = 0.08$) than those with other genotypes.

**Time 2 – LSCQ.** At Time 2, there were no LSCQ domain score mean differences found based on sex, age group, SCD genotype, or disease severity groupings; however, differences were found between those receiving additional SCD treatments and those not receiving additional treatments on the Physical Functioning domain, with higher mean scores reported for those receiving additional treatments for SCD, $F(1, 98) = 5.29, p = .024$, with a small effect size ($\eta^2 = 0.05$).

**Time 2 – PedsQL.** On the PedsQL About My Feelings domain, youths who were not receiving additional treatments for SCD reported higher mean scores than those receiving
additional treatments, $F\ (1,98) = 4.24,\ p = .042$. The mean PedsQL Total Score was also higher for youths who were not receiving additional treatments at Time 2, $F(1, 98) = 4.20,\ p = .04$, with a small effect size ($\eta^2 = 0.04$). At Time 2, significant differences were found by genotype grouping on the PedsQL About School domain, with youths with HbSS disease reporting higher mean scores, corresponding to better QoL, than youths without SS disease, $F(1,98) = 14.7,\ p = .000$, with a medium effect size ($\eta^2 = 0.13$).

**Question 4. Do child and parent factors predict domain-level and overall HRQoL when using the disease-specific instrument (LSCQ) in the same manner found for generic HRQoL instruments?**

Linear regression analyses were carried out to examine the predictability of the domain scores and total score of the LSCQ and PedsQL from child and parent characteristics at both time points. Child dichotomous variables entered as predictors included child characteristics of sex, age group (child or adolescent), genotype grouping (HbSS disease or other sickle genotype), severity grouping (mild or other than mild), treatment group (additional treatments or no additional treatments), number of disease-related complications reported (one or fewer complications or two or more complications), and WASI Full-Scale IQ score (continuous variable). Parent variables entered included parent education (high school or beyond high school), parent employment status (employed or not employed), and family income (below, or greater than/equal to $25,000 annually). Variables were not entered in order as the relative importance in explaining variance was not hypothesized in advance.

**Predictors of LSCQ domain and total scores**

*Time 1.* At Time 1, there were no significant relations between predictor variables and domain and Total scores of the LSCQ, $R^2 = .075$, adjusted $R^2 = -.03,\ F(9,81) = .73,\ p = .68$;
Cognitive/Psychological functioning domain score, $R^2 = .04$, adjusted $R^2 = -.06$, $F(9,81) = .40$, $p = .93$; Social Functioning domain score, $R^2 = .09$, adjusted $R^2 = -.01$, $F(9,81) = .90$, $p = .53$; Physical Functioning domain score, $R^2 = .09$, adjusted $R^2 = -.01$, $F(9,81) = .92$; and for Total Score, $R^2 = .07$, adjusted $R^2 = -.03$, $F(9,81) = .67$, $p = .74$.

**Time 2.** The regression equation was significant for LSCQ Total Score at Time 2 using child predictors alone, $R^2 = .22$, adjusted $R^2 = .12$, $F(10, 80) = 2.26$, $p = .022$, as was the regression model generated when parent/family variables were included with child predictors, $R^2 = .16$, adjusted $R^2 = .09$, $F(7, 83) = 2.29$, $p = .035$; however, addition of parent variables did not appear to offer increased predictive power to the equation ($R^2$ change = .06, $F(3, 80) = 2.00$, $p = .121$).

Regression equations were nonsignificant for the LSCQ at Time 2 for domain level scores: Somatic Sensation domain score, $R^2 = .08$, adjusted $R^2 = -.03$, $F(9, 81) = .73$, $p = .683$; Cognitive/Psychological domain score, $R^2 = .18$, adjusted $R^2 = .09$, $F(9,81) = 1.98$, $p = .053$; Social Functioning domain score, $R^2 = .15$, adjusted $R^2 = .05$, $F(9,81) = 1.55$, $p = .144$; and Physical Functioning domain score, $R^2 = .21$, adjusted $R^2 = .12$, $F(9,81) = 2.35$, $p = .04$.

**Predictors of PedsQL domain and total scores at Time 1 and Time 2**

**Time 1.** At Time 1, regression equations generated using child and family predictors were nonsignificant for the PedsQL total score level, $R^2 = .16$, adjusted $R^2 = .05$, $F(10, 80) = 1.51$, $p = .15$, and for domain-level scores, Health and Activities/Physical Summary Score, $R^2 = .10$, adjusted $R^2 = .004$, $F(9,81) = 1.04$, $p = .42$; About My Feelings domain score, $R^2 = .14$, adjusted $R^2 = .05$, $F(9,81) = 1.52$, $p = .16$; How I Get Along with Others domain score, $R^2 = .05$, $F(9,81) = .43$, $p = .92$; About School domain score, $R^2 = .11$, adjusted $R^2 = .02$, ...
$F(9,81) = 1.15, p = .34$; and Psychosocial Summary score, $R^2 = .15$, adjusted $R^2 = .06$, $F(9,81) = 1.64, p = .12$.

*Time 2.* At Time 2, regression equations using child and family predictor variables were significant for the About My Feelings domain score, $R^2 = .46$, adjusted $R^2 = .22$, $F(9,81) = 2.46$, $p = .016$, and About School domain score, $R^2 = .20$, adjusted $R^2 = .11$, $F(9,81) = 2.27$, $p = .025$. Regression equations were not significant for Health and Activities/Physical Summary score, $R^2 = .17$, adjusted $R^2 = .08$, $F(9,81) = 1.84, p = .074$; How I Get Along with Others domain score, $R^2 = .10$, adjusted $R^2 = .01$, $F(9,81) = .95, p = .49$; Psychosocial Summary score, $R^2 = .10$, adjusted $R^2 = .004$, $F(9,81) = 1.05, p = .41$; and Total Score, $R^2 = .14$, adjusted $R^2 = .04$, $F(10, 80) = 1.34, p = .23$. 
Chapter 4: Discussion

The present study focused on HRQoL reports of children and adolescents with SCD living and receiving care in a major Canadian metropolitan setting. The demographic and socioeconomic data profile of a large Canadian sample of pediatric patients with SCD has not been presented previously. Descriptive statistics obtained for the present study show that the participant sample had a balanced male-to-female ratio within each age grouping. Most subjects were in the pre- to early adolescent age range (mean age of 11.7 years). Approximately two-thirds of the sample had been categorized by their healthcare team as having a moderate or severe disease course within the previous year to two years based upon the working definition of severity used in the study. Just over one half (56%) of participants were identified as having two or more disease-related complications; however, the mean number of complications was 1.7. Intellectual functioning (represented by the WASI FSIQ-2 score), infrequently reported in HRQoL studies, measured toward the lower end of the Average range, with a mean standard score of 89.7, which ensured adequate reasoning ability to meet the demands of the tasks administered. Most parents responding were female, married, employed, and low-income earners. The sample is therefore largely comprised of pre-adolescent children from intact, low-income, two-parent homes. Child participants had average-range intellectual functioning, and were for the most part living with moderate to severe disease with some disease-related complications.

Interpretation of study findings for both the LSCQ measure and the widely used PedsQL measure would benefit from consideration of the unique characteristics of the sample. Canadian pediatric patients with SCD might share commonalities with children in other geographic regions, but could also differ from them in important ways. Although data from Canadian SCD
patients is typically merged with other samples as part of large-scale, multi-site (and international) studies, it could be of value to treat these participants as a distinct group. Variability of disease course among individuals with SCD is typical. It is also likely that ethnocultural, language, and family constellation-based factors are present that might influence children’s experiences, functioning, health, and health-related quality of life differently across international settings. While country of origin and ethnicity were not areas of focus for the present study, they are factors that may be relevant when contextualizing PedsQL and LSCQ data locally and when attempting to make comparisons to HRQoL data originating from other clinical centre. The PedsQL Acute version scores obtained in the present study were much higher than published self-report data (clinical and non-clinical samples) from the United States for pediatric patients ascertained during an SCD pain event (Brandow et al., 2010). For the US study, a median score range of 20.0 to 40.0 for domains, and 28.3 for Total Score during the pain event and median scores of 56.3 to 80.0 for domains, and 68.3 for Total Score reported for historical controls. Although patients in the present study’s sample were primarily those presenting for routine clinic visits and not necessarily experiencing active pain events in the manner of the clinical sample in the US study, it is notable that SCD patients in the present study’s sample reported overall QoL scores that exceeded those of healthy historical controls’ in the comparison study. This may speak to differences in symptom activity for individuals with SCD and variability in disease severity and course between samples, but perhaps points to population health differences that might exist internationally as well.

The LSCQ measure under study did not perform in like manner to the PedsQL gold standard. Aspects of each measure’s design could be one reason that young users might engage with the PedsQL and LSCQ differently, resulting in different patterns of response and response
consistency. For example, while both questionnaires use Likert-type scales, they differ in terms of numerical range, verbal anchors used, and even manner of presentation (computer-based versus pencil-and-paper-based). Young respondents must attend to these differences when filling out the scales. Although higher scores are associated with better HRQoL for both measures, at item level initially (prior to score transformation on the PedsQL), low values correspond to more difficulty in a given area on the LSCQ but are interpretable as absence of difficulty on the PedsQL following score transformation. When moving from one scale to another, respondents must attend to several kinds of ‘switches’ (in scaling direction, for example), and maintain this cognitive set while progressing through each measure. Printed, static instruction sets presented on paper for the PedsQL are helpful prompts in this regard, whereas verbal anchors change depending upon item content of the LSCQ and are only displayed on screen for the item being completed when progressing through the scale. Further, when completing the LSCQ, respondents must comprehend and interpret the spoken questions’ requirements with accuracy, contemplate and reflect upon a given experience, for example, pain or tiredness, and take care to restrict this assessment to the time period of interest, and then analyze the impact or interference of the experience as it manifests in different contexts and particular situations, such as when doing things with family or friends, or when taking part in sports. This could place more of a memory and reasoning demand upon the LSCQ respondent than would the PedsQL, which limits pain and fatigue experience to two individual items and asks about them in a non-specific way.

Differences in cognitive demand that may be required to complete the LSCQ and PedsQL measures may be linked to the nature of working memory demand that underlies their formats. The LSCQ, as a computer-based measure, relieves some burden upon the responder by having the computer read items aloud. Question text and response options remain on screen with audio
during the time that the item is active. Although young respondents did not navigate back-and-
forth through the program to revisit or alter previously-completed items for the sake of response
consistency, it was possible to do so. While requiring basic reading ability, the paper and pencil
form of the PedsQL readily facilitates back and forth movement among items, and the
opportunity to change or refer to previously-completed items during the process of completion, a
task less easily performed on the computer-based LSCQ measure. All items and relevant
instruction prompts (specifically, the one-week retrospective period of interest, the domain of
focus, whether school, emotional, social, or physical, and the numerical rating scale with verbal
anchors) remained visible on the paper questionnaire, in a ‘static’ form, at all times during the
questionnaire completion process, potentially easing some tracking and self-monitoring of
response functions and perhaps reducing the overall cognitive difficulty of the task.

The PedsQL devotes a relatively greater amount of item coverage to aspects of mobility,
treating physical functions of walking, running, and lifting separately, while also inquiring about
the ability to participate in activities of daily living such as doing chores and self-care. The
LSCQ, in contrast, places greater emphasis on emotional impact and possible meanings of
illness. Othersomeness of future worries pertaining to illness, disruptive effects of pain, fatigue,
treatment, and illness prevention steps on social activities involving friends and family are
queried. In addition, disease impact upon physical functioning, such as play and participation in
sports on HRQoL, is probed.

Response pattern differences observed between PedsQL and LSCQ scales likely reflect
expected differences in content specificity between generic and disease-specific instruments as
well as differences in theoretical frameworks and organizing principles underlying generic and
disease-specific measures. The LSCQ and PedsQL differ in terms of scope of their content and
thematic coverage. This may be observed when differences in treatment of pain and tiredness concepts between measures are examined. For the LSCQ measure, the four traditional domains serve as overarching organizers for their component items. In addition to the individual items querying pain and tiredness located within the Somatic Sensation domain, the impact of pain and tiredness is also examined as it might manifest in cognitive/psychological, social and physical functioning contexts. Pain and tiredness experiences are therefore queried in terms of their distributed effects across multiple domains. The LSCQ therefore provides different levels of specificity for determination of impact or interference of pain and fatigue, experiences central to the SCD experience, within the same questionnaire. The generic PedsQL measure, in contrast, devotes two individual items to the query of impact of pain (‘I hurt or ache’) and fatigue (‘I have low energy’) and confines them to the Physical Functioning domain alone. These concepts are not referenced elsewhere in the measure. Content contributing to a domain unique to the PedsQL, ‘School Functioning,’ is represented in both the Cognitive/Psychological and ‘Somatic Sensation’ domains of the LSCQ.

Finally, cross-format differences may play a role in the manner in which questionnaires are approached and completed by users. This is the basis for performing side-by-side comparisons or validation studies of paper and electronic measure formats of the same scale undertaken by many researchers as part of their investigations to verify equivalence. Although the purpose of the present study was not comparison of questionnaire formats, the possible impact of differences in questionnaire format referenced above, in addition to item content differences between measures, is not currently known, nor can its impact on observed response patterns between measures be determined without additional data.
Psychometric properties of the LSCQ

The findings regarding properties of the LSCQ will now be discussed as observed at separate timepoints.

Reliability

The LSCQ emerges as an instrument with high internal consistency. Cronbach’s alpha values for the domains ranged from .77 to .88 at Time 1 and .73 to .90 at Time 2. Item-total and item-scale correlations (between each item and its parent domain, presented in Appendix I for both timepoints), are within the ‘moderate’ to ‘strong’ range. The range of mean scores for individual items suggests that the lower to middle range of each rating scale, rather than the upper extreme (corresponding to ‘None of the Time’ or ‘Not Bothered’) was used by patients most often as a response option. Mean item-level scores for Somatic Sensation, Cognitive/Psychological Functioning, and Social Functioning items tended to fall in the lower range of the scale, corresponding to the verbal anchors of ‘Quite Bothered’ and ‘A good bit of the time,’ which suggests that participants experienced significant interference or impact of SCD within these domains. Item-scale associations that were highest between each item and its assigned domain at Time 1 and Time 2 demonstrated good item discrimination. There was modest evidence of stability in domain scores across timepoints, although associations were negatively-signed for each comparison. It is notable that most score fluctuations between Time 1 and Time 2, whether representative of worsening or improvement, occurred within the Social Functioning domain. This fits with the notion that disruption of socially-based activities by SCD symptoms might have particular salience for children and adolescents. The findings might also highlight the relatively greater sensitivity of socially-themed questionnaire items to changes in health status within an acute recall period.
Validity

Predictions were made regarding associations between LSCQ domains and PedsQL domains based on apparent similarities in thematic content. As has been noted, cross-measure associations between the LSCQ and PedsQL were decidedly less robust than within-measure associations at each timepoint. This was particularly true for the LSCQ, where domain intercorrelations were very high, statistically significant, and positively-signed. This suggests strong relations among items of the LSCQ. Correlations among the PedsQL domains were far more variable at both timepoints, in most cases failing to achieve statistical significance. These trends might arise from differences in the structure or theoretical framework underlying disease-specific and generic measures, with interdependence of items and domains anticipated in the disease-specific context (LSCQ), and relative independence of domains anticipated in the generic (PedsQL) context.

