Utilizing Patient-Reported Outcomes to Assess the Impact of Complex Medical Disorders in Children

A Dissertation Presented by

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In the Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in

Clinical and Translational Sciences

TUFTS UNIVERSITY

Sackler School of Graduate Biomedical Sciences

December 2015

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Abstract

Medical advances have extended survival for many conditions that were previously fatal in childhood. As a result of their underlying medical condition, children often experience decreased health-related quality of life (HRQL). In addition, parent caregivers, who often play a central role in the child's medical care, face newfound demands. Understanding the impact of complex medical conditions on children and their families will lead to better provision of care and improved health outcomes.

The objectives were (1) to assess the relationship between child HRQL and parent emotional functioning among children undergoing hematopoietic stem cell transplant (HSCT); (2) to determine whether the child's HRQL predicts future healthcare utilization among children with chronic respiratory insufficiency (CRI); and (3) to develop custom physical functioning short forms and explore scale scores and preliminary psychometric properties among children with CRI who are at risk for decreased physical functioning.

First, we utilized structural equation modeling (SEM) and linear regression modeling to assess the relationship between child HRQL and parent emotional functioning among 258 parent-child dyads undergoing pediatric HSCT. Both parent-proxy and child report were used to collect child HRQL. These analyses adjusted for child age. Second, we used negative binomial regression modeling to determine the relationship between parent-proxy report of child HRQL and total healthcare contact days in the 6-month window following the HRQL assessment among 120 children with CRI. This included inpatient days and days with emergency department or outpatient visits. These analyses adjusted for child age, physician-rated clinical severity, and years enrolled in a care coordination program. For the third dissertation objective, we developed two custom

parent-proxy physical functioning short forms that targeted the lower range of functioning using pediatric item banks from the Patient Reported Outcomes Measurement Information System (PROMIS). We explored the initial validity and psychometric properties of these custom short forms in 57 children with CRI.

Results from the SEM analysis revealed that our conceptual model that linked generic child HRQL to child HSCT-related worry, and then to parent emotional functioning provided a better fit than the conceptual model that placed child HSCT-related worry before generic child HRQL in relation to parent emotional functioning. Both the linear regression models and SEMs demonstrated relationships between child emotional functioning, child HSCT-related worry, and parent emotional functioning. However, there were some differences by parent-proxy and child raters. In the second project, three-quarters of children with CRI had any healthcare utilization and 32% were hospitalized during the 6-month window. We found that lower levels of child global HRQL and general health were both associated with more total healthcare contact days and inpatient days compared with those with better global HRQL and general health status, even after adjustment for clinical and demographic characteristics. Results from the third project showed that physical functioning scores were three standard deviations lower in children with CRI than in the general pediatric population. Preliminary psychometric validity was shown for the custom short forms, but many children still scored at the lowest end of the scale, and items about assistive devices proved inadequate in this sample.

These collective results help give a better understanding of the experience of children with complex medical conditions and their families. We observed associations between child emotional functioning, child HSCT-related worry, and parent emotional functioning

in the HSCT population. We observed high levels of healthcare utilization and decreased physical functioning among children with CRI. However, we also found opportunities to use patient- (or parent-proxy) reported outcomes to help identify patients who are at increased risk for negative health outcomes. Based on this, we can provide tailored clinical or psychosocial interventions that can improve health outcomes, reduce healthcare utilization, and provide better quality care.

Acknowledgements

This dissertation project would not have been possible without the support, commitment, and encouragement of a number of people. As the saying goes, it takes a village to raise a child (or in this case, a researcher). I am deeply grateful for their investment in helping me complete my doctorate, while making the experience enjoyable.

Susan K Parsons, my thesis committee chair, and my project and career mentor. It's been an absolute pleasure working with you over the past 8+ years. I'm lucky to have found such a devoted mentor with whom I share many research interests. You have always had faith in my abilities and have pushed me beyond my comfort zone. Thank you for always being there for me, both professionally and personally.

Norma Terrin, my statistical mentor. Your wealth of statistical knowledge has been a great resource while completing my doctorate and working on other research projects. Thank you for allowing me the independence to try new methods, while being there to bounce ideas off of, answer questions, and provide guidance.

Laurel K Leslie, my project and career mentor. Our collaboration on research projects and my dissertation over the past several years has provided me with an opportunity to learn many new research skills (and even some pediatric cardiology) and to experience working as part of a multi-disciplinary team. Thank you for always seeing the big picture and helping me to frame my research findings to reach the right stakeholders and have the most impact.

Robert J Graham, my project and career mentor. You have provided me with an invaluable opportunity to see the patients behind the data that I analyze. Thank you for

bringing me on CAPE home visits, allowing me to meet the clinical team, and most importantly, the CAPE families. Your patients are lucky to have such a compassionate and dedicated clinician.

I would also like to thank all of my colleagues in the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center. They have been with me for more than 11 years as I have grown from research assistant to faculty member. I have learned so much from our collaborations and have thoroughly enjoyed working together and getting to know you all.

I am grateful to my instructors at the Sackler School of Graduate Biomedical Sciences for educating and guiding me throughout the doctoral program. I am also thankful to all of my classmates for providing valuable input, constructive criticism, and sometimes-needed clinical context. Thank you to Program Director **David Kent** and Associate Director **Jessica Paulus**. In addition to your teaching skills, you both have been accessible, supportive, and always open to suggestions for improving the program. Thanks to **Nina Bonnoyer** and **Elizabeth Wiltrout** for the programmatic support that was always provided with a smile and positive attitude.

Finally, I would like to thank my family and friends. To my loving and always supportive mother and to my dad, who was always my number one fan. Although my dad will not be here to see me complete my doctorate, I know he would be brimming with pride as he called me Dr. Angie Mae Rodday. And to Tim, who has successfully taken on the role of being my number one fan.

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aGVHD	Acute graft versus host disease
AIC	Akaike information criterion
ANOVA	Analysis of variance
CAPE	Critical Care, Anesthesia, Perioperative Extension
ED	Emergency department
CAT	Computer adaptive testing
CFA	Confirmatory factor analysis
CFI	Comparative fit index
cGVHD	Chronic graft versus host disease
CHRIs	Child Health Ratings Inventories
CRI	Chronic respiratory insufficiency
HRQL	Health related quality of life
HSCT	Hematopoietic stem cell transplant
HSCT-CHESS	Hematopoietic Stem Cell Transplant-Comprehensive Health Enhancement Support Study
ICU	Intensive care unit
IRB	Institutional review board
IRT	Item response theory
JTR	Journeys to Recovery Study
MD	Muscular dystrophy
PEDI-CAT	Pediatric Evaluation of Disability Inventory-Computer Adaptive Test
PedsQL	Pediatric Quality of Life Inventory
PROMIS	Patient Reported Outcomes Measurement Information System
RMSEA	Root mean square error of approximation

SEM	Structural equation modeling
SMA	Spinal muscular atrophy
SRMR	Standardized root mean square residual

Chapter 1

Introduction

Chronic medical conditions are increasingly common among children and adolescents. An estimated 25% of children in the US suffer from at least one chronic health problem,[14] ranging from single to multi-system conditions. Technological advances in diagnosis and treatment have extended survival for many medical conditions that were previously fatal in childhood (e.g., complex heart disease, muscular dystrophy, cystic fibrosis, cancer). In addition to improvements in survival, technological advances have also allowed for a shift of care from the inpatient setting to outpatient or community settings. For example, portable ventilators allow children with ventilator-dependence to be cared for at home.[29, 31] Similarly, patients who are dependent on dialysis can receive peritoneal dialysis in the home. However, the increasing technology-based care at home places newfound demands on the parent caregiver, who often plays a central role in the child's medical care.

For nearly a decade as a member of a research program, I have collaborated on studies of two clinical populations that represent complex pediatric medical conditions: those undergoing hematopoietic stem cell transplant (HSCT) and those with chronic respiratory insufficiency (CRI). HSCT is a procedure used to treat a variety of malignant and non-malignant diseases in children.[76] Malignancies may include cancers of the blood or bone marrow, such as acute leukemia or lymphoma, or solid tumors, including neuroblastoma, bone cancers, and brain tumors. Non-malignancies may include disorders of the blood or bone marrow, such as bone marrow failure syndromes or hemoglobinopathies (e.g., sickle cell anemia or thalassemia), or disorders of the immune system or metabolism. CRI, which often requires artificial airway support and/or mechanical ventilation, can result from various underlying medical conditions, such as neuromuscular disease, spinal cord injuries, lung disease of prematurity, and organ transplant with residual lung disease. These populations provide a heterogeneous group

of children in which to better understand the range of health outcomes experienced by children with complex illness and the impact on their caregivers and families.