The hypothesized relations between the four domains of the LSCQ and comparable domains of the PedsQL did not occur in the expected direction or at the expected level of strength, as none of the correlations were found to be statistically significant. Nonetheless, weakly positive associations were found between the Somatic Sensation and Physical Functioning scales of the LSCQ and the PedsQL’s Health and Activities scale, suggesting some correspondence in content (and response consistency by participants) between these subscales of the two instruments. Low correlation values found for other cross-domain comparisons might have arisen as a consequence of limited sample size, differences in scaling between measures, and low response consistency on the part of participants from one scale to another.
Correlations between the Cognitive/Psychological domain of the LSCQ and the About My Feelings and About School domains of the PedsQL were not in the expected direction either within or across administration points and were also non-significant. There are a number of factors that might explain these findings. While the domains are broadly similar in content, there are also notable differences in coverage of the content between measures. Attention difficulties, for example, are addressed in the PedsQL’s About School domain but are not specifically measured by the LSCQ. Differences in specificity of item coverage were also present. For example, the LSCQ examines worries about future pain or SCD crisis as well as worries related to SCD’s effects on the future and potential offspring, whereas a single item of the PedsQL pertains to worry and queries it in a more generalized, open-ended way. It is reasonable that the future-oriented items included in the LSCQ might have been most meaningfully-interpreted by older adolescents, who made up a smaller proportion of the study sample than did younger children. This difference in the proportion between child and teen participants might have masked the particular impact of teen respondents’ contributions to these scores, and perhaps suggests the utility of having separate child and adolescent versions of the LSCQ. It is reasonable to anticipate differing patterns between disease-specific and generic measures given that patients may respond differently when reflecting upon aspects of their functioning as directly attributable to disease than when taking a more generalized view of factors underlying their overall well-being, as cued by the type of questionnaire that they are completing. The imperfect correspondence of the associations between the LSCQ and PedsQL items thus appears reflective of expected complementarity between generic and disease-specific measures and their ability to provide differing levels of specificity (construct representation; American Educational Research Association, American Psychological Association, National Council on Measurement in
about items and domains of interest.

The LSCQ Social Functioning scale and the PedsQL How I Get Along with Others scale were found to be weakly and negatively associated at both administration timepoints. This is an unexpected result, but as previously noted, may also arise from differences in item scope. The generic PedsQL measure refers to quality of social relationships in a general way but also includes items concerning peer exclusion and teasing that are not queried in the disease-specific measure, for example. As with other LSCQ domains, there is a fine-grained examination of the effects of pain and fatigue on social interactions in the Social Functioning domain, with a particular focus on personal social interactions and also social avoidance practices intended to minimize illness risk (for example, keeping away from others with colds or flu to avoid becoming ill), and querying the family impact of the disease arising from having to change plans or stay at home due to the child or teen with SCD’s illness. Differences in specificity, then, may also underlie discrepancies between domains that would appear similar in content across measures.

Differences observed in item content and specificity between given domains of the PedsQL and LSCQ may also arise from the manner in which item content was initially prioritized by study participants during measure development. As mentioned previously, a clinimetric ‘importance rating’ and item weighting approach was used to identify and retain items that would eventually make up the LSCQ. Ultimately, every questionnaire is a reflection of the developmental methods, processes, and even the nature of the respondents involved, with different developmental methods yielding different measures (Streiner & Norman, 2003). The pattern of findings appears to reflect concurrent similarity and complementarity in content
between the LSCQ and PedsQL and thereby, appears to demonstrate the merits of co-
administration of generic and disease-specific measures as a means of gathering comprehensive HRQoL information.

**Sensitivity**

For the present study, sensitivity of the LSCQ measure to change was measured by comparing observed change in LSCQ ratings between timepoints to a separate measure, the Global Rating of Change in Health scale, administered at the second visit. In the absence of statistically significant findings, it is noted that a small *decrease* in domain score ratings, perhaps too small to be meaningful, did occur for the group that did not endorse change. Difference scores for the group that did perceive and report change were positively-signed, suggesting that a mean QoL score increase had occurred between timepoints. This finding might imply that some *improvement* in HRQoL was perceived across timepoints by those endorsing a change in overall health, although of insufficient magnitude to reach significance.

There were also difficulties observed with use of the Global Rating of Change measure with respect to its ability to reflect both reported change and stability in PedsQL scores across timepoints. Significant change was detected between timepoints on PedsQL scores for both the group endorsing change in health and the group that did not endorse change in health based on the global rating. Notably, change (difference) scores were largest for Physical and Psychosocial Summary scales. Although these results did not reach significance, large effect sizes (absolute values ranging from .81 to .86) were observed for the group endorsing change in health, as might be expected, and smaller effect size absolute values (ranging from .02 to .69) were observed for the group that did not endorse change.
These results appear to highlight a number of common challenges with measurement of change. First, in the absence of some known intervention applied between timepoints, it is not possible to know if change detected between Time 1 and Time 2, whether improvement or worsening, has been detected ‘by chance’ or represents a true finding (Streiner & Norman, 2003). Consistency in response style is an additional consideration affecting interpretation of results, and is difficult to determine from two measurement points alone. Streiner and Norman (2003) acknowledge the complications that variability in individual responses contribute to the picture, and the (additive) interpretive difficulties that may arise given that “this same variability…is being used [to determine] the measure of responsiveness.” (p. 201). This creates a circular problem that can render outcome data difficult to interpret. Omission of a planned or prescribed intervention between testing administration points also prevented measurement of minimally-important change or minimum change in HRQoL that patients would identify as important and meaningful.

Inconsistencies in participants’ use of the 15-point Global Rating of Change Scale might also have affected efforts to determine the LSCQ’s sensitivity. Completion of the study measures required participants to make a ‘shift’ in timeframe and retrospective period, first, from one one-week recall measure to another (LSCQ, PedsQL), and at the second timepoint, to a two-week recall period when estimating change. This might increase the risk of recall bias, as the most recent events are likely to have enhanced salience and to have a greater likelihood of being recalled, and to form the basis of ratings. The process by which youths might go about summarizing and reporting on their experiences is not clear from the available data. Indeed, Streiner and Norman (2003) note that asking individuals to report change is frequently a flawed strategy due to recall difficulties and vulnerability of judgements regarding change to bias. Thus,
neither sensitivity to change nor responsiveness to clinically-meaningful change was successfully determined for the LSCQ during the study. Indeed, information regarding the events of the intervening period between testing points is needed to contextualize change scores through objective means. Obtaining this additional data, whether by interviewing participants or parents regarding salient health-related events (for example, SCD and non-SCD symptoms experienced; visits to the Emergency Room; completion of real-time pain diaries), or through collected laboratory data, could be a useful strategy for addressing these issues in future studies.

As noted by Brandow and colleagues (2010) and Dale and colleagues (2011) in their pediatric SCD HRQoL studies, short-term and chronic treatment events occurring close in time to child ratings of HRQoL (for example, home administration of pain-relieving medication), might reduce symptoms successfully and therefore influence participants’ perception and evaluation of their pain and overall health. To ensure that pertinent events were being included in the recall and estimation of overall health, it might have been useful to structure the task further by asking participants to identify and focus upon salient health-related events or to conduct a brief review of pertinent events since Time 1 with participants, perhaps involving parents, and to use nominated events as ‘anchors’ to aid the estimation and rating process. It is possible that the cognitive strategies required to estimate a concept like overall change in health are similar to those required for rating overall HRQoL in terms of summarizing multiple events and assigning this information an appropriate score. Disease-specific measures call for ratings of specific disease-attributed events that might infrequently occur during the period of interest, and therefore might not be taken into consideration by patients when rating health. The process by which respondents estimate or summarize health experiences and then translate them into a change score cannot be determined from review of the ratings or scores alone. Further, the
process by which SCD and non-SCD-related health events are distinguished by participants is unclear, and in the absence of direct questioning or prompts, the nature of the events that patients are recalling and incorporating when formulating their ratings is difficult to discern. Thus, the LSCQ’s apparent poor sensitivity to change might be related to the recall demands of the measures and the within-subject and between-subject variability in disease course inherent in the sample. Availability of objective, corroborative data about concurrent health-related events would support rating accuracy and interpretation of rating of change data, as mentioned. Furthermore, planned administration of the study measures prior to or concurrently with clinically-meaningful health events or known changes in health status, such as an admission for a pain-related episode (e.g., Brandow et al., 2010), would be a useful mechanism for testing the sensitivity of the LSCQ to changes in health status more directly.

Limitations of the study

The purpose of the present study was to establish the psychometric properties of the LSCQ to help determine its readiness for use. A number of methodological and instrument-based improvements might be made to improve the measure and facilitate future clinical and research use.

Generalizability

Generalizability refers to applicability of the results of a given study to a wider population beyond the testing sample or population. The source of data for this study may be one limitation to potential generalizability of the findings beyond the participating sample. All data were collected in a single specialized pediatric clinic setting and not through primary care physicians or other tertiary or community health sites. Contacts were also made during the
course of routine clinical care, and not at the time of Emergency Room presentation or post-admission (e.g., Brandow et al., 2010). Although the recruitment setting selected is unique in the region for its size and specialization and theoretically captures the majority of all active pediatric SCD patients from a variety of referral sources, newcomers unaffiliated with a primary care physician who have not yet been referred for services or received Emergency Room-based care, or those lost-to-follow-up given relocation or non-attendance over a period of time would not have been contacted as part of the recruitment process. In addition, there might be unknown but important differences in hospital clinic attendance for families living in close proximity to the hospital site versus those living in more distant parts of the Greater Toronto Area in terms of willingness to participate in the study. The characteristics of those not responding to an invitation to participate in the study are not known; however, differences between participants and non-participants, should they exist with regard to disease severity, complications, and course, English language facility, parent education and family functioning could also have consequences for generalizability. Although a response rate of 26% was achieved, a larger sample size would have been advantageous given the nature of the planned statistical analyses. Difficulties with recruitment rates for clinical and social science research have been reported for studies with a focus on SCD (Bonham, Haywood, & Gamble, 2007), and it has been suggested that opportunities exist to improve communication and foster trust relationships with identified racial groups that might promote greater openness to future study participation.

Age of the participants is another possible issue in the context of generalizability. Given that mean age of young respondents was less than 13 years for the present study, the findings may be most relevant to youth in that age range.
An additional barrier to generalizability may involve the apparent lack of Canadian, and specifically, African-Canadian child and adolescent norms for the PedsQL Generic Core Scales 4.0 (including the Acute Version of the measure) for the purposes of well-peer comparison. The Acute Version PedsQL data obtained for the present study were compared to available reference data reported in the literature for African-American children who had been administered the PedsQL Generic Core Scales (four-week version), and a single acute-care study using the acute/one-week version. Although the results obtained as part of the present study appear indicative of better QoL relative to those reported in the US-based studies referenced, a more contextualized understanding of the scores is hindered by the absence of available age- and gender-peer data for typically-developing of children without SCD. It is not clear, for example, whether Canadian and US samples would overlap significantly in terms of shared characteristics given probable differences in socioeconomic, geographic, and ethno cultural background, and in particular, possible differences in access to health care associated with differences in the funding of Canadian and American health care models. The absence of Canadian PedsQL normative population data thus hampers comparison of the current sample’s data to typical QoL profiles for children sharing similar health service access, educational, socioeconomic, and family or neighbourhood influences.

**Systematic measurement of pain, fatigue, mood, and anxiety, and their relationship to HRQoL**

Questionnaires with a specific pain, fatigue, anxiety, depression, coping, or locus of control focus were not incorporated into the present study’s design, which represents a limitation given the centrality of these constructs to QoL. Pain, mood and anxiety states, and appraisals about illness have been associated with poorer HRQoL in children with SCD and other chronic
illness in previous research (e.g., Burlew et al., 2000; Thompson, Gustafson, et al., 1998). Although the LSCQ and PedsQL questionnaires both devote a limited number of individual items to measurement of general pain and fatigue experience of patients (LSCQ item example, “How much were you bothered by [pain or tiredness] in the last week”), these items require patients to estimate or summarize the overall impact of pain or tiredness without the specificity in measurement of pain and fatigue concerns afforded by use of a dedicated questionnaire. In the present study, these constructs were not examined with specific instruments, primarily due to the increased response burden for participants and accompanying risks for attrition or incomplete data.

In addition, proxies used to infer the amount of interference of pain, such as the severity categories used in the present study, were reliant upon on counts of recorded clinic, Emergency Room, or hospital admissions that occurred within the previous year, and potentially underestimate pain episode counts occurring outside of these settings (Shapiro et al., 1995). Disease severity estimates tend to rely upon these medical chart-based counts, but no single pediatric SCD severity categorization is universally applied, making cross-study comparisons challenging (van den Tweel, van der Lee, Heijboer, Peters, & Fijnvandraat, 2010).

Pain, perhaps the most prominent symptom experienced by SCD patients, has been identified as a strong predictor of multiple domains of HRQoL in several pediatric SCD studies (for example, Fuggle et al., 1996; Kater et al., 1999; Schlenz et al., 2012), and has also been shown to contribute to decreased HRQoL in other child chronic illness populations (for example, spina bifida; Oddson, Clancy, & McGrath, 2006). Shapiro and colleagues (1995) note that pain episodes may typically be managed at home rather than in the hospital or clinic setting, and therefore may not be part of the patient’s clinical record. This makes tracking of daily pain
experienced outside of hospital or clinic contacts essential for capturing a patient’s typical experience. The PedsQL Multidimensional Fatigue Scale (Panepinto et al., 2014) and Sickle Cell Disease Module (Panepinto et al., 2013) forms, the latter developed following inception of the present study, exemplify the benefits of having dedicated scales which devote greater item coverage and allow more comprehensive assessment of the impact of fatigue and pain, respectively, on HRQoL. Use of validated pain and fatigue-specific measures in tandem with tools such as pain diaries for capturing well-being between assessment points might have been helpful for corroborating and interpreting experiences reported on the LSCQ and PedsQL as part of the current validation study, especially given that response consistency was of concern. Schlenz and colleagues (2012) also note the difficulty of determining and isolating the effects of pain given its inherent relationship or “shared variability with related constructs” (p. 779), those being the many child, family, and environmental variables that have been found to influence HRQoL in SCD in previous studies. Administration of a specific measure of pain might have been useful for determining how easily distinguishable the multiple forms of pain arising from SCD rather than other causes might be from the child or adolescent’s perspective, and whether participants were making these distinctions when completing the study measures.

Inclusion of screening measures for mental health concerns, particularly depression and anxiety, which are reported with some frequency in the pediatric and adult SCD literature, would also have strengthened the present study. It is not known whether there was increased or decreased presence or risk for these internalizing difficulties in this particular group of patients compared to those taking part in other reported SCD studies, nor is it clear that the administration of the LSCQ and PedsQL, which devote a varying number of items to mood and worry, were sufficient for discriminating between children with or without these concerns.
Coping, and with it, conceptualization of patients’ locus of control and self-efficacy, were not explored during this study, but have been linked to HRQoL. Indeed, the value of self-report is to gain information regarding patients’ perceptions of their health. Examination of patients’ valuation of health states was not a part of the present study’s objectives, but might have provided highly meaningful information. One British study (Constantinou, Payne, & Inusu, 2015) has employed a ‘gap theory’ approach to determining the discrepancy between perceived and actual or desired health from the young patient with SCD’s perspective. Health preferences (e.g., health utilities; Horsman, Furlong, Feeny, & Torrance, 2003) require similar valuation of health states from the perspective of patients and thereby, may provide a window into domains where intervention is needed most.

Recent studies of pediatric and adult SCD have also examined the nature of health-care contacts themselves, including patient-caregiver communication and care utilization patterns, as they pertain to patient well-being. While data on this topic were not captured as part of the present study, young SCD patients’ perspectives about and comfort with engagement with the healthcare team could reasonably have an impact on their perceived and reported HRQoL, as has been demonstrated with adults with SCD (Smith et al., 2005). Measuring the nature of these relationships might also have provided an opportunity to examine the manner of Canadian pediatric patients with SCD’s engagement with the healthcare system and any perceived barriers to care, as these may influence HRQoL. Measuring the quality of healthcare interactions and other potential barriers associated with treatment such as medication costs or travel distance might also be useful from the point of view of evaluating adherence to treatment (Barakat et al., 2005; Fisak, Belkin, von Lehe, & Bansal, 2012).
As previously mentioned, collection of additional objective and corroborative clinical data to accompany parent-reported disease complications in this study would have added descriptive specificity and information about pervasiveness of SCD’s effects on functioning. Beyond notation of SCD genotype and caregiver-assigned severity categories, the patient information collected might be expanded to include laboratory values that might modify pain experience, for example, persistent fetal hemoglobin, which reduces severity by disrupting HbS polymerization; hematocrit, as an indicator of anemia severity as well as blood viscosity and risk for associated complications (Rosse, Narla, Petz, & Steinberg, 2000); and hemoglobin levels, with higher values having been associated with better self-reported HRQoL in social and school functioning (Williams-Hooker, Olivi, Smeltzer, & Wang, 2012). More detailed data collection regarding school functioning, attendance patterns, grades, students’ assessment data, including cognitive, psychological, and adaptive functioning reports, along with confirmation of any diagnosed learning problems or school-designated learning exceptionalities beyond parent report alone (e.g., Anie, 2005; Fuggle et al., 1996) might also have helped to better contextualize the findings.