Although survival has improved, children with complex medical conditions are at heightened risk for negative health outcomes and associated medical costs. Moreover, the child and family may experience negative effects in other areas, such as health-related quality of life (HRQL).[10] According to the World Health Organization definition, health is not merely the absence of disease. Instead, health and HRQL are multidimensional constructs that incorporate many areas of functioning, such as physical, emotional, and social.[30] In their Conceptual Model of Patient Outcomes, Wilson and Cleary link biological features of disease to symptoms, functioning, and quality of life.[104] Dimensions of HRQL can be affected differently depending on health status or the particular health condition. Of note, researchers have found that physical conditions affect domains related to depression or anxiety,[82] in addition to physical functioning. Patient- (and parent-proxy) reported HRQL provides valuable information about clinical outcomes and the patient experience; information that may not be immediately apparent to the clinician. Depending on the research question or clinical purpose, HRQL can be used either as an outcome or as a predictor of other outcomes of interest, including future clinical events (e.g., deteriorating health, death) and healthcare utilization.[28, 41, 49, 86, 90]

There are many considerations when assessing HRQL. Measures exist for generic domains of HRQL, such as physical, emotional, and social functioning, that are relevant to everyone, regardless of their health status or underlying disease.[102] On the other hand, there are disease-specific HRQL instruments that measure areas of HRQL that are specifically affected by a given disease or medical condition.[38, 46] Generic measures

allow for comparisons across people with different diseases (or no disease) while disease-specific instruments allow for comparisons among people with a specific disease. Historically, HRQL "legacy" measures included a fixed set of items within a given domain designed to capture a broad range of functioning for the majority of the population with the least amount of respondent burden. However, these fixed measures may not always include questions that focus on the extremes of the domain. As an alternative to using legacy HRQL measures, expanded item banks, such as those compiled by the Patient Reported Outcomes Measurement Information System (PROMIS),[12, 16, 39, 73, 97] can be used to create data-driven measures, either as computer adaptive testing (CAT) or custom short forms, based on the performance of individual items across the full spectrum of functioning.

In addition to generic versus disease-specific measures, and legacy measures versus measures developed from larger item banks, consideration of the appropriate rater is important. In the case of pediatric medical conditions, either child report or parent-proxy report can be used to assess the child's HRQL. For school-aged children and adolescents, it is often recommended that both child/adolescent and parent-proxy raters be included as each may have different perspectives of the child's HRQL.[67, 70] This difference in perspectives refers to information and criterion variance where each rater has different access to information (information variance) and/or places different value on information (criterion variance). However, there are some situations when child report may not be possible due to developmental, cognitive, or functional limitations of the child. For HRQL domains that are more observable, such as physical functioning, agreement between child and parent-proxy raters is usually higher than for domains that are non-observable (also referred to as "beneath the skin"), such as emotional functioning.[67, 70] Interestingly, agreement between child and parent-proxy raters is higher

among children with chronic conditions compared with healthy children,[23] which is likely due to the close proximity (referred to as “shared reality”) between the parent and child when faced with a serious pediatric illness.

Children with chronic conditions, such as asthma, cancer, depression, and diabetes, experience decreased HRQL in a variety of domains compared with healthy children.[16, 26, 60, 96] Having multiple chronic conditions or poor disease control is associated with larger decrements in HRQL.[16, 82] For example, the literature suggests that children undergoing active cancer treatment report worse HRQL than cancer survivors.[16] However, the negative impact of cancer treatment on HRQL can persist after completion of therapy, particularly when compared with healthy controls.[19, 87] Among patients with Duchenne muscular dystrophy, HRQL, and especially physical functioning, is lower than the general population, and decreases with disease progression.[48, 95] Further, children with dependence on technology for their care experience negative emotional and social impact.[56]

Parents and families of children with complex pediatric diseases also experience decreased HRQL and functioning. Many parents of children with serious illness have reported psychological distress or decreased emotional functioning, manifested as depression, anxiety, post-traumatic stress syndrome, burnout syndrome, and sleep instability.[55] The parent faces the uncertainty of risky treatments, lack of available treatments, treatment complications, or fear of their child’s worsening health or even death.[91, 94] As primary caregivers, parents often find themselves taking on the role of both parent and nurse, which requires mastering a new set of skills that can take an emotional toll.[45] In addition, parents report social isolation from having to be the child’s primary caregiver and find it difficult to maintain a life outside of their child.[100] Clearly,

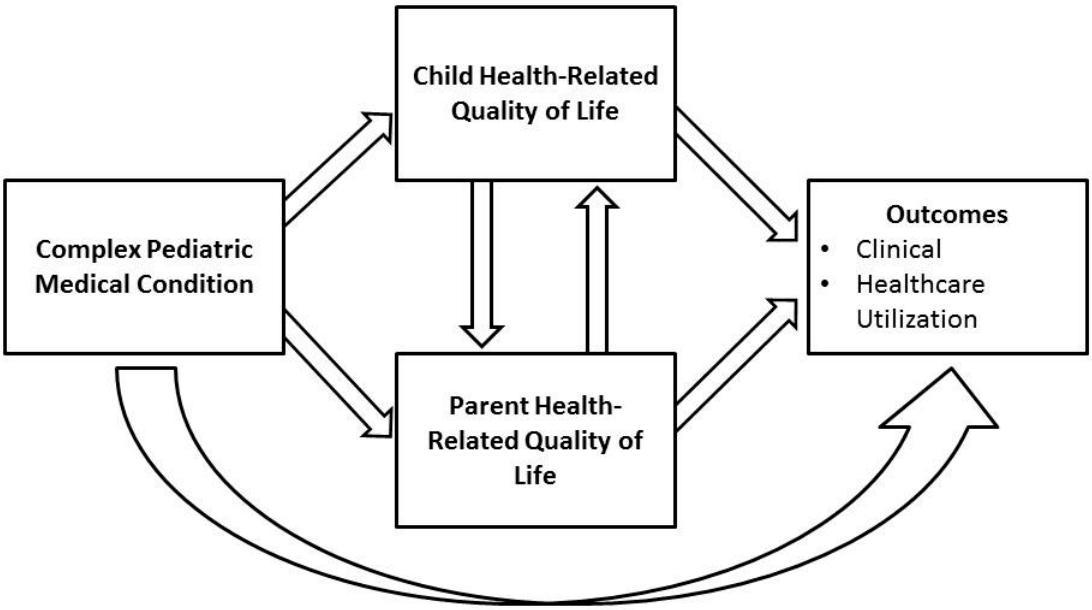
parents of children with complex diseases face challenges that affect their own HRQL, well-being, and emotional functioning, which can then affect their ability to care for their child.[15, 71, 72]

In order for the parent caregiver to help ensure the best health outcomes for their child, they must be an activated (i.e., informed and capable of taking action, even under stress) member of the care team.[71, 72, 99] According to the Chronic Care Model proposed by Wagner and colleagues,[99] individual, family, community, and healthcare system factors all lead to productive interactions between the activated patient (or parent caregiver in the case of childhood illnesses) and the prepared clinical team. Similarly, the Individual and Family Self-Management Theory links contextual factors (i.e., disease specific, physical and social environment, family and individual) to the process of self-management (i.e., self-efficacy, self-regulation, social facilitators), and to outcomes such as health status and quality of life.[85] Each of these models highlights the importance of an activated parent caregiver, which may be difficult to maintain when faced with internal or external stressors. For example, activation levels are affected by decreased emotional functioning, which is often seen among parents of children with serious illnesses.[72] Similarly, external factors, such as changing clinical status and complications or changes in financial status, have also been shown to affect levels of activation.[71] Therefore, identifying system-level or psychosocial supports or interventions that can help bolster the parent caregiver are needed to optimize child health outcomes.

Figure 1.1 presents the conceptual framework underlying this dissertation, which includes the interplay between the child's medical condition, the child's HRQL, the parent's HRQL, and the child's future health outcomes. In developing this framework, we began with Wilson and Cleary's Conceptual Model of Patient Outcomes[104] to link

disease with HRQL, which provides the basis for this entire dissertation project. Understanding the relationship between the child's HRQL and the parent's emotional functioning (goal #1) can help us to identify opportunities to provide psychosocial support to parents, which is necessary for improved child health outcomes according to both the Chronic Care Model[99] and the Individual and Family Self-Management Theory.[85] Using HRQL scores to predict future health outcomes (goal #2) will allow identification of at-risk children for whom system-level intervention or support,[99] such as more frequent home visits, increased nursing hours, or social work intervention, can be provided to help avoid negative health outcomes. Finally, within the context of the child's HRQL, reliably measuring the domain of physical functioning (goal #3), which often includes the ability to perform activities of daily living, is necessary to target clinical or system-level interventions.

Figure 1.1: Conceptualization of child and parent health-related quality of life and health outcomes in the context of complex pediatric medical conditions



Specifically, the goals of this dissertation research were to:

1. Assess the relationship between child HRQL and parent emotional functioning among children undergoing HSCT.
2. Determine whether the child's HRQL predicts future healthcare utilization among children with CRI.
3. Develop custom physical functioning short forms and explore scale scores and preliminary psychometric properties among children with CRI who are at risk for decreased physical functioning.

Better understanding the health outcomes and HRQL among children with complex medical conditions will allow for improvements in care delivery and support for the children and their families. This should then result in improved health outcomes, reduced costs, and better quality of care, aligning with national calls for the "triple aim" of healthcare improvement efforts.[5] The following sections in this chapter provide background on each of the dissertation projects.

1.1 Understanding the Relationship Between Child Health-Related Quality of Life and Parent Emotional Functioning in Pediatric Hematopoietic Stem Cell Transplant

Many parents of children with serious illness, and cancer in particular, face psychological distress, such as anxiety, depression, post-traumatic stress syndrome, and burnout syndrome,[6, 62, 78] and decreased emotional functioning.[6, 54, 79, 106] In addition to the psychological distress associated with having a child with cancer, the parent caregiver must deal with the uncertainty of high-risk treatments. Although treatments offer a potential cure for these life-threatening pediatric medical conditions, they are not without risks, including both short- and long-term morbidity, as well as the possibility of treatment failure, relapse, or death.

Parents of children undergoing HSCT, which is a treatment for a variety of malignant and non-malignant diseases, represent one example of parents facing uncertainty and distress about their child's future health. Malignancies treated by HSCT may include cancers of the blood or bone marrow, such as leukemia or lymphoma, or as "rescue therapy" for aggressive treatment of solid tumors, including neuroblastomas, bone cancers, and brain tumors. Non-malignancies may include disorders the blood or bone marrow such as bone marrow failure syndromes or hemoglobinopathies (e.g., sickle cell anemia or thalassemia), or disorders of the immune system or metabolism.

The HSCT course can be divided into pre-transplant evaluation and preparation, peri-transplant hospitalization, and post-discharge follow-up phases. During the pre-transplant phase, children and their families (or a parent caregiver) may be relocated to the transplant center to undergo the extensive pre-transplant evaluation and preparation

for the HSCT. During the preparative period, the patient receives a conditioning regimen that may include chemotherapy with or without radiation. Following the transplant infusion/reinfusion, the child remains hospitalized, awaiting successful engraftment and reconstitution of normal blood cells. During this period, the child may be at risk for acute complications, such as infection and organ toxicity; some patients are also at risk for acute graft versus host disease (aGVHD). In the later follow-up period, the child is at risk for chronic graft versus host disease (cGVHD) and late-onset infection. The possibility of relapse or death exists throughout the entire HSCT course.

Parent emotional functioning is influenced by the child's HSCT course, including such complications as aGVHD, organ toxicity, cGVHD, and infection.[91] However, the interplay between the child's HRQL during the HSCT course and the parent's emotional functioning is less well understood. Our conceptual framework builds on the Wilson and Cleary model that links biological features of disease to symptoms, functioning, and quality of life.[104] The HSCT course, and its resulting complications and adverse effects (e.g., aGVHD, infection), may cause the child to worry about their future health. These adverse effects and worry about future health may result in decreased child HRQL.[62, 80] As a result, the parent's HRQL, and notably their emotional functioning, may be affected. Alternatively, the complications and adverse effects of HSCT can cause decreased child HRQL and functioning, which may result in increased child worry about their future health, and finally affect the parent's emotional functioning. The parent may then have difficulty being an effective caregiver in the presence of this psychological distress.[71, 72]

Given the parent's important role as the child's primary caregiver, describing the relationship between the child's HRQL and the parent's emotional functioning is paramount to understanding how to support the parent, which should then lead to

improved clinical and HRQL outcomes in their child. As such, this dissertation project explored which components of the child's HRQL were associated with parent emotional functioning at the acute post-transplant phase, a period where the risk for adverse effects is high and HRQL is near its nadir. Specifically, we assessed whether the child's worry about their future health affected different domains of their HRQL, which in turn affected the parent's emotional functioning. We also assessed an alternative model that placed child HRQL before child worry about their future health in relation to parent emotional functioning. Both parent-proxy ratings of their child's HRQL and child ratings of their own HRQL were used to examine whether the interplay between the child's HRQL and the parent's emotional functioning differed by rater.

1.2 Predicting Healthcare Utilization for Children with Respiratory Insufficiency Using Parent-Proxy Ratings of Children's Health-Related Quality of Life

Chronic respiratory insufficiency and need for intermittent or continuous mechanical ventilation can occur in association with a variety of pediatric medical conditions, including intrinsic lung disease, neuromuscular disorders (e.g., muscular dystrophy [MD], spinal muscular atrophy [SMA]), skeletal dysplasias, and spinal cord injury. Recent technological innovations have allowed many children with these medical conditions to receive home-based care in their communities.[65] Despite this shift to home-based care, including mechanical ventilation, children requiring technology assistance are significantly more likely to develop a severe acute illness that will result in unscheduled and costly hospitalizations with care delivered in the intensive care setting.[18, 21] Identifying patients at risk for acute clinical events, and associated healthcare utilization, would help to optimize health outcomes, reduce costs, and improve the child's and family's care experience, aligning with national calls for the triple aim of healthcare improvement efforts.[5]

HRQL assessments provide valuable information about clinical outcomes and healthcare quality and can also serve as predictors of future outcomes, such as prognosis and survival.[13, 24, 28, 41, 90] Limited studies have shown that HRQL scores predict healthcare utilization;[43, 49, 66, 84, 86, 103] even fewer studies have focused on pediatric populations. As examples, a study among children enrolled in a managed care plan[86] and a study among children with inflammatory bowel disease[84] both found that HRQL predicted healthcare utilization, independent of demographic and clinical factors. These findings imply that clinical factors alone do not fully explain healthcare utilization and that HRQL

assessments add nuances to the patient experience that provide differentiation beyond clinical factors. Therefore, HRQL assessment may help predict clinical events and healthcare utilization and serve as a marker to intervene and preempt high-cost acute care.

The objective of this dissertation project was to determine whether brief parent-proxy report of their child's HRQL was associated with future healthcare utilization in a population of children with CRI. Secondarily, we sought to understand if parent-proxy report of their child's HRQL provided additional information above and beyond physician-rated clinical severity in predicting healthcare utilization. This cohort of children is at high risk for urgent and unplanned healthcare utilization, making it a highly relevant group in which to examine potentially avoidable high-cost healthcare utilization.

1.3 Leveraging Pediatric PROMIS Item Banks to Assess Physical Functioning in Children at Risk for Severe Functional Loss

Chronic illnesses of childhood, including the muscular dystrophies, spinal muscular atrophy, skeletal dysplasias, and spinal cord injuries, may result in decreased HRQL, notably in the domain of physical health.[34, 75] The physical functioning component of physical health can be measured using clinical assessments and/or by self- (or parent-proxy) report questionnaires. Typically, self- or proxy report measure physical functioning using items or questions assessing varying levels of difficulty from mild to strenuous. Historically, legacy HRQL measures included a fixed set of items within a given domain to capture a broad range of functioning for the majority of the population. However, many of these scales included items about walking, exercising, and lifting,[68, 101, 102] which may not adequately capture physical functioning among patients with severe functional loss or allow for discrimination among patients with different levels of functional loss.[27] Thus, assessing physical functioning in a population that is expected to have low functioning using existing measures has proven challenging.

In the clinical setting, several measures are used among those with limitations due neuromuscular disorders, including the Performance of the Upper Limb (PUL),[63] the Brooke Upper Extremity Scale,[9] the North Star Ambulatory Assessment for ambulatory children,[52] the Hammersmith Functional Motor Scale (used in patients with SMA),[50] and the Egen Klassifikation (EK) scale for non-ambulatory children.[88] These measures are typically completed by a trained clinician (e.g., physiotherapist) as part of the clinic visit. Disease-specific HRQL measures, such as the Pediatric Quality of Life Inventory (PedsQL™) Neuromuscular module rely on self- (or parent-proxy) report to measure areas of HRQL specifically affected by a given disease or medical condition, but only

allow for comparison within the disease group. In some instances, such comparisons within diseases or medical conditions are important or desired. However, our goal was to use a generic tool, rather than a clinical assessment or disease-specific instrument, to collect and compare HRQL domain scores across a range of different diagnoses and ages, and particularly in children with low physical functioning. Using a generic tool is important because each of these illnesses is relatively rare. Secondary complications, such as CRI, are often managed in multi-disciplinary clinics, spanning various underlying medical conditions. In addition, unlike clinical assessments, HRQL measures do not require clinician involvement, so they can be administered remotely by self- or parent-proxy report, possibly between or during clinical visits, and can provide unique information about the patient experience not available from clinical assessments.

PROMIS, created in 2004 as part of a trans-National Institutes of Health (NIH) initiative to enhance the tools of clinical research, offers a new and improved method for generic HRQL assessment across a full spectrum of functioning. PROMIS investigators utilized standardized procedures to create item banks in many domains including emotional distress, fatigue, pain, physical functioning, and peer relationships.[73] The item banks have undergone extensive psychometric evaluation including assessment of validity and reliability.[12, 16, 39, 97] For example, the pediatric item banks have been validated in general populations and in children with sickle cell disease, obesity, cancer, rheumatic diseases, chronic kidney disease, and rehabilitative needs. Item banks can be administered as computer adaptive tests or fixed length short forms with high relative validity across a broad range of functioning. Additionally, item banks can be used to construct custom short forms. Because PROMIS item banks were evaluated using item response theory (IRT),[77] scores from any subset of items from the bank (e.g., custom short form, CAT) produce standardized scores on the same scale, regardless of which items from the

bank are included in the measure. This enables construction of a custom short form that specifically targets lower levels of physical functioning that would be hypothesized to better distinguish patients in this lower range of functioning.