**Comparison measure breadth, formats and respondents**

The present study employed side-by-side comparison of a widely used general HRQoL measure with a new measure under development. While co-administration of scales in this manner is a standard approach to new measure validation, a possible limitation of the method in the context of this study was comparing measures of different formats, i.e., computer-based and pencil-and-paper forms. At the time of this study, a pencil-and-paper version of the LSCQ had not been developed or validated, but could have been useful to control for differences in user experience. Questionnaire formats must be chosen with care given known differences in
cognitive demand introduced by format as well as risk of bias. For example, paper-and-pencil measures could reduce working memory load inherent in computer-based measures by keeping key question text, information and prompts displayed and accessible at any time. Back-and-forth movement or navigation through the instrument is also easily done on a paper form, which might improve response consistency. On the other hand, having the computer-based questions read aloud in a standardized fashion potentially controls for difficulties with reading ability. Recall bias is a common issue for all formats; however, electronic self-administration is thought to reduce user demand and to lower the risk of social desirability response bias more effectively than interviewer or paper self-administered formats (Bowling, 2005).

Use of a single informant, in this case, a child or teen providing self-report data, rather than a multi-informant approach to validation, might also be seen as a limitation. Inclusion of parent- or caregiver-reported data has been mentioned in the research literature and cited as an important aspect of HRQoL assessment in children and youth. Concordant or complementary parent-child perspectives on child functioning may be revealed when compared to self-reported information (Connelly et al., 2005; Matza, Swensen, Flood, Secnik, & Leidy, 2004; Morrow, Hayen, Quinte, Scheinberg, & Craig, 2011; Varni, Limbers, & Burwinkle, 2007). Inclusion of the parent version of the PedsQL Generic Core Scales 4.0 Acute Version, which has been co-administered with the child self-report form to measure outcome in a pediatric SCD sample (e.g., Brandow et al., 2010) might have been one method of capturing both child and parent perspectives on child HRQoL and the relationships between them. In studies of children and adolescents with SCD, the consistency of youth self-reports could be unreliable where there is evidence of neurobehavioral complications, particularly attentional and other cognitive difficulties that might affect the ability to self-report with accuracy and optimal consistency.
(McClellan et al., 2008). Not all studies report concordant or complementary perspectives of child and parent HRQoL ratings in the chronic disease context and parent reports can vary significantly from youth reports, at times under- or overestimating distress or difficulty (e.g., Bakas, et al., 2012). In pediatric SCD studies, for example, parent reports of child HRQoL tend to report worse physical functioning than self-report of youths with severe SCD (McClellan, Schatz, Mark, et al., 2009; Panepinto et al., 2005). In addition, parent reporting of children’s internalizing states is dependent upon the quality of behavioural observations and extent of childrens’ health- and emotion-related disclosures to parents, and may differ significantly from child or youth’s self-report (Dampier et al., 2010). The well-being of parents themselves can influence reporting of their child’s HRQoL. Parent distress, mental health, coping, and family functioning have been linked to perceptions of distress in their child, particularly the child with a severe disease course, and potentially affect accuracy of proxy-evaluation of child well-being in pediatric SCD studies (Gil et al., 1997; Panepinto et al., 2010). Given the importance of parent functioning and child environment to HRQoL determination, Schlenz and colleagues (2012) have suggested collection of information about immediate family environment, including parent locus of control, and even neighbourhood and community-related factors as areas meriting further study. Parent reports remain a cornerstone of child HRQoL assessment given parents’ typical role in initiating and driving child engagement with medical services and their involvement in medical decision making (Janicke, Finney & Riley, 2001; Seid et al., 2004). Parents might also provide insight into aspects of child functioning outside of the context of clinic attendance, enriching or potentially capturing information pertinent to their child’s care that might have been under- or unreported by their child.
An alternative source of proxy-reports of child or youth HRQoL might be a ‘control group’ of peers matched on relevant demographic variables. Given shared environments, sibling controls have been included in some studies of SCD to study impact of a chronically ill child on family functioning as well as to measure parent or caregiver distress. Although there is not a shared diagnosis of SCD typically present, it has been noted that siblings of youths with SCD may also experience significant distress, worry, and different access to parental attention and resources (Radcliffe, Barakat, & Boyd, 2006). Taken together, reports from family members could also prove a useful means of screening for family functioning support needs.

Pediatric SCD studies that focus upon academic achievement and attainment have typically included classroom age or grade peers or siblings as a comparison group or have employed normative questionnaire data, when available, to provide context for the findings (e.g., Schatz et al., 2001). Indeed, such studies have been helpful means of comparing and contrasting obtained data with ‘typical’ profiles of children with and without chronic illness matched on relevant demographic bases. This is of particular value from the standpoint of understanding learning, developmental, and social milestone attainment, as well as what is typical with respect to internalizing or externalizing behaviour.

**Future directions**

Future refinements to the LSCQ will require a larger sample size and examination of the replicability of the present study. The measure would be strengthened by improved clarification of wording of items through additional testing and piloting, possible removal of items less likely to show change over acute periods, and increased information gathering regarding the internal and external influences on child and adolescent decision-making about their quality of life. Usability data and examination of side-by-side performance of computer- and pencil-and-paper-
based versions of the LSCQ will help determine what role questionnaire format might play in response patterns. Further validation steps might include addition of other generic HRQoL measures validated for use with SCD that differ in terms of domain breadth and scope, as these would be helpful for understanding the LSCQ’s performance and could potentially contribute to the collective knowledge base regarding HRQoL in African-Canadian youth. Indeed, there are now opportunities to test the LSCQ alongside an existing disease-specific HRQoL measure, the PedsQL Sickle Cell Module, mentioned previously, along with the PedsQL Generic Core Scales as part of a validation process. In time, a proxy or parent report form of the LSCQ measure might be developed, allowing for inclusion of proxy-reported data obtained from parents and perhaps siblings or peers, which could be helpful for examining concordance or complementarity of response patterns among various informants. Collection of qualitative data using think-aloud tasks or interviews, perhaps as part of a mixed-methods study design, would be particularly helpful where evaluation of perceived change in health is concerned. Adoption of more universal scaling or response stems, such as those available through PROMIS Pediatric Instrument Banks (e.g., Forrest et al., 2014) or drawn from frequently used generic QoL measures might be a method of improving response consistency during further validation steps. As previously mentioned, inclusion of more detailed objective or corroborative information that could be compared to HRQoL self-reports, such as laboratory values, pain diaries, and dedicated coping, mood, anxiety, self-efficacy, or locus of control measures might improve understanding of the roles that these constructs play in HRQoL assessment from the respondent’s point of view. Further work with the LSCQ instrument could lead to generation of separate versions of the LSCQ for child and adolescent respondents. As analyses suggest that pain and fatigue concepts are interwoven within each of the LSCQ’s domains, investigation into separability of these
constructs will be of value. Inclusion of additional questionnaire administration points may also be useful so that a sense of ‘baseline’ HRQoL scores may be obtained over time.

Ideally, administration of the LSCQ could be planned to coincide with a known treatment intervention so that pre- and post- measures, particularly of patient-reported change in health in response to intervention, could be determined against an objective, salient event, perhaps minimizing effects of recall bias. On a more routine basis, the LSCQ might be easily administered prior to, concurrent with, or in follow-up to physician assessment as part of patient monitoring. This would permit clinicians to quickly derive a child’s HRQoL profile and thereby enable rapid targeting of intervention in particular domains that are likely to produce important change for patients. Processes engaged to further refine the LSCQ measure may well identify items or domains not included in the current version of the LSCQ, for example, spirituality, that support and optimize child and youth functioning. They might also further our understanding of factors which contribute to resilience of children and adolescents with SCD, an area that is currently developing in the research literature (Karlson et al., 2012; Mullins et al., 2015) and is likely to expand the manner in which HRQoL scores might be interpreted. There is also a potential opportunity to collect valuable data using the disease-specific HRQoL measure prior to and during the process of transition from pediatric to adult SCD care to inform patient needs assessment, monitoring, and intervention planning. Finally, collection of further usability information on the LSCQ and refinements made to improve user experience would build upon earlier work with use of health technologies (e.g., McClellan, Schatz, Puffer, Sanchez, Stancil, & Roberts, 2009) in health outcome assessment in pediatric SCD.
Chapter 5: Conclusion

The LSCQ instrument demonstrates potential for discriminating between HRQoL of patient subgroups based upon the number of reported disease-related complications) and treatment status. Findings from the present study of the LSCQ’s psychometric properties confirm high internal consistency on an individual item and domain basis as well as for summary-level scores. Face validity was demonstrated by measuring associations between the LSCQ and domains of similar content making up a generic measure of HRQoL, with some expected differences in degree of coverage of thematic areas arising from differences in disease-specificity of the measures. The LSCQ was studied as part of a longitudinal rather than cross-sectional study design typical of most studies of HRQoL in this population. Sensitivity to change across timepoints, as evaluated by a patient-completed global measure of perceived change in health, was not established. This might have been related to inconsistency in patients’ self-reports about change, or to aspects of patient decision-making about change that are not objectively measurable. In addition, the inter-administration interval of two weeks might have been too brief a period to allow for and to capture meaningful change among the domains under study. Predicted correspondences across instrument domains and administration points were not confirmed; however, the study provides valuable longitudinal information concerning behaviour of the LSCQ and disease experience of pediatric SCD patients.

Overall, the LSCQ contributes to the literature by presenting results of a computer-administered, disease-specific HRQoL instrument for pediatric SCD to support a growing area of psychological and medical inquiry. It confirms that within the disease-specific context, domains of importance may differ from those measured by generic instruments and that some complementarity may exist between these types of measures. The computer-based format is
convenient and likely to engage children and youth. It could serve as a tool for rapid information delivery to the health care team to guide focused support for the child or youth, and could also be used as a relatively unobtrusive measure to monitor disease-specific quality of life status over time.

The study provides important self-report based information about a unique and understudied group with regard to psychological and holistic health outcomes. The study also provides unique and rarely reported longitudinal information about the HRQoL of Canadian children and adolescents with SCD. The primary value of the instrument and the present validation study might lie in the emphasis on engagement of children in reporting on their health, in order to capture what is normative or problematic for them in domains of functioning meaningful for them. It demonstrates that HRQoL in the disease-specific context might be at once unitary and multidimensional in nature. By asking young people with SCD about their health directly and valuing the patient’s perspective, we enable and empower them to guide us as providers toward actions likely to bring about optimal outcomes and concrete, meaningful improvements that will make a difference in their everyday lives.
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children and adolescents: natural history and impact on school attendance. *Pain, 61*, 139-44.