The purpose of this project was to create two custom parent-proxy physical functioning short forms using the PROMIS item banks for Upper Extremity function and Mobility and explore scores and preliminary psychometric properties and validity among children with CRI due to diverse underlying neuromuscular illnesses that put them at risk for low levels of physical functioning. We assessed construct validity by comparing custom short form scores with scores on physical and mental health items from the Child Health Ratings Inventories (CHRIs) global HRQL scale. Given the developmental, cognitive, and functional limitations in this population of children, we relied on parent-proxy report. Although agreement between child report and parent-proxy report is not always high for domains that are “beneath the skin,” such as emotional or social functioning, there is generally better agreement on more objective domains, such as physical functioning.[67, 98]

Chapter 2

Materials and Methods

2.1 Understanding the Relationship Between Child Health-Related Quality of Life and Parent Emotional Functioning in Pediatric Hematopoietic Stem Cell Transplant

Sample

This analysis used data collected as part of two longitudinal studies: (1) the Journeys to Recovery (JTR) study, which described the 12-month HRQL trajectory following HSCT, and (2) the HSCT-Comprehensive Health Enhancement Support Study (CHESS^{TM}), which was a randomized, controlled trial of a web-based intervention designed to improve the health-related knowledge, skills, and quality of life of parents of children undergoing HSCT. Together, these studies were conducted at eight HSCT centers across the United States from 2003 to 2011 and included 363 parent-child dyads. Eligibility included a working knowledge of English and having a parent/legal guardian who could consent on behalf of the child. Parental consent and age-appropriate assent were obtained. The studies were approved by the institutional review board (IRB) at each clinical center and at Tufts Medical Center. Because the HRQL measures used in this analysis were developed for use in children and adolescents aged 5-18 years, parent and child dyads were removed from the analysis if the child was less than five years old (n=53). Although these studies collected data longitudinally, only data from the 45-day assessment were used in the current analysis because this time period captures the acute phase following transplant while still maintaining a large sample size not available at later time periods. After excluding an additional 52 dyads that were missing the 45-day assessment, our finalize sample size was 258.

Measures

Child Health Ratings Inventories: This validated measure has rater- and age-specific versions and separate modules for generic and HSCT-specific HRQL.[68, 69] The parental version of the CHRIs includes two sections: (1) parent-proxy report of the child's health and functioning and (2) parent report of their *own* functioning. The school-aged child version (ages 5-12 years) of the CHRIs elicits child report of their own health and functioning using pictorial response sets, while the adolescent version (ages 13-18 years) is text-based with parallel wording to the parent version. The 20 items from the CHRIs-General module form three domains of generic HRQL: physical, emotional, and functioning. To supplement the CHRIs-General, a 10-item HSCT module was developed and validated in the 1990's to measure three domains of child HRQL related to the HSCT: hassles, worry about transplant-related outcomes (infection, rehospitalization, relapse), and body image. While variability in clinical practice has become more apparent across clinical sites and over time in protective isolation practices and medication use, rendering the domains of hassles and body image less reliable across clinical sites (Cronbach's alpha 0.45 to 0.63), HSCT-related worry remains reliable, regardless of clinical site, indication for transplant, or treatment era. Thus, only the child HSCT-related worry domain was used in the current analysis. See Table 2.1 for complete CHRIs item content by domain. All CHRIs items use an acute, 1-week recall period because of the rapidly changing health status of pediatric patients undergoing HSCT. All response sets have five options with scores ranging from 1-5. Using established conventions for generic and disease-specific scales, higher scores on the CHRIs-General domains connote better HRQL, whereas higher scores on the HSCT-related worry domain connote more worry.

Table 2.1: HRQL items by domain

Parent emotional functioning (k=7)
1. Nervous
2. Happy or sad
3. Calm and peaceful
4. Down-hearted
5. Happy
6. Hassled
7. Stressed
Child physical functioning (k=5)
8. Exercise hard/Play hard
9. Exercise moderate/Play ball
10. Walk blocks/Swing
11. Lift, carry, climb
12. Housework
Child emotional functioning (k=7)
13. Rest
14. Doing
15. Fun
16. Nervous
17. Happy or sad
18. Energy play
19. Pain
Child role functioning (k=4)
20. Family
21. Pay attention
22. Concentrate
23. Friends
Child HSCT-related worry (k=3)
24. Hospital
25. Infection
26. Disease

Demographic and medical information: As part of the baseline assessment in both studies, demographic variables on the patients and their parents were obtained. Trained research staff collected clinical data from medical records, including the following baseline variables: transplant type (autologous, related allogeneic, unrelated allogeneic), causal diagnosis (malignancy vs. non-malignancy), and duration of illness in months.

Throughout the transplant course, data on clinical outcomes, including infection, treatment toxicity, aGVHD, and cGVHD were collected. A binary, composite variable for complications by 45 days post-transplant was created. This included aGVHD grade 2 or higher or systemic infection, based on widely used clinical grading scales.

Statistical Analysis

Demographic and clinical variables and HRQL scores were summarized using means (standard deviations (SD)) or medians (25^{th}-75^{th} percentiles) for continuous variables or using frequencies and percentages for categorical variables. Using chi-square tests or two-sample t-tests, we compared baseline characteristics of parents and children completing the 45-day assessment to those who did not complete the assessment to detect for differences that could affect generalizability of the findings. Cronbach's alpha was used to assess internal consistency reliability of the CHRIs domains and Pearson correlations between domains were reported. For Cronbach's alpha, values should exceed 0.80 for established scales.[61] For Pearson correlations, we considered correlations <0.30 as low, 0.30-0.60 as moderate, and >0.60 as high.

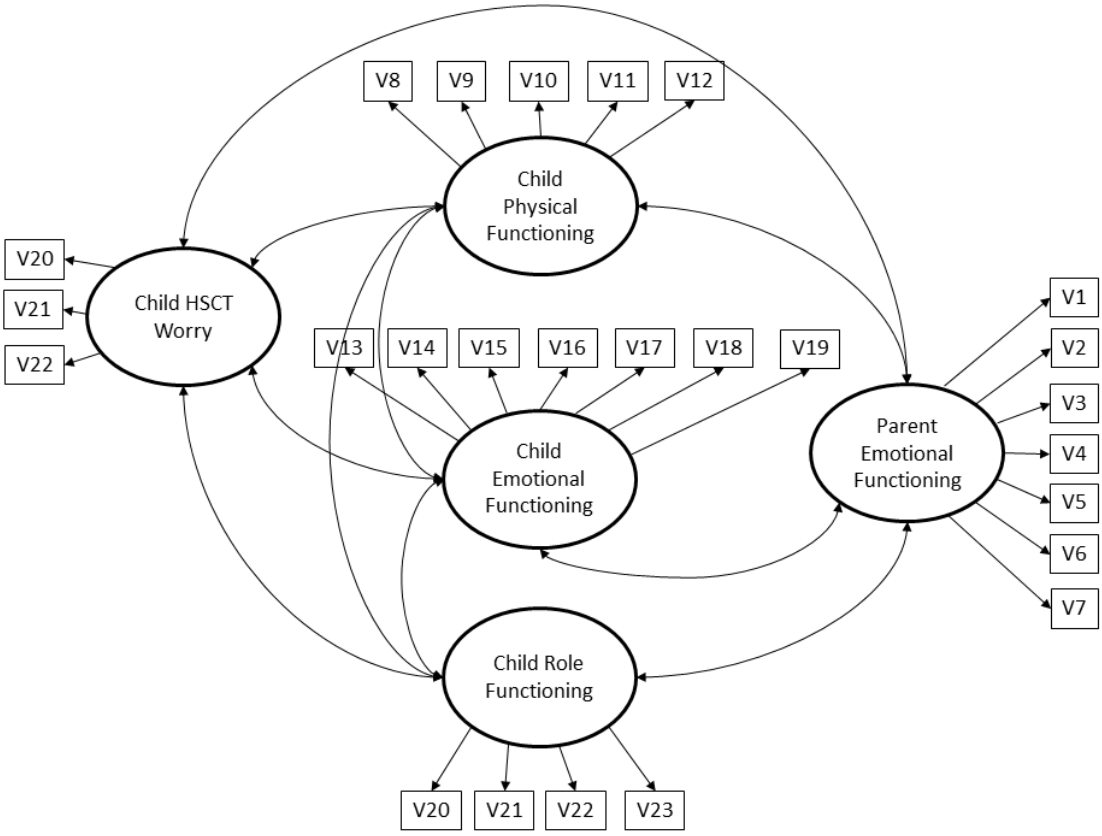
Two separate analytic techniques (linear regression and structural equation modeling [SEM]) were used to assess the relationship between the different domains of child HRQL and parent emotional functioning. Linear regression allows examination of direct relationships between dependent and independent variables, but does not allow examination of pathways between independent variables or indirect pathways leading to the dependent variable. On the other hand, SEM allows variables to be both dependent and independent, and it allows examination of indirect pathways leading to the dependent variable. Given the larger number of parameters estimated in SEM, a sample size of at least 200 observations is recommended.[7, 92] For each analytic technique,

separate sets of models were constructed using child report of their own HRQL and parent-proxy report of the child's HRQL. Parents reported on their own emotional functioning for all models. For the linear regression models, all of the HRQL domains were scored using the half scale rule, which requires that at least half of the items in a scale be completed in order to calculate a score. The items are averaged together to create a summary scale score, and then transformed to a 100-point scale. On the other hand, all of the HRQL domains (i.e., latent variables) used in the SEM analyses were scored using the solution to the confirmatory factor analysis (CFA). Rather than weighting each item equally, as is done when items are averaged together, this method uses a weighted combination of the item scores based on the factor loadings. The factors loadings and scores are obtained using the maximum of the posterior distribution, also known as the Regression Method.[59] We used the untransformed 5-point item scoring for this method and resulting scores had a mean of 0.