## Appendices

### Appendix A: Summary of studies providing self-report child and adolescent HRQoL data for SCD

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study description and objective</th>
<th>Subjects and outcome measures</th>
<th>Summary of findings</th>
<th>Implications for HRQoL in SCD</th>
</tr>
</thead>
</table>
| Fuggle, Shand, Gill, & Davies (1996) | To examine frequency and severity of all pain and illness events experienced by children and adolescent with SCD in the home and school environment  
- Comparison of children with SCD to healthy controls  
- Comparison of frequency and severity of pain in children with HbSS and HbSC disease  
- To survey children’s ability to discriminate SCD-related and non-SCD pain  
- Assessment of impact of pain on QoL and ways of coping with pain | N=25 children with SCD (14 HbSS, 11 HbSC) and N = 25 matched controls of similar age, gender, ethnic background and schooling (age range: 6 to 16 years)  
Measures:  
Children’s Health Diary, a semi-structured daily record of general health ratings and presence of 24 symptoms, including pain intensity, location, duration, coping methods, and whether pain was related or unrelated to having SCD (completed daily for 4 weeks)  
Chart review | - SCD group reported pain in 14 days, on average  
- Most pain events were treated at home  
- SCD group was more likely to treat pain events with medications than controls  
- Pain reported by SCD group was of significantly longer duration and frequency and higher levels than controls  
- Children with SCD able to discriminate SCD and non-SCD pain  
- 73% of pain events in SCD group reliably preceded by a symptom of poor health, including increased sleep disturbance | SCD group missed 3% of school days and social/recreational activities due to pain events  
Children with SCD were 7 times more likely to miss school due to pain events than controls |
| Kater, Heijboer, Peters, Vogels, Prins & Heymans (1999) | To compare parent-rated HRQoL of children with SCD with healthy immigrant children using multidimensional HRQoL measures | N=45 parents of children with SCD (child age range: 8 to 15 years), children 8 to 15 years of age in the sample, matched parent and child controls from a healthy reference group  
Measures:  
TACQOL (TNO-AZL Children’s Quality of Life Questionnaire – Parent form)  
TACQOL Child form for children 8 to 15 years of age | Children with SCD and their parents had significantly lower ratings/scores on physical, motor, independent daily functioning, and occurrence of negative emotions items.  
No significant group differences were observed for cognitive function, school performance, social functioning and occurrence of positive emotions items | Children with SCD experienced reduced physical functioning and possibly psychological well-being, but did not endorse decrements in cognitive or social domains of HRQoL |
| Palermo, Schwartz, Drobat, & McGowan (2002) | Multidimensional assessment of child HRQoL and parental burden in SCD patients and families; relationships between demographic risk factors, disease-related complications and child QoL. Demographic risk factors (lower parent education, unemployment, single marital status) predicted to relate to reduced HRQoL. Child age and gender (adolescence and male gender), high number of complications predicted to limit HRQoL. | N = 178 African-American children and adolescents (58 with SCD, 120 healthy controls) 5 to 18 years (mean age of 10.07 years) and caregivers.  
Measures:  
Demographics (caregiver report) and disease complications (chart review)  
Child Health Questionnaire (CHQ PF50) parent rating of child QoL in previous 4 weeks | Lower physical, psychological and social QoL, greater impact of child’s health on emotional well-being, personal time, and family activities reported by caregivers of children with SCD  
Physical health limitations in children with SCD predicted by older child age, female gender, and number of disease-related complications  
Children with SCD had more limited general health, physical functioning, limited schoolwork, and peer activities due to physical health, and more behavioral and mental health difficulties compared to controls | SCD significantly affects the HRQoL of children and adolescents  
Less adequate physical and psychological health in children and adolescents with SCD |
<table>
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<tr>
<th>Author (Year)</th>
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</tr>
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</table>
| Palermo & Kiska (2005) | To examine the relationship between pain, subjective sleep disturbance, functional disability, depression and HRQoL in adolescents with several pain-related conditions, to test depressive symptoms as a general risk factor for sleep disturbance. Authors hypothesized that, more intense, more frequently occurring and longer-lasting pain would be associated with increased sleep disturbance; depression symptoms would place adolescents at risk for more sleep disturbance, increased sleep disturbances would be associated with decrements in adolescents' daily functioning and QoL. | N=86 adolescents with juvenile idiopathic arthritis (JIA), chronic headache, and SCD (n=21 with HbSS and HbSC). Mean age of entire sample: 14.73 years, 67% female. Measures:  
  - Parent demographics questionnaire  
  - Provider assessment form (physician's classification and details of current treatments)  
  - Adolescent questionnaire: self-reported pain experiences in previous 4 weeks (frequency, intensity, duration, emotional upset)  
  - Functional Disability Inventory (self-report measure of ability to complete tasks of daily living)  
  - Major Depressive Disorders Subscale of the Revised Child Anxiety and Depression Scale (self-report child anxiety and depression measure)  
  - School Sleep Habits Survey (self-report measure of sleep habits during the previous 2 weeks)  
  - Child Health Questionnaire (CHQ-CF87) – generic self-report of HRQoL for adolescents | Similar sleep patterns and behaviours observed across groups except for daytime sleepiness, which was higher in adolescents with headache than other groups.  
  - Low but significant relationship between pain symptoms and sleep observed for the full group  
  - Headache group reported more daytime sleepiness, depression and disability compared to the JIA and SCD groups  
  - Depressive symptoms predictive of severity of sleep disturbances when demographics, pain, and functional impact controlled for. | Moderate to high correlations (relationships) between depressive symptoms, daily functioning, HRQoL and sleep; sleep disturbances linked to mood disturbance resulting in decreased daily functioning and HRQoL |
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<td>Pauerpuno, O’ Mahan, DeBaun, Rennie, &amp; Scott (2004)</td>
<td>To determine the validity of the Child Health Questionnaire (CHQ) as a measure of HRQoL for SCD by examining HRQoL and disease severity relationship in children not acutely ill. Authors hypothesized that patients with greater disease severity (based on disease complications) will have lower HRQoL compared to those with fewer acute complications. The CHQ was also predicted to discriminate between children with mild and severe disease.</td>
<td>Caregivers of 95 children and adolescents with SCD (mean age=10.2 years).  Measures: Chart review (neurobehavioural comorbidities, health status, demographics) and a priori classification of patients as mild or severe (more than 3 hospitalizations for vaso-occlusive crises in previous 3 years), independent of genotype. Child Health Questionnaire—Parent Form (PF-28) — parent completed HRQoL measure based on child’s health in previous 4 weeks.</td>
<td>Reliability of each CHQ subscale (except General Health Perceptions) acceptable (0.75 on average) and comparable to previously-published data in healthy children. Children with mild disease reported better physical QoL than those with severe disease. Mild disease group had higher scores on Global Health, Physical Functioning, Role/Social. No differences in psychosocial HRQoL were observed between the mild and severe groups. No differences in physical QoL observed between group treated with hydroxyurea or chronic transfusion and those receiving neither treatment.</td>
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<td>Stegenga, Ward-Smith, Hinds, Routhneaux, &amp; Woods (2004)</td>
<td>Semi-structured individual and group interviews to determine impact of CTT on child’s QoL from the child’s perspective. Use of a phenomenological qualitative design for theme extraction and analysis.</td>
<td>Children with HDSS disease receiving chronic transfusion therapy (CTT) • N=10 participants (4 male, 6 female); 6 – 12 years of age (M= 9.5 yrs) • Time on CTT: range of 13 to 102 months • n = 5 with previous history of stroke Measures: Six interview questions re: child perceptions of general impact of SCD on daily life, impact of CTT on child’s lifestyle, beliefs about perception by others; what child would and would not want others to know about own CTT.</td>
<td>Five themes identified, each related to having SCD: Pain (physical and psychological impact); school issues (low attendance and impact on progress and teacher/peer relations); disease knowledge; transfusion therapy; having a stroke.</td>
<td>- Confirms impact of CTT on QoL of children with HDSS  - CTT as a positive medical intervention, especially for those with history of stroke  - Necessity of hospitalization during CTT has greatest impact on QoL.</td>
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<td>Barakat, Luz, Nicolaou, &amp; Lash (2005)</td>
<td>To investigate associations among parent locus of control, family functioning, and QoL of children with SCD. External parent locus of control predicted to be related to lower family functioning and poorer child QoL; reverse relationship expected for internal parent locus of control. Mothers of children with greater disease severity predicted to report greater external locus of control than mothers of children with milder disease.</td>
<td>M=31 primary caregivers of children with SCD (newborn through 11 years of age). Measures: Parent Locus of Control Scale McMaster Family Assessment Device Miami Pediatric QoL Questionnaire Demographics Medical chart review</td>
<td>Higher levels of external locus of control reported by parents with children with SCD than parents of healthy children (normative data) No association found between disease severity and parent locus of control found Total parent locus of control score negatively correlated with family functioning.</td>
<td>Parent locus of control associated with child QoL, especially for self-competence. Marginal significance with QoL social competence.</td>
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| Panevinto, O'Mahar, DeBau, Lobeniza, & Scott (2005) | To describe HRQoL of children with SCD from parent and child perspectives, and to compare the relationship between the two. To determine the association of parent, child, and disease characteristics on HRQoL of SCD | N=53 children and adolescents with SCD (age range: 5 to 18 years) and N=95 parents Measures: Parent and child demographic data Comorbidities (medical and neurobehavioural) Medical chart review Child Health Questionnaire (CHQ-PF28 completed by parents of children 5 to 18 years; CHQ-CF87 self-report completed by children and adolescents 10 to 18 years only) | Parents reported worse child HRQoL compared with child report in domains of overall perception of health, physical functioning, behaviour and self-esteem Children and adolescents reported poorer physical functioning than healthy peers (significantly lower physical and psychosocial domain scores) Strong parent-child agreement in terms of impact of bodily pain on HRQoL; moderate agreement in physical functioning, behaviour, general health, self-esteem and changes in health domains. Children did not view themselves as having worse psychosocial HRQoL as peers Neurobehavioural comorbidities (e.g., attention problems) were associated with worse psychosocial HRQoL Disease status, neurobehavioural comorbidities and parent education positively associated with child HRQoL. | Children with SCD have lower HRQoL as measured by standardized, generic measures, especially in terms of physical functioning There is concordance between parent and child ratings of HRQoL and impact of bodily pain, and ratings of physical functioning, behaviour, general health, self-esteem. Including both parent and child perspectives in the measurement of child HRQoL is recommended. The presence of two or more neurobehavioural comorbidities has a significant impact on HRQoL, particularly psychosocial functioning.
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<td>Patel &amp; Pathan (2005)</td>
<td>To assess QoL in SCD by developing an interview-based multidimensional disease-specific scale. To identify specific domains most affected in children with SCD and sickle cell trait.</td>
<td>N=52 children 8 to 14 years of age (n=25 with 'sickle cell anemia'; 12 with sickle cell trait; 13 normal controls)  Four domain (Functional, Health Perception, Opportunity and Morbidity) interviewer administered scale validated for use in the study.</td>
<td>Children with SCD more affected than children with sickle cell trait and healthy children on all areas measured.</td>
<td>Children with SCD report decreased functioning in social, cognitive and physical domains, and note the impact of pain on functioning compared to healthy peers.</td>
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<td>Palermo, Riley &amp; Mitchell (2008)</td>
<td>“To examine relationships between individual/family and neighbourhood socioeconomic distress, pain, functional outcomes in children with SCD”</td>
<td>N=47 children 8 to 17 years (mean age 12 yrs) with HbSS, n=5 HbSC, n=4 HbSβ+ Thalassemia. 57% male sample. Child: Faces Pain Scale: Revised Child Anxiety and Depression Scale (Major Depressive Disorder subscale based on previous week’s symptoms); Functional Disability Inventory. Physician (attending hematologist): pain severity rated by attending hematologist based on Visual Analog Scale (&quot;not severe at all&quot; to &quot;extremely severe&quot;). Parent: Child Health Questionnaire (PF50) based on previous 4 weeks; Functional Disability Inventory.</td>
<td>Increased depression correlated with increased disability. Family income a predictor of child report of functional disability. Higher family income associated with less disability. Distressed neighborhood associated with reduced physical HRQoL. Greater depression and disease severity associated with worse psychosocial HRQoL. Higher family income associated with worse psychosocial HRQoL. Higher parent education associated with better psychosocial HRQoL. Neighborhood distress not a predictor of psychosocial HRQoL.</td>
<td>Demonstrates the impact of child mood and family income/SES on child disability in SCD. Parent education is shown to be related to better psychosocial HRQoL. Depression and more severe disease are associated with poorer child psychosocial HRQoL by parent report. Environment (neighbourhood) distress is tied to child physical HRQoL, believed due to school funding limitations, community safety concerns, and limited physical education opportunities for children.</td>
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<td>McClellan, Schatz, Sanchez, &amp; Roberts (2009)</td>
<td>Evaluation of the validity of the PedsQL for SCD</td>
<td>( N = 84 ) children 5 to 18 yrs (Mean: 12 yrs) at pediatric haematology/oncology clinic. Half of the sample was female and most insured through the state Medicaid program. &quot;Low&quot; mean haematocr (28.6%) at intake. pedestriansQL core scales (one month retrospective period). Parent proxy-report and youth self-report, medical chart review and parent report of disease and learning complications and comorbidities within the last 2 years.</td>
<td>Reliability: parent report Cronbach's ( \alpha ) values 0.8 or higher for all scales but School Functioning (low internal consistency for all responders). Youth reported lower values for all scales but Total score and Psychosocial Summary score. Young children provided lower internal consistency scores for self-ratings than older children. Validity: Cross-informant correlation for parent and child report was ( r ) (16) = .41 for total sample, ( r ) (36) = .32 for children &lt;13 yrs, ( r ) (32) = .52 for children &gt;13 yrs and older (all correlations significant at .05 level and lower). School functioning rated significantly lower than Physical Health, Emotional Functioning and Social Functioning across informants. Youth rated Emotional Functioning as significantly lower than Social Functioning, while parents rated Emotional functioning and Social functioning significantly higher than Physical Health. Total scores measured significantly lower than population-based African American sample for both self- and parent report. Parents of children with neurobehavioral complications reported lower total and domain-based HRQoL than parents of youth without these concerns. Parents reported poorer School functioning and youth reported lower HRQoL when history of major pain episodes present.</td>
<td>Internal consistency data and weak evidence of discriminant validity suggest PedsQL may best serve as an overall measure of HRQoL than a domain-based one, due to instrument limitations for those underlying HRQoL in SCD. When criterion groups (pain vs. neurobehavioral complications) compared, youth reported differences in school functioning only (neurobehavioral group). Youth with pain episode history reported lower HRQoL than those without this history. Some queries re: validity of self-report for HRQoL in children with neurologic disease after Panepinto et al. 2005. Parent proxy-report may not be as sensitive to pain-related effects on functioning as self-report. Obtaining both parent and child report may be of particular value when evaluating young patients with neurological and pain histories.</td>
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<td>Panevoto, Pajewski, Feurster, Sabans, &amp; Hoffman (2009)</td>
<td>To determine the impact of family income on the HRQoL of children with SCD</td>
<td>N=104 children with SCD, 74 age-matched controls (children without SCD). Participants were drawn from academic children's hospital (children with SCD) and from an urban centre (controls, majority on public insurance). Measures: PedsQL generic scale (4-week retrospective): parent proxy report (by age category/questionnaire version: 2 to 4 years; 5 to 7 years; 8 to 12 years and 13-18 years) and child self-report (5-18 yrs.); stratified family income (&lt;$20,000 USD, between $20,000 USD and $40,000 USD, more than $40,000 USD annually, a priori SCD severity rating as severe (history of stroke, acute chest syndrome, three or more hospitalizations for vaso-occlusive pain events within the 3 previous years and/or recurrent priapism) or mild (not meeting these criteria): parent-report of one or more medical comorbidities (e.g., diabetes, epilepsy, asthma, allergies) and neurobehavioural conditions (e.g., anxiety, attention, depression, intellectual disability, speech, learning problem)</td>
<td>Sixty-six of participants with SCD had HS5S disease, 26 had HbSC disease. Asthma was the most commonly-reported medical comorbidity in children with SCD, though controls reported more medical comorbidities than did those with SCD. Of the SCD group, parents reported 40.4% of children had some neurobehavioural comorbidity (attention, behaviour, learning most frequent; comparable for controls) and 28% had some medical comorbidity (asthma most frequent for SCD and controls). Based on parent-reported PedsQL values, children with SCD had significantly lower PedsQL summary scores, social and school functioning scores. On PedsQL self-report, children reported significantly lower physical health summary score only. Children with SCD were found to have (4.66 times) higher odds of having worse total HRQoL than controls. Having medical comorbidities, older age, lower family income were associated with worse physical HRQoL. Children with SCD were found to have increased odds of poorer psychosocial HRQoL compared with controls. Older child age and presence of medical or neurobehavioural comorbidities was linked to poorer psychosocial HRQoL. Based on child self-report, severe disease was associated with 3.33 times increased odds of worse physical HRQoL. No disease group or poverty level interactions with HRQoL were found.</td>
<td>Children with SCD have lower HRQoL than children without SCD adjusting for income and other covariates. Older child age, severe SCD with comorbidities, and low family income associated with poorest HRQoL. Impact of SCD is made greater given that many children live in poverty and also have neurobehavioural and medical comorbidities present. SCD patients are a unique group as no other chronic disease primarily affects individuals from poor minority background. Effect of family income found for both SCD patients and for controls, whose family income was lower. Research into impact of treatment for comorbidities affects disease status. Further work also needed into whether disease and poverty lower child perception of HRQoL. Disagreement between child and parent reports is not unusual as past research cites discrepancies between proxy and self-report of child HRQoL. Lack of a disease-specific tool may have reduced ability to detect impact of disease and family income on child self-report. Study limitations include cross-sectional design: no info about family income over time. Other measures of SES, such as material deprivation not recorded. Drawing participants from convenience sample might’ve meant results less generalizable.</td>
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<td>Brandow, Brousseau, Pajewski, &amp; Panebunto, 2010</td>
<td>To study HRQoL of pediatric patients with SCD at medical visit for a painful event to examine generic HRQoL measure’s ability to detect change over time during a painful event.</td>
<td>N = 57 patients, 52% female, mean age 10.7 yrs. Presenting to the Emergency Department of a U.S. children’s health center. Historical SCD group for comparison (data not shown). Parent-reported demographic information. A priori categorization as having frequent or infrequent pain events in the 3 years prior to study participation. Pain scale used in Emergency Dept triage (0 to 10 from no pain to worst pain). PedsQL Acute Version (7-day recall period) generic core scales, Parent and Self-Report, administered in the Emergency Department and again one week following discharge by telephone.</td>
<td>Child self-reports: median HRQoL scores were significantly lower at Emergency Dept visit summary and subscale scores for children with pain events than controls. Parental reports followed a similar pattern, though no significant differences for social and school functioning; and QoL scores at Emergency Dept. presentation were higher than child self-reports. Median HRQoL scores increased significantly between the two time-points for all subscales except parent report of school functioning. All child report subscale scores met criteria for ability to detect Minimal Clinically-Important Difference.</td>
<td>Children appear to return to baseline HRQoL following discharge post-painful event. Generic measure of HRQoL shown responsive to change during an acute vaso-occlusive painful event. Acute painful events significantly affect child physical, social, emotional, and school functioning. Supports notion that parents may tend to rate HRQoL more highly than child, particularly for the most severe pain episodes. Child age, nature of the HRQoL domain, child pain level and nature of parent HRQoL and well-being may play a role in self-perceptions of pain events.</td>
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<td>Dampier, Lieff, LeBeau, Rhee, McMurray, Rogers, Smith-Witterly, Wang, &amp; CSMM CTC Site Investigators (2010)</td>
<td>Purpose was to produce a descriptive study of HRQoL in pediatric SCD, as measured by the PedsQL version 4.0 generic core scales and fatigue scales</td>
<td>N = 1772 subjects (35% boys, mean age 9.6 yrs. 68% of sample SS or SβThal genotype; remainder made of up SC or Sβ Thal genotype. PedsQL generic core scales and multidimensional fatigue scale were parent- and self-administered for 8 to 18 year olds and interviewer-administered for 5 to 7 year-olds. Medical record review of medical conditions, disease complications, co-morbidities; Parent and self-report of number of acute care visits for pain and number of missed school and work days due to pain in previous year.</td>
<td>Parent scale reliabilities (Cronbach’s alpha values) were higher (range: 0.79 to 0.95) than child self-reports (0.69 to 0.88). Mean PedsQL scale scores typically higher for self vs. parent report, but lower than healthy age-matched controls. Female child gender associated with worse parent-reported physical functioning and sleep/rest fatigue scales and worse child-reported physical, emotional, total, general, sleep/rest and cognitive fatigue scales. Higher parent-reported QoL scores for the SC-Sβ-thalassemia group vs. SS/Sβ for total physical, school functioning and self-reported total, physical and social functioning. Lower parent and self-report for groups with hospitalizations vs. none in prev. 2 yrs. School/work days missed predicted with lower QoL measures, esp. school.</td>
<td>Lower self and parent-reported HRQoL, especially for physical and social functioning domains for children and adolescents with SS/Sβ-Thal than SC-SA-thal-SB. Increased frequency and prevalence of chronic complications with age and gender differences (worse for females) in pain frequency replicated, per the literature. Complications of avascular necrosis of hip/shoulder or sickle cell pain and arthralgia emerge as predictors of poorer parent-reported physical functioning and sleep/rest fatigue scales, and poorer parent-reported school functioning. Priapism history also linked with poorer outcome. School and (parent) work absenteeism associated with poorer parent and self-reported HRQoL.</td>
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<td>Hijmans, Fijervandaat, Oosterlaan, Heijboer, Peters, &amp; Grootenhuis (2010).</td>
<td>Aim is to determine HRQoL of children with SCD compared to healthy sibling in the Dutch population</td>
<td>N = 40 randomly-selected children with SCD and 36 healthy age- and gender-matched siblings 6 to 18 years of age from an Amsterdam Children's Hospital. KIDSCREEN Generic self-report measure (one-week retrospective period). Cognitive debriefing for younger participants.</td>
<td>Children with SCD had significantly lower HRQoL score on the Physical Well-Being domain only compared to healthy siblings. When compared to larger Dutch population, children with SCD had significantly lower scores on Physical Well-Being, Moods &amp; Emotions, Autonomy, Parent Relation and Financial Resources domains. Healthy sibling controls also scored significantly lower on Mood &amp; Emotions, Parent Relation and Financial Resources compared to Dutch norms. Six to eleven year-olds with SCD had significantly lower HRQoL on Physical Well-being, Moods &amp; Emotions, Self-Perception, Autonomy, Parent Relation, Financial Resources, and Bullying domains compared to Dutch norms. Their siblings had significantly lower than norm scores on Autonomy, Parent Relation, and Financial Resources scales. Twelve to 18 year-olds with SCD had lower Autonomy than healthy siblings and Dutch norm population. Healthy sibs in this older age group differed from Dutch norms on Moods &amp; Emotions scale only. Proportion of siblings with impaired Moods &amp; Emotions, Autonomy, Parent Relation and Financial Resources domain was greater than proportion in Dutch population.</td>
<td>HRQoL in children with SCD is lower across scales compared with healthy peers. Implies reduced HRQoL in children with SCD linked to low SES. Physical functioning and autonomy domains may be particularly affected in children with SCD. Scores may reflect focus on self-report procedure, and absence of parent proxy response. Adolescent group appears more resilient than other studies would predict, perhaps due to coping style and adjustment, which should be investigated further in longitudinal manner. Youths with SCD did not report social and school environment difficulties, perhaps reflecting adjustment to functioning in these environments.</td>
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<td>Dale, Cochran, Roy, Jernigan, &amp; Buchanan (2011)</td>
<td>Purpose is to assess HRQoL in children and adolescents with SCD</td>
<td>( N = 124 ) children and adolescents (Mean age: 13.0 years), 52% male sample, average of 3 days of reduced activity with need for care due to SCD, 50% hospitalization rate and 74% Emergency Dept visit rate in the previous year for sample. Sample was homogeneous, composed of HbSS and HbSS+Thal patients only. Parent and self-report versions of the PedsQL 4.0 generic core scales administered. Demographic information and details of impact of child illness on missed school days and family (including missed parent work days), number of days of hospitalization and Emergency Dept time collected.</td>
<td>Children with SCD had significantly lower overall HRQoL than reported for healthy children and African American child samples (more than one SD below norm by both parent and self-report). Increased hospitalizations were associated with lower HRQoL, school functioning scores. Number of hospitalizations and Emergency Dept. visits was inversely related to overall HRQoL. Parents tended to perceive report lower HRQoL than did children and adolescents themselves.</td>
<td>Children with SCD have reduced HRQoL compared to healthy peers. Greater number of hospitalizations associated with lower school functioning and overall QoL. Parent and child report of HRQoL were discordant, with parents tending to report lower QoL than children did.</td>
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<td>Ziadni, Patterson, Pulgaron, Robinson, &amp; Barakat (2011)</td>
<td>Study aim was to examine the way that stress processing variables (that is, appraisals, and pain coping style/strategies) support resilient (adaptive) behaviour in adolescents with SCD</td>
<td>( N = 44 ) adolescents with SCD from an urban health centre, 87.2% African American and 52.3% male, mean age 15.3 years. Information form and medical chart review. Means Pediatric Quality of Life Questionnaire: (generic measure) self-report, Children’s Hope Scale (self-report), Coping Strategies Questionnaire (self-report), Behavior Assessment System for Children (BASC) self-report.</td>
<td>QoL was positively associated with BASC Interpersonal Relations and Self-Esteem scales, and more weakly related to Relations with Parents and Personal Adjustment Composite. Coping Strategies Questionnaire scores was positively correlated with BASC Personal Adjustment Composite, Interpersonal Relations and Self-Esteem; more weakly linked with Relations with Parents. Adherence (Coping Strategies Questionnaire) was not related to Self-Reliance. Hope associated with Self-Esteem but not other adaptive behaviours of the BASC. At higher levels of Hope, higher HRQoL was associated with higher adaptive behaviour, and poorer HRQoL associated with lower adaptive behaviour. These findings were not observed for low levels of Hope. ‘Adherence’ on Coping Strategies Questionnaire was not a moderator of HRQoL and adaptive subscales.</td>
<td>Poorer HRQoL linked to less adaptive behaviour. Stress processing variables of adherence, hopeful appraisals were associated with more adaptive behaviours. There may be a moderating effect of stress processing variables on HRQoL and adaptive behaviour, as adolescents using more adherence coping and Hope-oriented appraisals endorsed higher adaptive behaviour. Demands of self-care that adolescents with SCD build over time may build sense of competence. Reinforcing and supporting adherence behaviours i.e., medical recommendations may be of value to improve HRQoL.</td>
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<td>Lim, Welkow, Cohen, &amp; Osunkwo (2012)</td>
<td>To examine racial identity's role in moderating pain and thereby, effects of HRQoL in children with SCD.</td>
<td>$N = 100$ children with SCD from 8 to 18 yrs. (mean age: 13.0) attending outpatient care at a children's hospital. Sample was 59% female and made up of 69% patients with an HoSS diagnosis. Measures background information from: Pediatric Pain Questionnaire, Multidimensional Inventory of Black Identity, Pediatric Quality of Life Inventory, a priori disease severity determined by clinic nurse using Visual Analog Scale</td>
<td>No gender differences in overall pain. Males reported higher physical and emotional scores on the PedsQL than did females. Older age was associated with PedsQL social scale and disease severity measure. Disease severity was positively associated with overall pain and negatively correlated with PedsQL total and physical scales. Children with greater pain reported lower HRQoL. Regard (Identity measure) was positively correlated with PedsQL social subscale. Children with low pain and high regard racial identity reported higher QoL than those with low pain and low regard racial identity.</td>
<td>Pain and HRQoL negatively associated. Racial identity may serve as a protective factor for children with SCD and may be an important consideration in understanding the impact of pain and HRQoL for this population. Positive racial identity may support social and physical functioning in children with SCD, but may interact differently with other aspects of HRQoL.</td>
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<td>Schlenz, Schatz, McClellan, &amp; Roberts (2012)</td>
<td>To measure responsiveness of PedsQL (parent/caregiver report) to pain-related changes in physical, psychosocial, and overall HRQoL.</td>
<td>$N = 81$ caregivers of children with SCD. Children rated were mean age of 11.94 years, 46% female and 64% HoSS. $N = 49$ had a history of neurobehavioral complications, and $N = 61$ had a history of medical complications. Mean # pain episodes between Time 1 and Time 2 was 1.59. Measures PedsQL 4.0 generic core scales, parent version; medical chart review; collection of demographic information: history of healthcare contacts for pain between Time 1 and Time 2</td>
<td>For this sample, HRQoL scores were more variable at low levels of pain and less variable when number of pain episodes increased. Pain episode frequency between Time 1 and Time 2 predictive of changes in physical, psychosocial and overall HRQoL. Pain accounted for a significant amount of variance in all measures.</td>
<td>Important to examine responsiveness to change in specific aspect of health when evaluating a measure. Neurobehavioral complications did not emerge as significant predictors in the regression models. Caregiver reports may demonstrate sensitivity to changes in psychosocial HRQoL, an aspect that has been poorly estimated by proxy respondents in other studies. Reliance on healthcare utilization as a disease severity indicator may underestimate actual number of pain episodes, as most are treated at home.</td>
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<td>Beverung, Strouse, Hulbert, Neville, Lien, Imusa, Fuhr, King, Meter, Casella, DeBaun, &amp; Panepinto (2014)</td>
<td>To determine the effect of chronic transfusion on HRQoL of a group of children and adolescents with SCD</td>
<td>N = 99 patients randomized to a transfusion group (received monthly for 36 months) and N = 97 patients randomized to an observation group (standard care every 3 months received over 36 months). All participants ranged from 6 to 16 years (mean age: 9.55 yrs.), and sample was 43% female. Measures: parent-completed Child Health Questionnaire (PF50), admitted at entry to the study and following 36-month study period.</td>
<td>No significant baseline difference in HRQoL between the study groups. All differences were found at the study endpoint. Transfusion group had higher physical function, lower bodily pain, and improved overall (change in) health at Time 2. No significant changes in physical health, bodily pain and overall health were found for the observation group between Time 1 and Time 2.</td>
<td>Parents perceived benefit from chronic transfusion. Finding of improved physical, pain level and overall health as a result of chronic transfusion is supported by literature noting reduced pain, hospitalization and acute chest syndrome report for children with SCD on chronic transfusion therapy.</td>
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<td>Constantinou, Payne, &amp; Imusa (2015)</td>
<td>To examine the HRQoL of children in the United Kingdom; to measure child self-reports of HRQoL using a 'gap theory' measure (comparison of current QoL to ideal state QoL); to examine differences between self-reports and proxy (parent, health professional reports) of HRQoL, to determine relationships between demographic and disease severity variables where differences between groups exist.</td>
<td>N = 74 children with homozygous SCD in London, UK. Mean age 10.6 years, and sample was 65% female. Parent and health professionals also participated. Data from 65 healthy controls were used for comparison purposes. Generic Children’s QoL measure (CCQ) was completed by children with SCD, parents, and health professionals comparing perceived/current ratings with preferred/ideal self-ratings. Demographic data, medical admission, crisis and school absenteeism counts and neurological event data were also collected.</td>
<td>Good reliability on current and preferred form ratings for all participants. No significant differences found between children with SCD and matched controls on CCQ ratings. Parent proxy ratings of perceived and current scores were significantly lower than child self-ratings. Health care provider proxy ratings were higher, but not significantly different than child self-ratings. Few significant predictors of child QoL found from demographic and other health data collected.</td>
<td>Children with SCD have realistic expectations re: ideal self (QoL), likely attained over a lifetime of adaptation to illness. Inclusion of parent ratings may add to our understanding of child QoL. Focus on psychosocial functioning may be of benefit where improving overall child QoL is concerned.</td>
</tr>
</tbody>
</table>
Appendix B: Patient and Parent History Form

Information Form

I. CHILD PROFILE:

Child’s name: __________________________ Date of Birth (day-month-year): ________
Child’s current age: ________________ Sex: □ Male □ Female
Child’s birthplace: _____________________ Child’s first language: ________________
Child’s current grade: __________________
Number of siblings at home: _____________

Has your child ever been diagnosed with any of the following health concerns (check all that apply)?

☐ Vision problems ☐ Learning problems ☐ Seizures ☐ Head injury
☐ Hearing problems ☐ Attention problems ☐ Developmental disability
☐ Speech problems ☐ Behaviour problems ☐ Sleep problems
☐ Stroke ☐ Silent stroke ☐ Transient Ischemic Attack (TIA)
☐ Emotional problems (for example, anxiety or depression; please list): ________________
☐ Other health concern (please list): ______________________________________________

II. PARENT PROFILE

Your name: __________________________ Date of Birth (day-month-year): ________
Your current age: ________________ Sex: □ Male □ Female
Your country of birth: ________________ Your first language: ________________
Relationship to child: ________________

Your current marital status:
☐ Single ☐ Married
☐ Common Law/ Living with Partner
☐ Separated  ☐ Divorced  ☐ Widowed

☐ Other (please describe): ____________________________

The highest level of education you completed (check one):

☐ Elementary School  ☐ High School  ☐ College or University

☐ Graduate Degree  ☐ Professional School  ☐ Skilled Trade

☐ Other (please describe): ____________________________

Your current employment status:

☐ Employed full-time  ☐ Employed part-time  ☐ Not employed (student)

☐ Not employed (non-student) ☐ Other (please describe): ____________________________

Your Family’s Combined Yearly Income:

☐ 0 to $24,999  ☐ $25,000 to $39,999  ☐ $40,000 to $49,999

☐ $50,000 to $79,999  ☐ $80,000 to $124,999  ☐ $125,000 to $149,999

☐ > $150,000
Chart Review Data Collection Form

Patient Data

Study I.D. #
Age at Test (years)
Gender (M/F): 
SCD Genotype (e.g. SS/SC/Other)
Age at diagnosis (months):
Other illnesses, diagnoses or health concerns:

Current Medications (Type and dose):

If transfused, how often (in weeks):
   How long has patient been receiving transfusions (in months)?
   Frequency of transfusion therapy (weeks):
   Reason for transfusion (stroke/prophylaxis/SII/other):
   Chelation therapy type (oral/subcutaneous) and duration:

History of:
☐ Overt stroke  ☐ Silent infarct  ☐ TIA  ☐ Acute Chest Syndrome
☐ Septicemia  ☐ Surgery: 
☐ Other: 

Number of emergency room visits in the last year: _____
Emergency Visit 1
Date: 
Where: 
Reason: 
Admitted?: If yes, length of admission (days): _____

Emergency Visit 2
Date: 
Where: 
Reason: 
Admitted?: If yes, length of admission (days): _____

Emergency Visit 3
Date: 
Where: 
Reason: 
Admitted?: If yes, length of admission (days): _____

Emergency Visit 4
Date: 
Where: 
Reason: 
Admitted?: If yes, length of admission (days): _____
Emergency Visit 5
Date: 
Where: 
Reason: 
Admitted?: If yes, length of admission (days): 

Other Emergency Room Visit/Admission (select one):
Date: 
Where: 
Reason: 
Admitted?: If yes, length of admission (days): 

Other Emergency Room Visit/Admission (select one):
Date: 
Where: 
Reason: 
Admitted?: If yes, length of admission (days): 

Number of visits to family doctor or other physician for sickle-cell related causes in the last year (with reason for visit):
Visit 1: 
Visit 2: 
Visit 3: 
Visit 4: 
Visit 5: 
Visit 6: 
Appendix C: Revised text of the Living with Sickle Cell Questionnaire

Living with Sickle Cell Questionnaire

We would like to know how sickle cell affects the way that you feel and the things that you do.

These questions will ask how often something happened to you, or how often you were bothered by something in the last week. Think about the way that you have felt during the last week (including the past few days and today), then click on the answer that best describes how you feel or felt. After you finish the first page, answer the questions on the next page, and the next, until you are finished. Be sure to answer each question before going on to the next one. Do not skip any questions.

Remember to choose the answer that describes the way you felt during the last week.

7-Point Likert Scales

<table>
<thead>
<tr>
<th>Bothered scale (B)</th>
<th>Frequency scale (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Extremely bothered</td>
<td>1. All of the time</td>
</tr>
<tr>
<td>2. Very bothered</td>
<td>2. Most of the time</td>
</tr>
<tr>
<td>3. Quite bothered</td>
<td>3. A good bit of the time</td>
</tr>
<tr>
<td>4. Somewhat bothered</td>
<td>4. Some of the time</td>
</tr>
<tr>
<td>5. Bothered a bit</td>
<td>5. A little of the time</td>
</tr>
<tr>
<td>6. Hardly bothered at all</td>
<td>6. Hardly any of the time</td>
</tr>
<tr>
<td>7. Not bothered</td>
<td>7. None of the time</td>
</tr>
</tbody>
</table>

In the last week...