A series of linear regression models with parent emotional functioning as the outcome were built. These models included: univariate models for each child HRQL domain; all generic child HRQL domains together in one model; and the child HSCT-related worry domain and the generic child HRQL domains together in one model adjusting for child age. Standardized beta coefficients were also reported for easier comparison across models and to the estimates from the SEMs, which had a different range of possible scores based on the scoring method used. For standardization, the variances of dependent and independent variables were standardized to equal one, so the coefficients are interpreted as the number of SDs the dependent variable changes given a change of one SD in the independent variable.

Before constructing the SEMs, CFA was used to assess the measurement models (Figure 2.1) and calculate factor scores. The fit of the models were assessed using the root mean square error of approximation (RMSEA), the comparative fit index (CFI), the Tucker-Lewis Index (TLI), and the standardized root mean square residual (SRMR). The following criteria are indicative of acceptable model fit: RMSEA <0.06; CFI and TFI close to 0.95 or greater; and SRMR <0.08.[37] Model chi-square statistics were also reported. Non-significant chi-square statistics indicate acceptable model fit; however, given the large sample sizes used in SEM, the chi-square statistic is often statistically significant limiting its usefulness as a fit statistic.[42] To improve fit of the measurement models, additional parameters representing covariance between items were added to the model based on modification indexes >10 and the face validity of the relationship between the items. Items were not allowed to load onto other factors and no items were removed in order to maintain consistency with the original CHRIs domains. Making post hoc modifications to the measurement model, such as adding item-level covariances, should be justified and done with caution. These modifications may be specific to the analyzed sample and may not be generalizable to other samples. In this analysis, having a measurement model with adequate fit was necessary to achieve the study aim of assessing the different structural equation models. Therefore, we thought it was necessary to add item-level covariances to the measurement model to improve the fit, provided that the item relationships had face validity.

Figure 2.1: Measurement model demonstrating relationships between observed and latent variables



SEMs using maximum likelihood estimation were built with parent emotional functioning as the outcome and the child HRQL domains as latent factors, with child HSCT-related worry domain preceding the generic child HRQL domains, according to our primary conceptual model. Paths were eliminated one-by-one according to the largest p-value until all p-values for the paths were <0.1. Alternative SEMs were explored that placed the generic child HRQL domains before the HSCT-related worry domain in association with parent emotional functioning. This represents an alternative conceptual model where decreased child HRQL and functioning could lead to child HSCT-related worry. Akaike information criterion (AIC) values were reported for the different models allowing for comparisons of their fit, with lower AIC values indicating better fit. Comparable to the

linear regression models, the SEMs also adjusted for child age as a potential confounder of the relationships. Standardized coefficients were also reported for easier comparison across models and to the estimates from the linear regression models, which had a different range of possible scores based on the scoring method used. Variances for both dependent and independent latent variables were standardized to one (with the same interpretation as the standardized linear regression coefficients). For parents and children who completed the 45-day assessment, we assumed that any item-level missing data were missing at random (given that they had completed other items within that domain) and were therefore accommodated using full information maximum likelihood estimation, which uses all available information to estimate the model parameters. To further verify this assumption, we assessed item-level missingness to help determine if parents and children skipped any items more than others.

Sensitivity analyses: Several sensitivity analyses were done to understand whether the results differed by important subgroups, including school-aged (5-12 years old) versus adolescent (13-17 years old) children and those with the presence of complications by 45 days post-transplant. For child age, we added interaction terms between binary child age and each of the child HRQL domains included in the linear regression models. For treatment complications, we also added interaction terms between binary complications and each of the child HRQL domains included in the linear regression models.

Mplus (Version 7)[58] was used to fit the measurement and structural models. All remaining analyses were conducted in SAS Version 9.4 (SAS Institute, Inc., Cary, NC). The type I error rate was set to 0.05.

2.2 Predicting Healthcare Utilization for Children with Respiratory Insufficiency Using Parent-Proxy Ratings of Children's Health-Related Quality of Life

Sample

Data come from a longitudinal HRQL study of families of patients receiving care through the Critical Care, Anesthesia, Perioperative Extension (CAPE) and Home Ventilation Program at Boston Children's Hospital, previously described.[32] Briefly, the CAPE Program provides integrated, home-based care to pediatric patients with CRI from a variety of underlying chronic conditions, including intrinsic respiratory and neuromuscular disorders. Eligible participants were receiving ongoing care from the CAPE Program, not living in a residential facility, and aged 30 days to 22 years, representing the full range of age eligibility in the clinical program. Parent caregivers were ≥18 years old, actively participating in their child's care, and able to complete measures in English or Spanish. In families with more than one eligible child, parents only participated on behalf of one. Of the 196 parents eligible between February 2012 and March 2013, 140 (71%) were enrolled in the HRQL study. This study was approved by the IRB at Boston Children's Hospital.

Measures

Child Health Ratings Inventories: The CHRIs,[68, 69, 80] a validated and reliable HRQL instrument with child and parent versions, was used to collect parent-proxy report of the child's HRQL. Parent-proxy report was used because of developmental, cognitive, and functional limitations of many children in this sample. The current analysis included parent-proxy reports of both the 5-item child global HRQL scale, which assesses physical, emotional, and social functioning, and a single item on the child's general

health. Items were scored from 1-5; scale scores were then transformed to 0-100, where higher scores indicate higher HRQL or better health. The global HRQL and general health scores were both categorized into three levels based on the distribution of responses in this sample, assessment of linearity (Table 2.2, Figure 2.2, Figure 2.3), and to ease interpretability: <50 points (poor/fair), ≥50 to <75 points (good), and ≥75 points (very good/excellent).

Table 2.2: Summary statistics for continuous variables

Variable	Mean (SD)	Median (25^{th}-75^{th} percentile)	Min	Max
Child global HRQL	62.8 (25.2)	50 (25, 75)	0	100
Child general health	48.1 (26.0)	65 (45, 40)	0	100
Clinical severity	5.7 (2.1)	6 (4, 7)	1	10
Child age in years	8.5 (6.2)	7.5 (3, 13)	0	22
Years enrolled in the CAPE Program	1.1 (1.1)	1 (0, 2)	0	4

Figure 2.2: Distribution of child global HRQL (top panel) and plot of Pearson residuals vs. child global HRQL (bottom panel)