Somatic Sensation domain:

(B) 1. How much were you bothered by pain?
(B) 2. How much were you bothered by tiredness?
(B) 3. How much were you bothered by any treatment for sickle cell, like taking medicine or coming to hospital?
(O) 4. How much time did you spend in the hospital for a clinic visit or overnight stay?
(B) 5. How much were you bothered by any sickness other than sickle cell, like a cold or the flu?

Cognitive/Psychological Functioning domain:

(O) 6. How often did pain make it harder to do schoolwork?
(B) 7. How much were you bothered by tiredness when doing schoolwork?
(O) 8. How much did feeling sad or down bother you?
(O) 9. How often were you angry, in a bad mood, or mean?
(O) 10. How often did you worry that you might have pain or a crisis?
Social Functioning domain:

(O) 11. How much were you bothered by pain when doing things with family or friends?
(B) 12. How much were you bothered by tiredness when doing things with family or friends?
(O) 13. How often did treatment for sickle cell interfere with doing things with family or friends?
(O) 14. How often did your family have to change plans because you were sick?
(O) 15. How often did your parents keep you from doing things because you might have pain or a crisis?
(O) 16. How often did you stay away from people or events so you wouldn't catch cold or the flu?

Physical Functioning domain:

(B) 17. How much were you bothered by pain when playing or taking part in sports?
(B) 18. How much were you bothered by tiredness when playing or taking part in sports?
(O) 19. How often did treatment for sickle cell interfere with play, sports, or getting around?
(O) 20. How often did you have trouble walking or getting around?
(O) 21. How often did the weather keep you from doing things outdoors?
(B) 22. How much were you bothered by pain that woke you up or kept you from sleeping?
Appendix D: Global Rating of Change in Health measure

*Global rating of change measure* (Juniper et al., 1994)

“Since our last meeting, has there been any change in overall quality of life (symptoms, emotions, participation in activities) related to having sickle cell disease?”

-7  A very great deal worse  
-6  A great deal worse  
-5  A good deal worse  
-4  Moderately worse  
-3  Somewhat worse  
-2  A little worse  
-1  Almost the same, hardly any worse at all  
0   No change  
+1  Almost the same, hardly any better at all  
+2  A little better  
+3  Somewhat better  
+4  Moderately better  
+5  A good deal better  
+6  A great deal better  
+7  A very great deal better
Appendix E: Cognitive interview script

Living with Sickle Cell

We would like to know more about the way that having sickle cell affects kids and teens, like the way that it makes them feel, and the and the things that they do at home, at school and at play.

Can you think of a way that having sickle cell has affected you and the things that you do?

A new questionnaire about living with sickle cell has been put together by researchers here at SickKids.

It is almost ready to use, but first, we'll need your help to make sure that kids can understand the questions, and the best way to answer them.

All questions will ask you about things that happened in the last week. Can you think of something that happened to you in the last week?

When did it happen? What was it?

(Hint, use the calendar to help you...)

Today is ____________

<table>
<thead>
<tr>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
</tr>
</thead>
</table>

How often...

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

If something happened often, what would you answer?

If something almost never happened, what would you answer?

How did you decide?
Some questions will ask you how much you were bothered by something that happened. There are special ways to answer this kind of question too, and you'll be given some choices. The choices are...

How bothered...
1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. hardly bothered at all
7. Not bothered

If something happened that really bothered you, what would you answer?

If something happened that didn't bother you much, what would you answer?

How did you decide?

Let's start the questions now. This part will take us about 10 minutes to do.
Each time I read a question to you, I'll ask:
+ What you think the question means
and
<<How you came up with your answer

I will write down/record your answers each time.

Do you have any questions before we start?

Here's the first question...

**Question 1**

**How much were you bothered by pain in the last week?**

1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. hardly bothered at all
7. Not bothered

**Question 2**

**How much were you bothered by tiredness in the last week?**

1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. hardly bothered at all
7. Not bothered
Question 3

How much were you bothered by any treatment for sickle cell in the last week?

1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. Hardly bothered at all
7. Not bothered

Question 4

How much time did you spend in the hospital last week?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 5

In the last week, how much were you bothered by any sickness other than sickle cell, like a cold or the flu?

1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. Hardly bothered at all
7. Not bothered

Question 6

How often did pain make it harder to do schoolwork in the past week?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 7

How much were you bothered by tiredness when doing schoolwork in the past week?

1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. Hardly bothered at all
7. Not bothered

Question 8

How often did treatment for sickle cell interfere with schoolwork in the past week?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time
Question 9

How often was it hard to remember what you learned in class in the last week?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 10

How much did feeling sad or down bother you in the last week?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 11

How often were you angry, in a bad mood, or mean in the past week?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 12

In the past week, how often did you worry that you might have pain or a crisis?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 13

In the last week, how often did you worry about how sickle cell could affect your future?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 14

In the last week, how often did you worry that your children could have sickle cell?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time
Question 15

How much were you bothered by pain when doing things with friends or family in the last week?
1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. Hardly bothered at all
7. Not bothered

Question 16

How much were you bothered by tiredness when doing things with friends or family in the past week?
1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. Hardly bothered at all
7. Not bothered

Question 17

in the past week, how often did treatment for sickle cell interfere with doing things with family or friends?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 18

How often did your family have to change plans because you were sick in the last week?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 19

in the last week, how often did your parents keep you from doing things because you might have pain or a crisis?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 20

in the past week, how often did you stay away from people or events so you wouldn’t catch cold or the flu?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time
Question 21

In the last week, how much were you bothered by pain when playing or taking part in sports?

1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. Hardly bothered at all
7. Not bothered

Question 22

How much were you bothered by tiredness when playing or taking part in sports in the last week?

1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. Hardly bothered at all
7. Not bothered

Question 23

In the past week, how often did treatment for sickle cell interfere with play, sports, or getting around?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 24

How often did you have trouble walking or getting around in the last week?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 25

How often did the weather keep you from doing things outdoors in the last week?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Question 26

In the past week, how much were you bothered by pain that woke you up or kept you from sleeping?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time
That was the last question. Great job!

Were there any questions that we left out/forgot to ask?

What would those questions be?

Do you have any questions or comments before we finish up today?

Thank you for your help today!
Appendix F: List of item modifications to the previous version of the LSCQ and final item list of current version

Original Item Text (Total: 22 Items)
- How much were you bothered by pain in the last week?
- How much were you bothered by pain when doing things with friends or family in the last week?
- How often did you stay away from people or events because you wouldn’t catch cold or the flu?
- How often did you have trouble walking or getting around in the last week?
- How often did the weather keep you from doing things outdoors in the last week?
- In the past week, how much were you bothered by pain that woke you up or kept you from sleeping?

Proposed Change (Total: 22 Items)
- In the last week, how much were you bothered by pain?
- In the last week, how much were you bothered by pain when doing things with friends or family?
- How often did you stay away from people or events because you wouldn’t catch cold or the flu?
- How often did you have trouble walking or getting around?
- How often did the weather keep you from doing things outdoors?
- In the last week, how much were you bothered by pain that woke you up or kept you from sleeping?

Summary of changes:
- Stem structure (8 Items)
- Last/post rewording (2 Items)
- Removal of non-contributory items - result of stats analysis (3 Items)
- Item elaboration (2 Items)
Appendix G: Study Consent and Assent forms

Title of Research Project:
The Living with Sickle Cell Questionnaire: Psychometric Properties of a New Disease-Specific Self-report Measure for Children and Adolescents with Sickle Cell Disease

Investigator(s):
Dr. Ross Hetherington
Director, AboutKidsHealth
Psychologist,
The Hospital for Sick Children
The University of Toronto

Dr. Isaac Odame
Staff Haematologist/Oncologist,
The Hospital for Sick Children
The University of Toronto

Sandra Newton, M.A.
Graduate student,
School and Clinical Child Psychology Program
OISE, The University of Toronto

Purpose of the Research:
The purpose of this 3-part study is to improve and test a new online questionnaire, The Living with Sickle Cell Questionnaire, that will look at how having sickle cell disease (SCD) affects the day-to-day lives of children and adolescents. Sickle cell disease is a hereditary disease of the blood. Young people with SCD often experience pain events or ‘crises’ that can last for days and may require treatment in hospital. Testing and improvement of the Living with Sickle Cell Questionnaire will provide a tool that can be used to measure symptom severity, treatment efficacy, and disease natural history. The model of quality of life that will result from this study will help understand how SCD affects domains of life experience for these children and youth.

Description of the Research:
There are 3 parts to this research study. You and your child have the choice of taking part in one or more of these.

PART 1: Interviews: A small number of children and adolescents with SCD will be interviewed using the Living with Sickle Cell Questionnaire. This part of the study can take place while you are at the hospital waiting with your child for your clinic appointment or at another time convenient for you. Questionnaire items will be read to your child by the interviewer or by a computer to help make sure that the meaning of questions is clear to younger and older children and adolescents. Your
child will have the chance to tell us things that might help to make the questionnaire better, and his or her comments will be recorded on audiotape. Your child will also be asked to do two short tests that measure thinking and reasoning skills. Parents will be asked to provide some information about their child (age, health history) and family. This information about your child’s health and the family will help us to understand the ways that they may affect quality of life. This part of the study takes approximately 30 minutes to complete.

PART 2: Instrument testing (Visit 1). This part of the study will take place while you are at the hospital waiting with your child for your clinic appointment or at another place that is easy for you to get to. Sentences from the Living with Sickle Cell Questionnaire will be read to your child. These will be read by an investigator or a computer. Your child will also be asked to complete a pencil and paper questionnaire about his or her health and feelings on his or her own, or with the help of the examiner. Your child will also be asked to do two short tests that measure thinking and reasoning skills (if not already completed in Part 1). While your child is working with the researcher, you will be asked to complete two questionnaires about your child (age, health history) and family (if not already completed in Part 1). A limited amount of information about your child’s medical history will also be collected from the hospital record during the study. This information about your child’s medical history and the family will help us understand how different things may affect quality of life. This part of the study will take about one hour to complete.

PART 3: Instrument testing (Visit 2). Some families that participated in Part 2 of the study will also be asked to complete Part 3. It will take place about two weeks after Part 2 has been completed, either at the hospital or at another place that is easy for you to get to. Your child will be asked to do the Living with Sickle Cell Questionnaire once more. Your child will also be asked to fill out the pencil and paper questionnaire about his or her health and feelings a second time. Your child will also be asked to rate how much he or she feels that his or her health has changed since doing Part 2 of the study two weeks earlier. There are no parent questionnaires to complete in Part 3. This part of the study will take about 30 minutes to complete.

Potential Harms:
We know of no potential harms in participating in this study.

Potential Discomforts or Inconvenience:
No major harms to children and families are expected as part of participating in this study.

We will be asking for you to spend some time (about 45 minutes to 1 hour) for each part of the study that you complete. We will schedule times to meet with you when it is most convenient to prevent missed activities.

Some participants may experience discomfort when remembering or discussing some sensitive topics or events related to their health. Some participants may mention that they are having a difficult time living with SCD when taking part in the study. If this happens while at the hospital, we will ask your permission to let a sickle cell clinic doctor or nurse know so that help can be arranged. If this happens while away from the hospital, we will ask your permission to contact a sickle cell clinic doctor or nurse so that help can be arranged. If major difficulties are discovered at any time during the research, we will make a note about the problem and let a sickle cell clinic doctor or nurse know so that they can make plans to assist you or your child.
Potential Benefits:
You and your child will not benefit directly from this study. We hope that this research will help to increase understanding about the ways that having sickle cell disease affects day-to-day lives of children. Any concerns identified in children participating in the study will be conveyed to parents and supervising clinic staff. At the end of the study, a short summary of the results will be prepared and sent to families to explain what we have found.

Confidentiality:
We will respect your privacy. No information about who you are or who your child is will be given to anyone or be published without your permission, unless required by law. For example, the law could make us give information about you if a child has been abused, if you have an illness that could spread to others, if you or someone else talks about suicide (killing themselves), or if the court orders us to give them the study papers.

The data produced from this study will be stored in a secure, locked location. Only members of the research team (and maybe those individuals described above) will have access to the data. This could include external research team members. Following completion of the research study the data will be kept as long as required then destroyed as required by Sick Kids policy. Published study results will not reveal your identity.

The results of the thinking and reasoning tests we describe in this form will be used only for this study. If another doctor or caregiver caring for you needs to see these results, you will have to give us your permission. We will ask you to sign a form saying that you agree that this person can see your (your child’s) results. We recommend that only a registered psychologist or doctor tell you what the results of these tests mean.

Reimbursement:
We will also provide your child with a $10 gift card as thanks for the time and effort given to the study.

Participation:
If you choose to let your child take part in this study you can take your child out of the study at any time. Children providing assent to this study may also withdraw from the study at any time. The care your child gets at Sick Kids will not be affected in any way by whether your child takes part in this study.

New information that we get while we are doing this study may affect your decision to take part in this study. If this happens, we will tell you about this new information. And we will ask you again if you still want to be in the study.

During this study we may create new tests or other things that may be worth some money. Although we may make money from these findings, we cannot give you or your child any of this money now or in the future because you or your child took part in this study.
Research Ethics Board

If you or your child become ill or are harmed because of study participation, we will treat you and your child for free. Your signing this consent form does not interfere with your legal rights in any way. The staff of the study, any people who gave money for the study, or the hospital are still responsible, legally and professionally, for what they do.

Sponsorship:
This research is funded by a SickKids Research Institute seed grant to the Principle Investigator.

Conflict of Interest:
I, and the other research team members have no conflict of interest to declare.

Consent:
By signing this form, I agree that:
1) You have explained this study to me. You have answered all my questions.
2) You have explained the possible harms and benefits (if any) of this study.
3) I know what I could do instead of having my child take part in this study. I understand that I have the right to refuse to let my child take part in the study. I also have the right to take my child out of the study at any time. My decision about my child taking part in the study will not affect my child’s health care at Sick Kids.
4) I am free now, and in the future, to ask questions about the study.
5) I have been told that my child’s medical records will be kept private except as described to me.
6) I understand that no information about my child will be given to anyone or be published without first asking my permission.
7) I agree, or consent, that my child________________________ may take part in Part (1/2/3) of this study.

Printed Name of Parent/Legal Guardian ________________________________ Parent/Legal Guardian’s signature & date

Printed Name of person who explained consent _______________________________ Signature of Person who explained consent & date

Printed Witness’ name (if the parent/legal guardian does not read English) _______________________________ Witness’ signature & date

If you have any questions about this study, please call Sandra Newton at (416)***-****.

If you have questions about your rights as a subject in a study or injuries during a study, please call the Research Ethics Manager at 416-813-5718.

Parent Consent - Version date:
Page 4 of 4
Research Consent Form
Child

Title of Research Project:
The Living with Sickle Cell Questionnaire: Psychometric Properties of a New Disease-Specific Self-report Measure for Children and Adolescents with Sickle Cell Disease

Investigator(s):
Dr. Ross Hetherington (416) 813-1086
Psychologist,
The Hospital for Sick Children
The University of Toronto

Dr. Isaac Odame (416) 813-5886
Staff Haematologist/Oncologist,
The Hospital for Sick Children
The University of Toronto

Sandra Newton, M.A. (416) ***-****
Graduate student,
School and Clinical Child Psychology Program
OISE, The University of Toronto

Purpose of the Research:
The purpose of this 3-part study is to improve and test a new questionnaire, The Living with Sickle Cell Questionnaire, that will look at how having sickle cell disease (SCD) affects the day-to-day lives of children and teens. Once tested, this questionnaire will be used to help doctors understand the lives of children and teens with SCD, and how treatment affects them.

Description of the Research:
There are 3 parts to this research study. You may take part in one or more of these.

PART 1: Interviews: A few children and teens with SCD will be interviewed using the Living with Sickle Cell Questionnaire. This part of the study can take place while you are at the hospital waiting for your clinic appointment or at another time convenient for you. You will have the chance to suggest things that might help improve the questionnaire. Your answers will be recorded. You will also be asked to complete two short tasks that measure knowledge and problem-solving. While you are working, your parents will be asked to provide some information about your health history and the family. This information will help us to understand how different things may affect your quality of life. This part of the study takes place once for about half an hour.

PART 2: Instrument testing (Visit 1): This part of the study will take place while you are at the hospital waiting for your clinic appointment or at another location convenient for you. You will be
asked to complete the Living with Sickle Cell Questionnaire on computer. You will also be asked to complete a pencil and paper questionnaire about your health recently. You will also be asked to complete two short tasks that measure knowledge and problem-solving if you did not do them in Part 1. While you are working, your parent will be asked to complete two questionnaires about your health history and the family (if not already done in Part 1). A limited amount of medical information from your hospital record will be collected during the study. This information about your medical history and family will help us to understand relationships among different things that may affect quality of life. This part of the study will take about 45 minutes to complete.

PART 3: Instrument testing (Visit 2). Some teens that participated in Part 2 of the study will also be asked to complete Part 3 about two weeks later. This can take place at the hospital or at another location convenient for you such as your home. You will be asked to complete the Living with Sickle Cell Questionnaire on computer a second time. You will also be asked to complete the pencil and paper questionnaire about your health and feelings a second time. The researcher will also ask you to rate how much you feel that your health has changed since participating in Part 2 two weeks earlier. There are no parent questionnaires to complete in Part 3. This part of the study will take about 45 minutes to complete.

**Potential Harms:**
We know of no potential harms in participating in this study.

**Potential Discomforts or Inconvenience:**
No major harms to teens and families are expected as part of participating in this study. We will be asking for you to spend some time (about 45 minutes to 1 hour) for each part of the study that you complete. We will schedule times to meet with you when it is most convenient to prevent missed activities.

Some teens may experience discomfort when remembering or discussing some sensitive topics or events related to their health. Some teens may mention that they are having a difficult time living with SCD when taking part in the study. If this happens while at the hospital, we will ask your permission to let a sickle cell clinic doctor or nurse know so that help can be arranged. If this happens away from the hospital, we will ask your permission to contact a sickle cell clinic doctor or nurse so that help can be arranged. If major difficulties are discovered at any time during the research, we will make a note about the problem and let a sickle cell clinic doctor or nurse know so that they can make plans to assist you.

**Potential Benefits:**
You will not benefit directly from this study. We hope that this research will help to increase understanding about the ways that having sickle cell disease affects day-to-day lives of children and teens. Any concerns identified in participants in the study will be conveyed to parents and supervising clinic staff so that help may be provided. At the end of the study, a short summary of the results will be prepared and sent to families to explain what we have found.
Confidentiality:
We will respect your privacy. No information about who you are will be given to anyone or be published without your permission, unless required by law. For example, the law could make us give information about you if a child has been abused, if you have an illness that could spread to others, if you or someone else talks about suicide (killing themselves), or if the court orders us to give them the study papers.

The data produced from this study will be stored in a secure, locked location. Only members of the research team (and maybe those individuals described above) will have access to the data. This could include external research team members. Following completion of the research study the data will be kept as long as required then destroyed as required by Sick Kids policy. Published study results will not reveal your identity.”

The results of the thinking and reasoning test we describe in this form will be used only for this study. If another doctor or caregiver caring for you needs to see these results, you will have to give us your permission. We will ask you to sign a form saying that you agree that this person can see your results. We recommend that only a registered psychologist or doctor tell you what the results of these tests mean.

Reimbursement:
We will also provide you with some compensation, a $10 gift card, in recognition of your time and effort. Teens collecting volunteer hours for high school requirements will be provided with a letter by the research team upon request.

Participation:
If you choose to take part in this study you can withdraw from the study at any time. The care you get at Sick Kids will not be affected in any way by whether you take part in this study.

New information that we get while we are doing this study may affect your decision to take part in this study. If this happens, we will tell you about this new information. And we will ask you again if you still want to be in the study.

During this study we may create new tests or other things that may be worth some money. Although we may make money from these findings, we cannot give you or your child any of this money now or in the future because you or your child took part in this study.

If you become ill or are harmed because of study participation, we will treat you for free. Your signing this consent form does not interfere with your legal rights in any way. The staff of the study, any people who gave money for the study, or the hospital are still responsible, legally and professionally, for what they do.

Sponsorship:
This research is funded by a SickKids Seed Grant.
Research Ethics Board

Conflict of Interest:
I, and the other research team members have no conflict of interest to declare.

Consent:
By signing this form, I agree that:
1) You have explained this study to me. You have answered all my questions.
2) You have explained the possible harms and benefits (if any) of this study.
3) I know what I could do instead of taking part in this study. I understand that I have the right to refuse to take part in the study. My decision about taking part in the study will not affect my health care at Sick Kids.
4) I am free now, and in the future, to ask questions about the study.
5) I have been told that my medical records will be kept private except as described to me.
6) I understand that no information about me will be given to anyone or be published without first asking my permission.
7) I________________, agree, or consent, to take part in Part (1/2/3) of this study.

________________________________________
Printed Name

________________________________________
Signature & date

________________________________________
Printed Name of person who explained consent
& date

________________________________________
Signature of Person who explained consent

________________________________________
Printed Witness’ name (if the parent/legal guardian does not read English)

________________________________________
Witness’ signature & date

If you have any questions about this study, please call Sandra Newton at (416)***.****.

If you have questions about your rights as a subject in a study or injuries during a study, please call the Research Ethics Manager at 416-813-5718.
Title of Research Project:
The Living with Sickle Cell Questionnaire: Psychometric Properties of a New Disease- Specific Self-report Measure for Children and Adolescents with Sickle Cell Disease

Investigator(s):
Dr. Ross Hetherington, Psychologist (416) 813-1086
Dr. Isaac Odame, Staff Haematologist (416) 813-5886
Sandra Newton, Graduate student (416) ***-****

Why are we doing this study?
We would like to know how sickle cell affects kids, the way that they feel, and the things they do, like being with friends, playing sports, and getting around. We are working on a questionnaire to help us find out more about this. Knowing about how sickle cell affects kids like you is important because if we know more, we can help you better.

What will happen during the study?
There are 3 parts to this research study. You can take part in any one of these, or more than one if you would like to. Here's how it works:

PART 1: Interviews: For this part of the study, you will meet with a researcher for about half an hour while waiting at the clinic for your appointment. First, the researcher will ask you to answer some questions and complete a puzzle to learn more about the way that you think and solve problems. Next, we will ask you questions about having sickle cell and the things you like to do using a computer program. You will be asked what you think each question means so that we can be sure that other kids your
age understand the questions. We will make a sound recording (tape) to keep track of the things that you tell us about the questions. You will also get to tell us what changes might make it easier for you to answer the questions. While you are working, your mom or dad will fill out a form to help us learn more about you, your health and your family.

PART 2: Instrument testing (Visit 1). You can complete this part of the study at the hospital while waiting for your clinic appointment. First, you will meet with a researcher who will ask you to answer some questions and complete a puzzle to learn more about the way that you think and solve problems (if you have not done this before for the study). Then, the researcher will ask you questions about having sickle cell and the things you like to do using a computer program. We will also ask you to fill out a paper questionnaire about your health, and the researcher can help you with this if you would like. While you are working, your mom or dad will fill out a form to help us learn more about you, your health and your family (if they have not done this before for the study). The research team will also make some notes about your health from your hospital file during the study. This part of the study will take about 45 minutes to do.

PART 3: Instrument testing (Visit 2). Some children that did Part 2 of the study will be asked to do Part 3 too. It can be done at the hospital or at another place that is good for you and your family. You will meet with the researcher for this part of the study too. You will be asked how much your health has changed since your last visit for the study. The rest of the things you do will be the same as for the last visit. You will answer some questions about your health on the computer and using a paper form. This part of the study will take about 45 minutes to do.

Are there good things and bad things about the study?
One good thing about the study is that it could help other kids just like you. The study might take up some of your extra time, so we will try to arrange things during a time that is good for you and your family. Some kids might feel a bit upset when thinking about some of the questions for the study. If this happens, we can take a break, talk about it, and find ways to help. You can stop doing the study at any time if you want to. No one will be angry or upset if you decide to stop.
Who will know about what I did in the study?
The research team and your parents will know about what you did in the study. If you and your parents want to let others know, they will need your parents’ permission to find out. If we identify any information that makes us feel that your health may be in danger, we may have to report your results to your doctor.

Can I decide if I want to be in the study?
Nobody will be angry or upset if you do not want to be in the study. We are talking to your parent/legal guardians about the study and you should talk to them about it too.

Assent:

"I was present when ____________________________ read this form and said that he or she agreed, or assented, to take part in this study”.

Printed Name of person who obtained assent ____________________________________________________________________________

Signature & Date ____________________________________________________________________________
Appendix H: Descriptive statistics for LSCQ items at Time 1 and Time 2

<table>
<thead>
<tr>
<th>Item</th>
<th>Time 1</th>
<th>Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>Skewness (SE)</td>
</tr>
<tr>
<td>Somatic Sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much were you bothered by pain?</td>
<td>2.96 ( 1.28)</td>
<td>0.67 (0.24)</td>
</tr>
<tr>
<td>How much were you bothered by tiredness?</td>
<td>3.33 ( 1.46)</td>
<td>0.37 (0.24)</td>
</tr>
<tr>
<td>How much were you bothered by any treatment for sickle cell, like taking medicine or coming to hospital?</td>
<td>3.07 ( 1.27)</td>
<td>0.74 (0.24)</td>
</tr>
<tr>
<td>How much time did you spend in the hospital for a clinic visit or overnight stay?</td>
<td>3.32 ( 1.16)</td>
<td>0.29 (0.24)</td>
</tr>
<tr>
<td>How much were you bothered by any sickness other than sickle cell, like a cold or the flu?</td>
<td>2.84 ( 1.32)</td>
<td>0.86 (0.24)</td>
</tr>
<tr>
<td>Cognitive/Psychological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often did pain make it harder to do schoolwork?</td>
<td>3.05 ( 1.27)</td>
<td>0.33 (0.24)</td>
</tr>
<tr>
<td>How much were you bothered by tiredness when doing schoolwork?</td>
<td>3.01 ( 1.19)</td>
<td>0.82 (0.24)</td>
</tr>
<tr>
<td>How much did feeling sad or down bother you?</td>
<td>3.08 ( 1.3)</td>
<td>0.5 (0.24)</td>
</tr>
<tr>
<td>How often were you angry, in a bad mood, or mean?</td>
<td>2.86 ( 1.31)</td>
<td>0.65 (0.24)</td>
</tr>
<tr>
<td>How often did you worry that you might have pain or a crisis?</td>
<td>3.06 ( 1.38)</td>
<td>0.74 (0.24)</td>
</tr>
<tr>
<td>Item</td>
<td>Time 1</td>
<td>Time 2</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>Skewness (SE)</td>
</tr>
<tr>
<td><strong>Social Functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much were you bothered by pain when doing things with family or friends?</td>
<td>2.99 (1.34)</td>
<td>0.58 (0.24)</td>
</tr>
<tr>
<td>How much were you bothered by tiredness when doing things with family or friends?</td>
<td>3.06 (1.21)</td>
<td>0.51 (0.24)</td>
</tr>
<tr>
<td>How often did treatment for sickle cell interfere with doing things with family or friends?</td>
<td>3.13 (1.35)</td>
<td>0.36 (0.24)</td>
</tr>
<tr>
<td>How often did your family have to change plans because you were sick?</td>
<td>3.17 (1.22)</td>
<td>0.88 (0.24)</td>
</tr>
<tr>
<td>How often did your parents keep you from doing things because you might have pain or a crisis?</td>
<td>3.19 (1.24)</td>
<td>0.55 (0.24)</td>
</tr>
<tr>
<td>How often did you stay away from people or events so you wouldn't catch a cold or the flu?</td>
<td>3.18 (1.39)</td>
<td>0.69 (0.24)</td>
</tr>
<tr>
<td><strong>Physical Functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much were you bothered by pain when playing or taking part in sports?</td>
<td>2.89 (1.21)</td>
<td>1.39 (0.24)</td>
</tr>
<tr>
<td>How much were you bothered by tiredness when playing or taking part in sports?</td>
<td>2.8 (1.21)</td>
<td>0.92 (0.24)</td>
</tr>
<tr>
<td>How often did treatment for sickle cell interfere with play, sports, or getting around?</td>
<td>2.84 (1.01)</td>
<td>1.1 (0.24)</td>
</tr>
<tr>
<td>Item</td>
<td>Time 1</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>Skewness (SE)</td>
</tr>
<tr>
<td>How often did you have trouble walking or getting around?</td>
<td>2.79 (1.29)</td>
<td>1.15 (0.24)</td>
</tr>
<tr>
<td>How often did the weather keep you from doing things outdoors?</td>
<td>2.89 (1.13)</td>
<td>1.08 (0.24)</td>
</tr>
<tr>
<td>How much were you bothered by pain that woke you up or kept you from sleeping?</td>
<td>2.87 (1.14)</td>
<td>0.92 (0.24)</td>
</tr>
</tbody>
</table>
Appendix I: Item-scale and item-questionnaire total Pearson $r$ correlations for the LSCQ