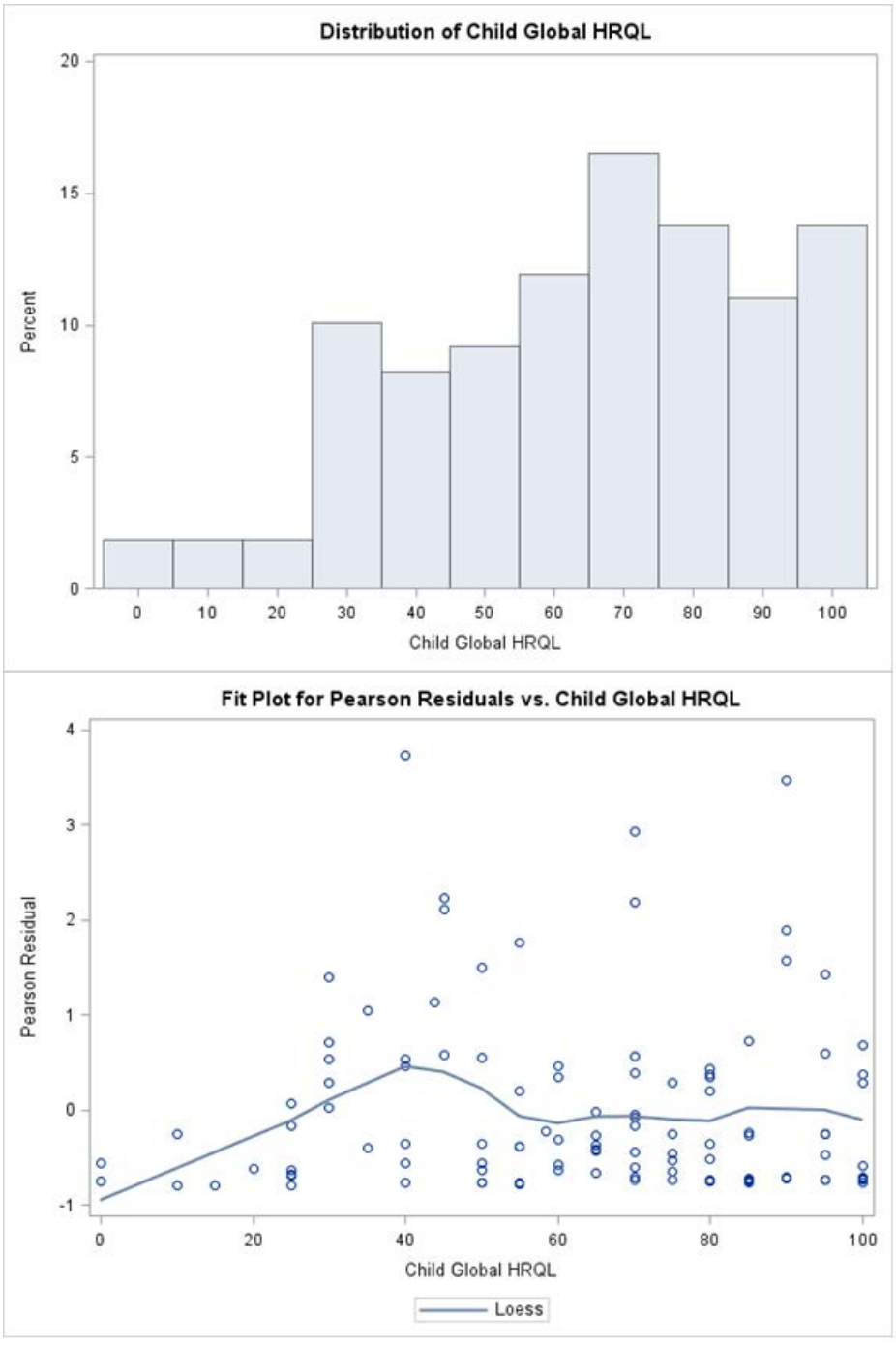
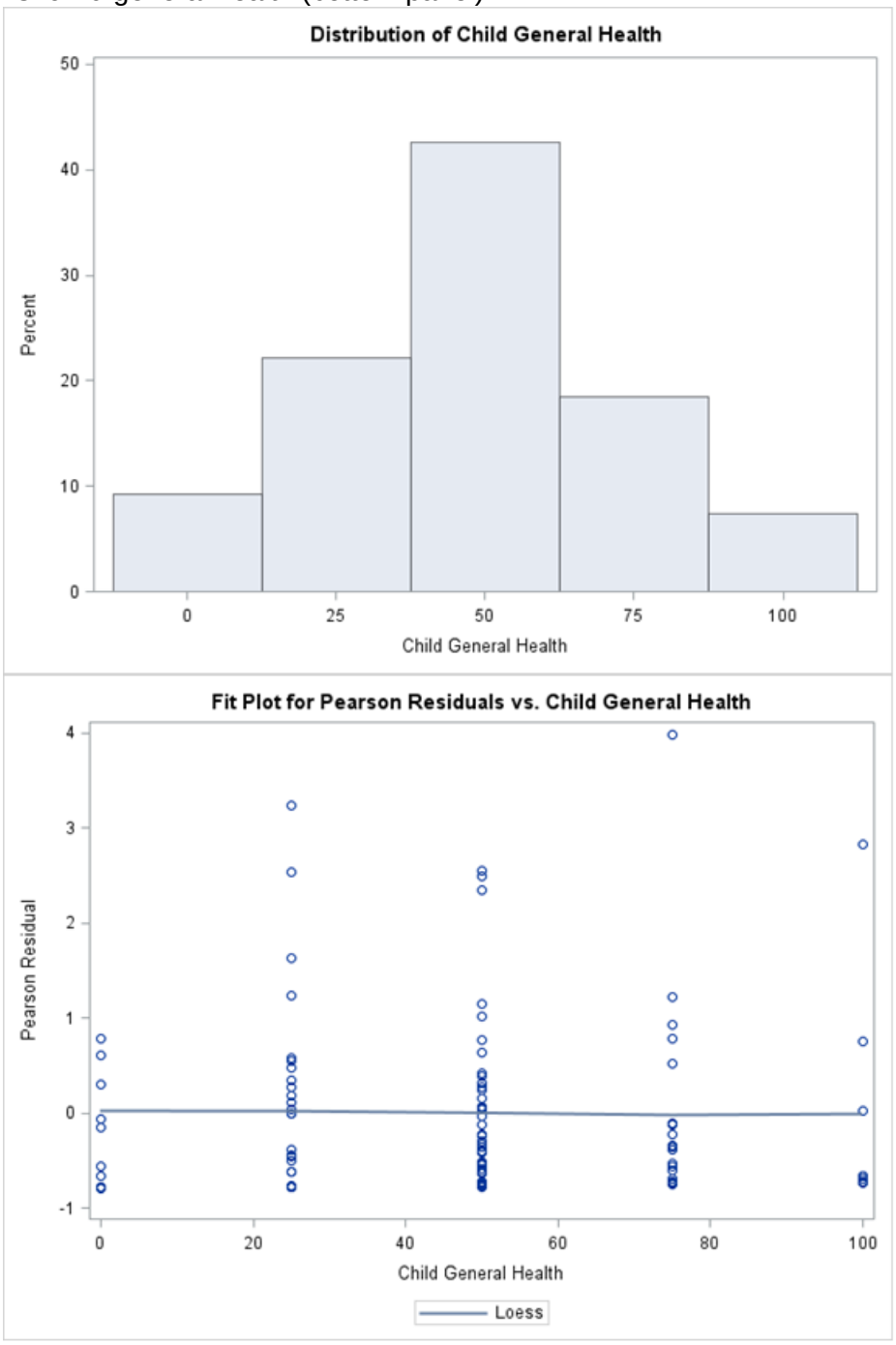


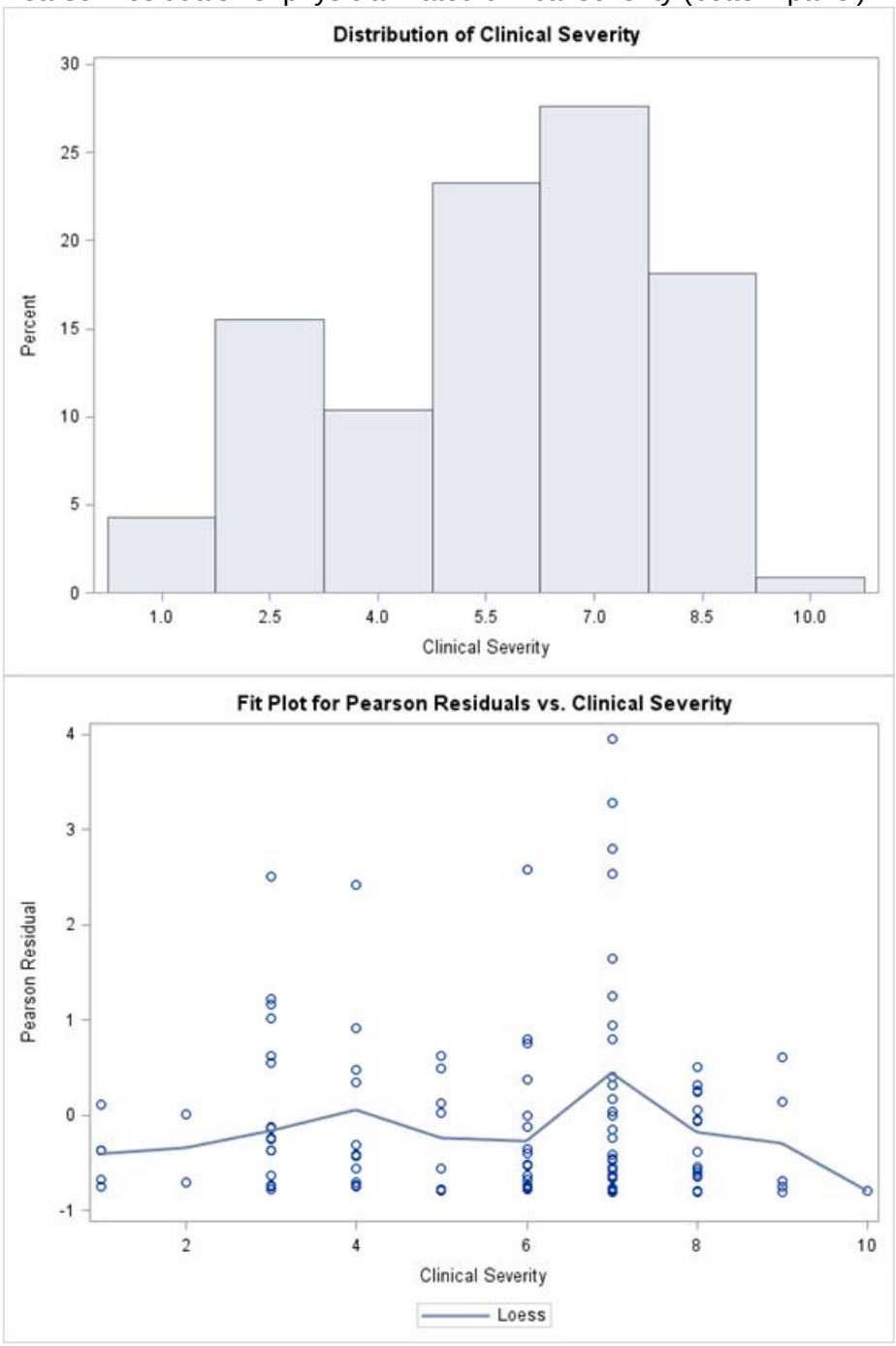
Figure 2.3: Distribution of child general health (top panel) and plot of Pearson residuals vs. child general health (bottom panel)



While parents completed measures about their child's HRQL every six months for up 18 months, depending on enrollment date into the HRQL study, this analysis focused on HRQL assessments collected at study entry only. Participants could complete measures either on paper or online via StudyTRAX (Macon, GA), a web-based data collection platform. (http://www.studytrax.com/).