### Time 1

<table>
<thead>
<tr>
<th>Item</th>
<th>Corrected Item-Total (parent domain)</th>
<th>SS Total</th>
<th>CP Total</th>
<th>Soc Total</th>
<th>Phys Total</th>
<th>Corrected Item-Total (22 items)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic Sensation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. How much were you bothered by pain?</td>
<td>.408</td>
<td>.621</td>
<td>.442</td>
<td>.279</td>
<td>.479</td>
<td>.428</td>
</tr>
<tr>
<td>2. How much were you bothered by tiredness?</td>
<td>.599</td>
<td>.779</td>
<td>.550</td>
<td>.326</td>
<td>.317</td>
<td>.428</td>
</tr>
<tr>
<td>3. How much were you bothered by any treatment for sickle cell, like taking medicine or coming to hospital?</td>
<td>.622</td>
<td>.773</td>
<td>.520</td>
<td>.270</td>
<td>.407</td>
<td>.389</td>
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<tr>
<td>4. How much time did you spend in the hospital for a clinic visit or overnight stay?</td>
<td>.544</td>
<td>.706</td>
<td>.595</td>
<td>.705</td>
<td>.467</td>
<td>.644</td>
</tr>
<tr>
<td>5. How much were you bothered by any sickness other than sickle cell, like a cold or the flu?</td>
<td>.568</td>
<td>.742</td>
<td>.625</td>
<td>.603</td>
<td>.563</td>
<td>.611</td>
</tr>
<tr>
<td>Cognitive/Psychological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. How often did pain make it harder to do schoolwork?</td>
<td>.569</td>
<td>.584</td>
<td>.738</td>
<td>.544</td>
<td>.427</td>
<td>.626</td>
</tr>
<tr>
<td>7. How much were you bothered by tiredness when doing schoolwork?</td>
<td>.624</td>
<td>.700</td>
<td>.814</td>
<td>.603</td>
<td>.506</td>
<td>.640</td>
</tr>
<tr>
<td>8. How much did feeling sad or down bother you?</td>
<td>.388</td>
<td>.528</td>
<td>.610</td>
<td>.349</td>
<td>.620</td>
<td>.580</td>
</tr>
<tr>
<td>9. How often were you angry, in a bad mood, or mean?</td>
<td>.566</td>
<td>.464</td>
<td>.741</td>
<td>.615</td>
<td>.517</td>
<td>.568</td>
</tr>
<tr>
<td>10. How often did you worry that you might have pain or a crisis?</td>
<td>.554</td>
<td>.478</td>
<td>.741</td>
<td>.682</td>
<td>.573</td>
<td>.703</td>
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<tr>
<td>Item</td>
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<td>CP Total</td>
<td>Soc Total</td>
<td>Phys Total</td>
<td>Corrected Item-Total (22 items)</td>
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<tr>
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<tr>
<td><strong>Social Functioning</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. How much were you bothered by pain when doing things with family or friends?</td>
<td>.638</td>
<td>.392</td>
<td>.599</td>
<td><strong>.758</strong></td>
<td>.527</td>
<td>.571</td>
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<tr>
<td>12. How much were you bothered by tiredness when doing things with family or friends?</td>
<td>.735</td>
<td>.555</td>
<td>.667</td>
<td><strong>.819</strong></td>
<td>.545</td>
<td>.636</td>
</tr>
<tr>
<td>13. How often did treatment for sickle cell interfere with doing things with family or friends?</td>
<td>.812</td>
<td>.527</td>
<td>.693</td>
<td><strong>.880</strong></td>
<td>.574</td>
<td>.717</td>
</tr>
<tr>
<td>14. How often did your family have to change plans because you were sick?</td>
<td>.757</td>
<td>.488</td>
<td>.606</td>
<td><strong>.835</strong></td>
<td>.590</td>
<td>.709</td>
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<tr>
<td>15. How often did your parents keep you from doing things because you might have pain or a crisis?</td>
<td>.568</td>
<td>.471</td>
<td>.548</td>
<td><strong>.696</strong></td>
<td>.520</td>
<td>.616</td>
</tr>
<tr>
<td>16. How often did you stay away from people or event so you wouldn’t catch a cold or the flu?</td>
<td>.688</td>
<td>.412</td>
<td>.571</td>
<td><strong>.797</strong></td>
<td>.410</td>
<td>.542</td>
</tr>
<tr>
<td><strong>Physical Functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. How much were you bothered by pain when playing or taking part in sports?</td>
<td>.721</td>
<td>.597</td>
<td>.601</td>
<td>.632</td>
<td><strong>.820</strong></td>
<td>.716</td>
</tr>
<tr>
<td>18. How much were you bothered by tiredness when playing or taking part in sports?</td>
<td>.700</td>
<td>.519</td>
<td>.627</td>
<td>.715</td>
<td><strong>.800</strong></td>
<td>.780</td>
</tr>
<tr>
<td>19. How often did treatment for sickle cell interfere with play, sports, or getting around?</td>
<td>.680</td>
<td>.552</td>
<td>.630</td>
<td>.475</td>
<td><strong>.774</strong></td>
<td>.699</td>
</tr>
<tr>
<td>20. How often did you have trouble walking or getting around?</td>
<td>.639</td>
<td>.430</td>
<td>.560</td>
<td>.454</td>
<td><strong>.763</strong></td>
<td>.591</td>
</tr>
<tr>
<td>Item</td>
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<td>SS Total</td>
<td>CP Total</td>
<td>Soc Total</td>
<td>Phys Total</td>
<td>Corrected Item-Total (22 items)</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------</td>
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<td>-----------</td>
<td>------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>21. How often did the weather keep you from doing things outdoors?</td>
<td>.715</td>
<td>.415</td>
<td>.525</td>
<td>.376</td>
<td></td>
<td><strong>.808</strong></td>
</tr>
<tr>
<td>22. How much were you bothered by pain that woke you up or kept you from sleeping?</td>
<td>.697</td>
<td>.363</td>
<td>.533</td>
<td>.470</td>
<td></td>
<td><strong>.795</strong></td>
</tr>
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</table>
**Time 2**

<table>
<thead>
<tr>
<th>Item</th>
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<th>SS Total</th>
<th>CP Total</th>
<th>Soc Total</th>
<th>Phys Total</th>
<th>Corrected Item-Total (22 items)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Item</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Somatic Sensation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. How much were you bothered by pain?</td>
<td>.408</td>
<td>.568</td>
<td>.510</td>
<td>.201</td>
<td>.430</td>
<td>.455</td>
</tr>
<tr>
<td>2. How much were you bothered by tiredness?</td>
<td>.599</td>
<td>.779</td>
<td>.565</td>
<td>.125</td>
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<tr>
<td>3. How much were you bothered by any treatment for sickle cell, like taking medicine or coming to hospital?</td>
<td>.622</td>
<td>.740</td>
<td>.462</td>
<td>.127</td>
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<td>.491</td>
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<tr>
<td>4. How much time did you spend in the hospital for a clinic visit or overnight stay?</td>
<td>.544</td>
<td>.686</td>
<td>.536</td>
<td>.595</td>
<td>.495</td>
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<tr>
<td>5. How much were you bothered by any sickness other than sickle cell, like a cold or the flu?</td>
<td>.568</td>
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<td>.571</td>
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<td>6. How often did pain make it harder to do schoolwork?</td>
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<td>.686</td>
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<td>7. How much were you bothered by tiredness when doing schoolwork?</td>
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<td>.700</td>
<td>.767</td>
<td>.452</td>
<td>.435</td>
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<td>8. How much did feeling sad or down bother you?</td>
<td>.388</td>
<td>.596</td>
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<td>9. How often were you angry, in a bad mood, or mean?</td>
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<td>.507</td>
<td>.452</td>
<td>.568</td>
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<tr>
<td>10. How often did you worry that you might have pain or a crisis?</td>
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<td>.460</td>
<td>.789</td>
<td>.663</td>
<td>.586</td>
<td>.703</td>
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<td>CP Total</td>
<td>Soc Total</td>
<td>Phys Total</td>
<td>Corrected Item-Total (22 items)</td>
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<tr>
<td>11. How much were you bothered by pain when doing things with family or friends?</td>
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<td>.174</td>
<td>.516</td>
<td><strong>.770</strong></td>
<td>.520</td>
<td>.571</td>
</tr>
<tr>
<td>12. How much were you bothered by tiredness when doing things with family or friends?</td>
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<td>.323</td>
<td>.514</td>
<td><strong>.841</strong></td>
<td>.493</td>
<td>.636</td>
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<tr>
<td>13. How often did treatment for sickle cell interfere with doing things with family or friends?</td>
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<td>.433</td>
<td>.667</td>
<td><strong>.906</strong></td>
<td>.461</td>
<td>.717</td>
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<tr>
<td>14. How often did your family have to change plans because you were sick?</td>
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<td>.447</td>
<td>.546</td>
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<td>.584</td>
<td>.709</td>
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<tr>
<td>15. How often did your parents keep you from doing things because you might have pain or a crisis?</td>
<td>.568</td>
<td>.461</td>
<td>.549</td>
<td><strong>.703</strong></td>
<td>.466</td>
<td>.616</td>
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<td>16. How often did you stay away from people or event so you wouldn’t catch a cold or the flu?</td>
<td>.688</td>
<td>.332</td>
<td>.521</td>
<td><strong>.789</strong></td>
<td>.300</td>
<td>.542</td>
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<td><strong>Physical Functioning</strong></td>
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<tr>
<td>17. How much were you bothered by pain when playing or taking part in sports?</td>
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<td>.607</td>
<td>.534</td>
<td>.556</td>
<td>.816</td>
<td>.716</td>
</tr>
<tr>
<td>18. How much were you bothered by tiredness when playing or taking part in sports?</td>
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<td>.465</td>
<td>.602</td>
<td>.744</td>
<td>.832</td>
<td>.780</td>
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<tr>
<td>19. How often did treatment for sickle cell interfere with play, sports, or getting around?</td>
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<td>.606</td>
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<tr>
<td>20. How often did you have trouble walking or getting around?</td>
<td>.639</td>
<td>.391</td>
<td>.594</td>
<td>.394</td>
<td>.761</td>
<td>.591</td>
</tr>
<tr>
<td>21. How often did the weather keep you from doing things outdoors?</td>
<td>.715</td>
<td>.398</td>
<td>.568</td>
<td>.304</td>
<td>.857</td>
<td>.584</td>
</tr>
<tr>
<td>22. How much were you bothered by pain that woke you up or kept you from sleeping?</td>
<td>.697</td>
<td>.274</td>
<td>.459</td>
<td>.377</td>
<td>.808</td>
<td>.538</td>
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Appendix J: Factor loadings and domains derived from Principal Components Analysis of the LSCQ

**Time 1**

<table>
<thead>
<tr>
<th>Item</th>
<th>Disease inference (pain, fatigue preoccupation, worry) on social and physical functioning</th>
<th>Pain/Physical Functioning</th>
<th>Pain, Fatigue and School</th>
<th>Treatment and Mood</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. How much time did you spend in the hospital for a clinic visit or overnight stay?</td>
<td>.745</td>
<td>-.277</td>
<td>.191</td>
<td>.306</td>
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<tr>
<td>5. How much were you bothered by any sickness other than sickle cell, like a cold or the flu?</td>
<td>.472</td>
<td>-.073</td>
<td>.256</td>
<td>.416</td>
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<tr>
<td>9. How often were you angry, in a bad mood, or mean?</td>
<td>.432</td>
<td>.243</td>
<td>.148</td>
<td>-.034</td>
</tr>
<tr>
<td>10. How often did you worry that you might have pain or a crisis?</td>
<td>.508</td>
<td>.304</td>
<td>.115</td>
<td>-.152</td>
</tr>
<tr>
<td>11. How much were you bothered by pain when doing things with family or friends?</td>
<td>.514</td>
<td>.293</td>
<td>.229</td>
<td>-.436</td>
</tr>
<tr>
<td>12. How much were you bothered by tiredness when doing things with family or friends?</td>
<td>.660</td>
<td>.081</td>
<td>.285</td>
<td>-.241</td>
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<tr>
<td>13. How often did treatment for sickle cell interfere with doing things with family or friends?</td>
<td>.874</td>
<td>.045</td>
<td>-.013</td>
<td>-.073</td>
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<tr>
<td>14. How often did your family have to change plans because you were sick?</td>
<td>.921</td>
<td>-.007</td>
<td>-.142</td>
<td>.043</td>
</tr>
<tr>
<td>15. How often did your parents keep you from doing things because you might have pain or a crisis?</td>
<td>.643</td>
<td>.113</td>
<td>-.164</td>
<td>.223</td>
</tr>
<tr>
<td>16. How often did you stay away from people or events so you wouldn't catch a cold or the flu?</td>
<td>.978</td>
<td>-.363</td>
<td>.021</td>
<td>.070</td>
</tr>
<tr>
<td>17. How much were you bothered by pain when playing or taking part in sports?</td>
<td>.456</td>
<td>.404</td>
<td>-.120</td>
<td>.328</td>
</tr>
<tr>
<td>Item</td>
<td>Disease inference (pain, fatigue preoccupation, worry) on social and physical functioning</td>
<td>Pain/Physical Functioning</td>
<td>Pain, Fatigue and School</td>
<td>Treatment and Mood</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
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<td>---------------------------</td>
<td>--------------------------</td>
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</tr>
<tr>
<td>18. How much were you bothered by tiredness when playing or taking part in sports?</td>
<td>.599</td>
<td>.373</td>
<td>-.140</td>
<td>.135</td>
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<tr>
<td>1. How much were you bothered by pain?</td>
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<td>.628</td>
<td>.458</td>
<td>.068</td>
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<tr>
<td>19. How often did treatment for sickle cell interfere with play, sports, or getting around?</td>
<td>.045</td>
<td>.494</td>
<td>.245</td>
<td>.275</td>
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<tr>
<td>20. How often did you have trouble walking or getting around?</td>
<td>.090</td>
<td>.598</td>
<td>-.015</td>
<td>.249</td>
</tr>
<tr>
<td>21. How often did the weather keep you from doing things outdoors?</td>
<td>-.137</td>
<td>.923</td>
<td>-.037</td>
<td>.130</td>
</tr>
<tr>
<td>22. How much were you bothered by pain that woke you up or kept you from sleeping?</td>
<td>.056</td>
<td>.889</td>
<td>-.142</td>
<td>-.007</td>
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<tr>
<td>2. How much were you bothered by tiredness?</td>
<td>-.125</td>
<td>-.074</td>
<td>.879</td>
<td>.218</td>
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<tr>
<td>6. How often did pain make it harder to do schoolwork?</td>
<td>.196</td>
<td>-.043</td>
<td>.742</td>
<td>-.018</td>
</tr>
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<td>7. How much were you bothered by tiredness when doing schoolwork?</td>
<td>.209</td>
<td>.026</td>
<td>.729</td>
<td>.075</td>
</tr>
<tr>
<td>3. How much were you bothered by any treatment for sickle cell, like taking medicine or coming to hospital?</td>
<td>-.154</td>
<td>.043</td>
<td>.515</td>
<td>.692</td>
</tr>
<tr>
<td>8. How much did feeling sad or down bother you?</td>
<td>.094</td>
<td>.377</td>
<td>-.112</td>
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### Time 2

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<th>Item</th>
<th>Disease inference (pain, fatigue, preoccupation, worry) on social and physical functioning</th>
<th>Pain/Physical Functioning</th>
<th>Pain, Fatigue and School</th>
<th>Treatment and Mood</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. How often did you worry that you might have pain or a crisis?</td>
<td>.623</td>
<td>.163</td>
<td>-.204</td>
<td>.382</td>
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<tr>
<td>11. How much were you bothered by pain when doing things with family or friends?</td>
<td>.820</td>
<td>.130</td>
<td>-.320</td>
<td>.093</td>
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<tr>
<td>12. How much were you bothered by tiredness when doing things with family or friends?</td>
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<td>.055</td>
<td>-.189</td>
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<td>13. How often did treatment for sickle cell interfere with doing things with family or friends?</td>
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<td>-.142</td>
<td>.035</td>
<td>.079</td>
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<td>14. How often did your family have to change plans because you were sick?</td>
<td>.771</td>
<td>.188</td>
<td>.145</td>
<td>-.208</td>
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<tr>
<td>15. How often did your parents keep you from doing things because you might have pain or a crisis?</td>
<td>.532</td>
<td>.043</td>
<td>.325</td>
<td>-.055</td>
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<tr>
<td>16. How often did you stay away from people or events so you wouldn't catch a cold or the flu?</td>
<td>.765</td>
<td>-.299</td>
<td>.378</td>
<td>-.113</td>
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<td>17. How much were you bothered by pain when playing or taking part in sports?</td>
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<td>.626</td>
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<td>18. How much were you bothered by tiredness when playing or taking part in sports?</td>
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<td>.528</td>
<td>.137</td>
<td>-.148</td>
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<tr>
<td>19. How often did treatment for sickle cell interfere with play, sports, or getting around?</td>
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<td>.579</td>
<td>.350</td>
<td>.206</td>
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<tr>
<td>20. How often did you have trouble walking or getting around?</td>
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<td>.598</td>
<td>.119</td>
<td>.120</td>
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<tr>
<td>Item</td>
<td>Disease inference (pain, fatigue, preoccupation, worry) on social and physical functioning</td>
<td>Pain/Physical Functioning</td>
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</tr>
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<td>-------------------------</td>
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<tr>
<td>21. How often did the weather keep you from doing things outdoors?</td>
<td>-.107</td>
<td>.929</td>
<td>-.032</td>
<td>.102</td>
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<td>22. How much were you bothered by pain that woke you up or kept you from sleeping?</td>
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<td>.886</td>
<td>-.145</td>
<td>-.045</td>
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<td>3. How much were you bothered by any treatment for sickle cell, like taking medicine or coming to hospital?</td>
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<td>.006</td>
<td>.903</td>
<td>.213</td>
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<tr>
<td>4. How much time did you spend in the hospital for a clinic visit or overnight stay?</td>
<td>.360</td>
<td>.126</td>
<td>.559</td>
<td>-.117</td>
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<tr>
<td>5. How much were you bothered by any sickness other than sickle cell, like a cold or the flu?</td>
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<td>-.168</td>
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<td>8. How much did feeling sad or down bother you?</td>
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<td>-.027</td>
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<td>1. How much were you bothered by pain?</td>
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<td>-.197</td>
<td>.742</td>
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<tr>
<td>2. How much were you bothered by tiredness?</td>
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<td>6. How often did pain make it harder to do schoolwork?</td>
<td>.257</td>
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<td>7. How much were you bothered by tiredness when doing schoolwork?</td>
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<td>-.098</td>
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<tr>
<td>9. How often were you angry, in a bad mood, or mean?</td>
<td>.397</td>
<td>.129</td>
<td>-.102</td>
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