Demographic and clinical variables: Parents reported on child and family demographic characteristics, including child and parent gender and age. Race/ethnicity was supplied from the clinical report together with insurance status, diagnosis, respiratory support status, and physician-rated clinical severity. Respiratory support status was categorized as artificial (tracheostomy), artificial + ventilator (tracheostomy and ventilator), non-invasive (continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP]), or none. This latter category commonly reflected the family's choice to limit mechanical support recognizing potential health and longevity implications. Those without respiratory support could still require supplemental oxygen. Physician-rated clinical severity (1=least severe, 10=most severe) was collected using a single item severity measure from the National Survey of Children with Special Health Care Needs.[93] This item was categorized into three levels based on the distribution of responses in this sample, assessment of linearity (Table 2.2, Figure 2.4), and to ease interpretability: ≤5 points (least severe), >5 and ≤7 points (moderately severe), and >7 points (most severe).

Figure 2.4: Distribution of physician-rated clinical severity (top panel) and plot of Pearson residuals vs. physician-rated clinical severity (bottom panel)



Healthcare utilization*:* Healthcare utilization was measured as the number of documented emergency department (ED), outpatient, and inpatient days on which the patient had contact with the healthcare system over the six months following the HRQL assessment. The source of healthcare utilization was billing data from Boston Children's Hospital. Participants who did not have available billing data for at least five months following their HRQL assessment were excluded from this analysis. This ensured that all participants had a comparable timeframe in which to experience healthcare utilization. However, to assess for differences in those who were excluded due to death, we compared HRQL scores and utilization among those who died in the assessment window and those who did not.

The number of ED, outpatient, and inpatient days were summed to create a "total healthcare days" variable. If multiple visits occurred on a given day, such as an ED visit and an inpatient admission, only one was counted. A separate variable that only included inpatient days was also created. We then created two binary variables for any healthcare utilization or any hospitalization during the 6-month window. The variable for any healthcare utilization was defined as "yes" if the patient had at least one ED, outpatient, or inpatient day, and was defined as "no" if they had none. The variable for any hospitalization was defined as "yes" if the patient had at least one inpatient day, and was defined as "no" if they had none. The primary outcome was total healthcare days within six months following the HRQL assessment. The secondary outcome was inpatient days during the same window.

In addition to examining utilization in the 6-month window following HRQL assessment, we also explored 1- and 3- month windows. To be included in the 1-month window,

patients had to be eligible for 3 weeks of data within the billing data; to be included in the 3-month window, patients had to be eligible for 2.5 months of data within the billing data.

Data Analysis

Demographic and clinical variables, HRQL scores, and healthcare utilization were summarized using means (SDs), medians (25^{th}-75^{th} percentiles), or frequencies and percentages. For days of healthcare utilization, median values excluding children with 0 days of utilization were also calculated ("non-zero median"). Healthcare utilization was described by the three categories of global HRQL, general health, and clinical severity.

To assess for differences in respondents and non-respondents, we compared child age, child gender, clinical severity, diagnosis, and respiratory support among those eligible to participate in the HRQL study (n=196) by enrollment status and inclusion in the current analysis. This was done using the two-sample test, Wilcoxon rank sum test, or chi-square test.

Generalized linear models (PROC GENMOD in SAS) with a negative binomial distribution and log link were used to assess the relationship between HRQL and days of healthcare utilization. The negative binomial distribution was used to account for overdispersion (i.e., more variability than expected) observed with the Poisson distribution (Table 2.3).

Table 2.3: Evidence of overdispersion for Poisson regression[a]

Model	Deviance/DF
Total healthcare days and global HRQL, fully adjusted	7.3084
Total healthcare days and general health, fully adjusted	7.5176
Inpatient days and global HRQL, fully adjusted	7.2899
Inpatient days and general health, fully adjusted	6.7991

[a] A primary assumption of Poisson regression is that mean is equal to the variance; this assumption is violated if there is overdispersion, which is present when the deviance divided by its degrees of freedom is greater than 2.

Separate models were built for categorical global HRQL and categorical general health. The first set of models was unadjusted, then we adjusted for categorical clinical severity, and finally for categorical clinical severity, years enrolled in the CAPE Program, and child age. Rate ratios and 95% confidence intervals were reported. Linearity was assessed for continuous variables using Pearson residuals plots. Child age was categorized as 0-4, 5-10, and 11+ years, based on graphical displays, to account for non-linearity (Figure 2.5). Continuous years enrolled in the CAPE Program met linearity assumptions (Figure 2.6). Continuous forms of global HRQL, general health, and clinical severity were considered, but general health and clinical severity did not meet linearity assumptions (Figure 2.2, Figure 2.3, Figure 2.4).

Figure 2.5: Distribution of child age (top panel) and plot of Pearson residuals vs. child age (bottom panel)

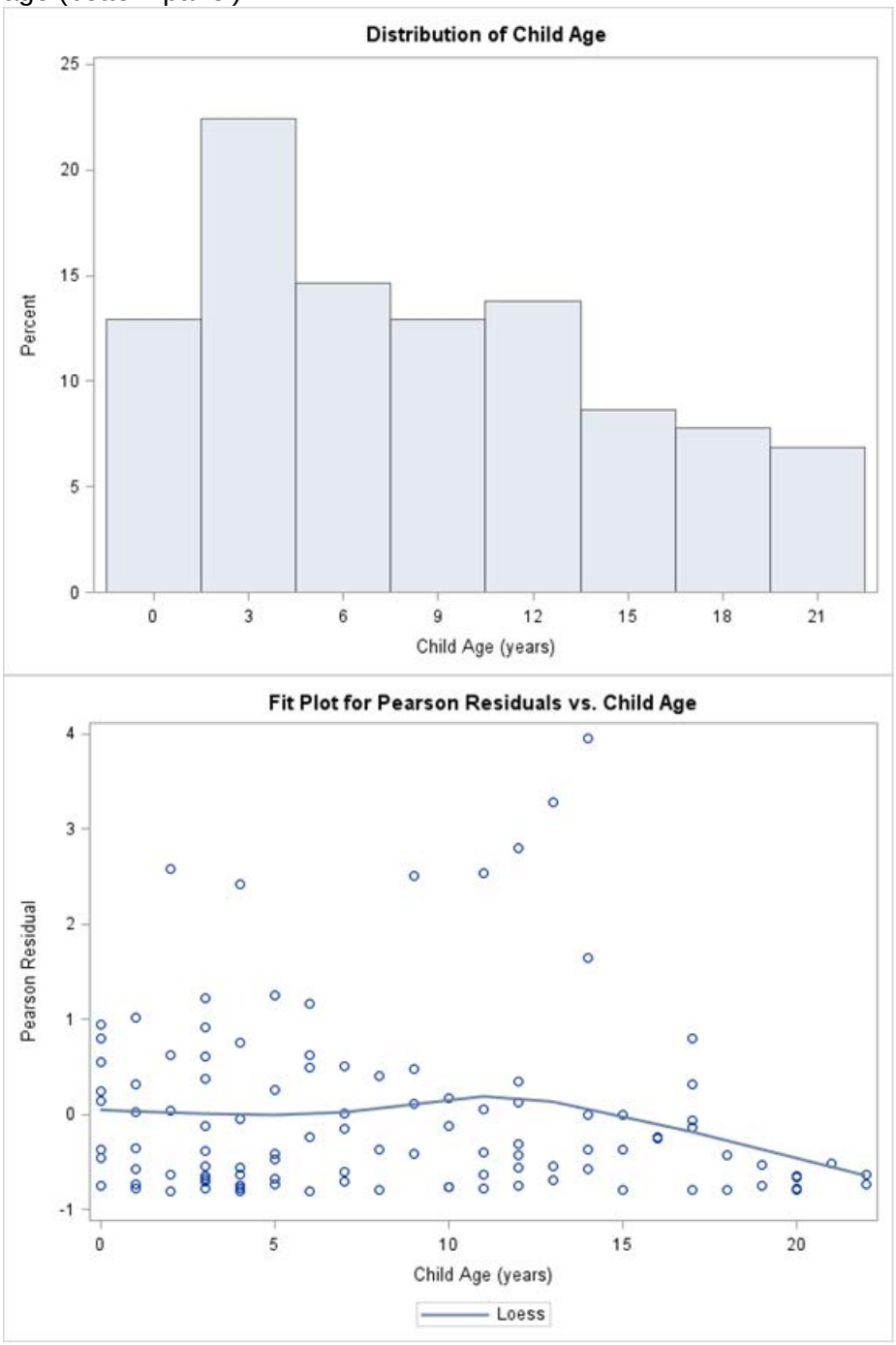
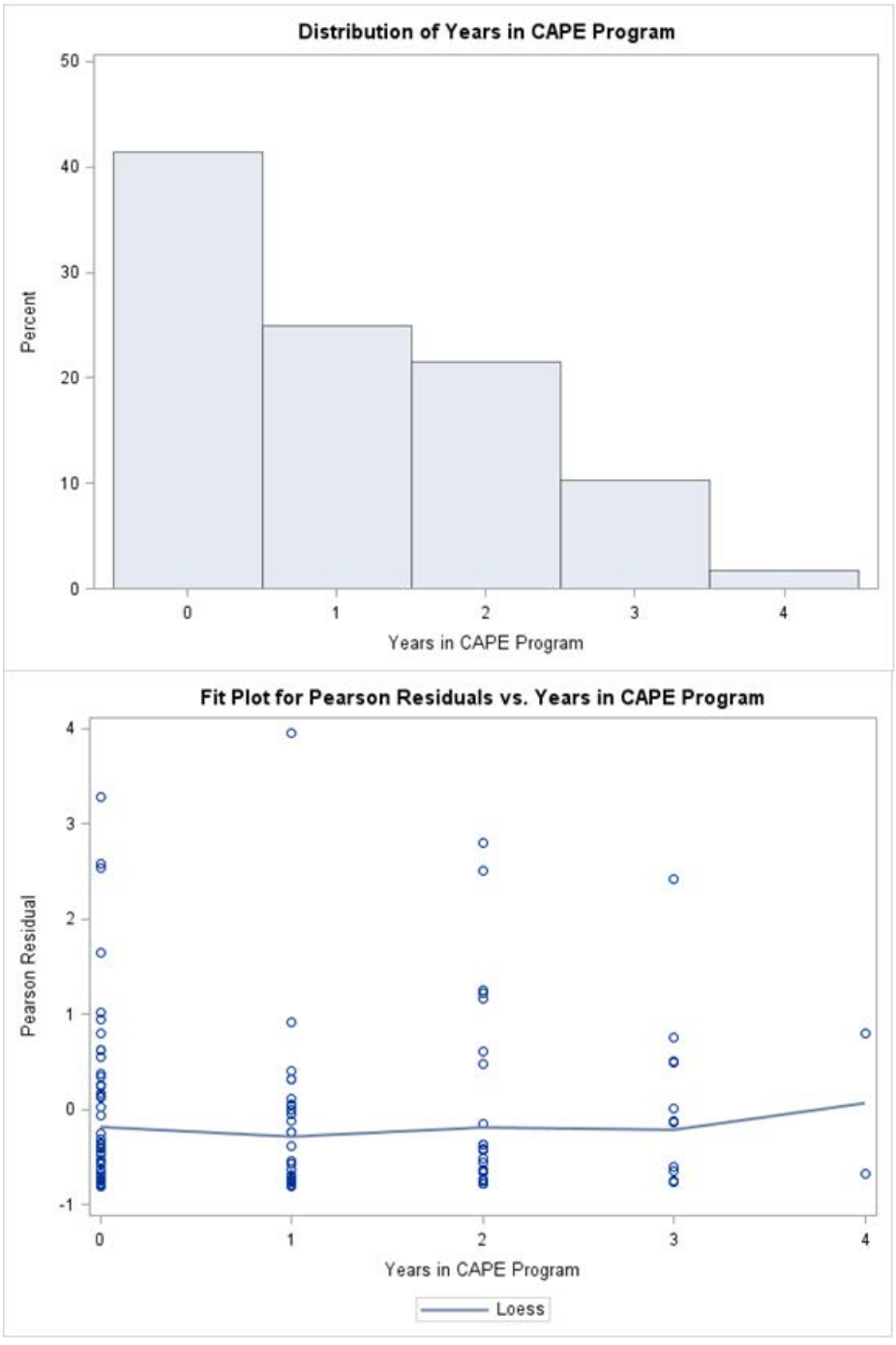


Figure 2.6: Distribution of years enrolled in CAPE Program (top panel) and plot of Pearson residuals vs. years enrolled in CAPE Program (bottom panel)



The type I error rate was set to 0.05 and analyses were conducted in SAS Version 9.4 (SAS Institute, Inc., Cary, NC).

2.3 Leveraging Pediatric PROMIS Item Banks to Assess Physical Functioning in Children at Risk for Severe Functional Loss

Sample

The CAPE and Home Ventilation Program at Boston Children's Hospital provides care coordination to pediatric patients with risk for CRI from a variety of underlying chronic illnesses, including muscular and neuromuscular disorders. As part of a larger effort to understand the impact of these medical conditions on children's functioning and well-being, parents were invited to participate in an HRQL study, described elsewhere.[32] Briefly, patients (ages 30 days to 22 years) who were receiving ongoing care from the CAPE Program and not living in a residential facility were eligible. Parent caregivers had to be at least 18 years old and actively participate in their child's care. Of the 196 parents eligible for screening as of March 31, 2013, 140 parents were enrolled in the HRQL cohort. This study was approved by the IRB at Boston Children's Hospital.

We evaluated a subset of parents in the HRQL cohort who had children ≥5 years old because PROMIS parent-proxy reported items were developed for this age range. A subset of children who were chronologically ≥5 years old, but developmentally <5 years old based on prior clinical evaluation and whose parents were completing the measures online were excluded due to project logistics. This resulted in 57 participants in the present analysis.

Measures

Parent participants completed measures about both their own HRQL and their child's HRQL every 6 months for up to four time periods. However, only the first completed assessment was used in the psychometric analysis, while all available time periods were

used to evaluate change in scores over time. Participants could complete measures either on paper or online via StudyTRAX (Macon, GA), a web-based data collection platform (http://www.studytrax.com/).

Custom PROMIS Parent-Proxy Upper Extremity and Mobility short forms*:* Two new custom parent-proxy short forms were created for this study using two PROMIS physical functioning item banks: (1) Upper Extremity (13 items selected from 29) and (2) Mobility (13 items selected from 24).[17] To create the custom short forms, a multi-disciplinary team, including PROMIS investigators, selected items using the following criteria: ability to capture a range of physical functioning activities, reflecting the full spectrum of neuromuscular activities (i.e., distal-proximal); relevance to activities of daily activity (e.g., eating, bathing, dressing); elimination of potentially insensitive items (e.g., items asking parents to compare their child's physical functioning to other children of the same age); and avoidance of redundant items. Item difficulties (theta), a metric used to determine the place on the latent trait that the item provides the most information about individual differences[1] were provided by PROMIS and were used to identify items that capture scores at the lower end of the scale. In addition, given the wide variation in these children's ability to ambulate due to their underlying medical conditions, questions about the use of assistive devices were included.

PROMIS investigators produced raw score to T-score look-up tables specifically for the two custom short forms based on item parameters. Item responses had five levels that ranged from 0="not able to do" to 4="with no trouble," with the exception of the two questions about use of assistive devices that ranged from 4="almost always" to 0="never." The T-scores for both short forms were centered on the PROMIS pediatric calibration population with a mean of 50 and a SD of 10, where higher scores represent

better functioning. IRT-based scoring allows comparisons to scores from other samples, even when they have answered different questions from the item banks. The Upper Extremity short form T-scores had a possible range of 11.5 to 52.5, while the Mobility short form T-scores had a possible range of 12.8 to 54.7.

Child Health Ratings Inventories Global HRQL Scale: The global HRQL scale[80] from the CHRIs-General,[68, 69] a validated and reliable generic HRQL tool with parent and child versions, was used to assess HRQL. As part of the CHRIs global HRQL scale, parents completed seven individual items about the child's global HRQL, including one item on overall mental health and another on overall physical health. Each item had a 5-level response set that varied from "poor" to "excellent," but was collapsed to three levels (poor/fair, good, very good/excellent) because of the limited sample size and the need to create known groups of sufficient size for comparison (Table 2.4).

Table 2.4: Distribution of CHRIs physical and mental health items before and after collapsing

Original	**Poor**	**Fair**	**Good**	**Very good**	**Excellent**
Physical health, n (%)	4 (7.0%)	16 (28.1%)	24 (42.1%)	9 (15.6%)	4 (7.0%)
Mental health, n (%)	0 (0.0%)	12 (21.1%)	22 (38.6%)	13 (22.8%)	10 (17.5%)
Collapsed	**Poor/Fair**		**Good**	**Very good/ Excellent**	
Physical health, n (%)	20 (35.1%)		24 (41.2%)	13 (22.8%)	
Mental health, n (%)	12 (21.1%)		22 (28.6%)	23 (40.4%)	

In addition to its use in collecting global HRQL, the CHRIs was also used on a subset of participants to collect parent-proxy report of their child's physical functioning. The 5-item physical functioning domain of the CHRIs targets a general population rather than those with lower levels of functioning. Each item has a 5-level response set that varied from

"not at all" to "excellent," and an additional option of "not applicable" was added for this study. The "not applicable" option would typically be treated as missing when scoring the measure. Physical functioning scores are calculated using that half scale rule, which requires at least half of the items to have valid responses, and are scaled from 0-100 where higher scores indicate better functioning. After baseline assessment, this scale was removed from the collected assessments because of its inability to capture those with low functioning and replaced by the custom PROMIS physical functioning short forms.

Demographic and clinical variables: At baseline, parents provided data about the following child and family demographic characteristics: child gender, child age, parent gender, parent age, and parent education. The child's race/ethnicity was supplied by clinical staff along with the following baseline clinical information: underlying diagnosis, respiratory support status, and physician-rated clinical severity (1=least severe, 10=most severe), the latter based on a validated single item severity measure from the National Survey of Children with Special Health Care Needs[92] that reflects judgment about the likelihood of clinical complications.

Statistical Analysis

Demographic and clinical variables were summarized using means (SDs) or medians (25^{th}-75^{th} percentiles) for continuous variables or using frequencies and percentages for categorical variables. To assess for differences between parents who completed the parent-proxy PROMIS physical functioning custom short forms and those who did not, we compared baseline child and clinical characteristics across the two groups. Given the small sample size, we used the Fisher exact test for categorical data and the Wilcoxon rank sum test for continuous data.

Psychometric Analysis: Means, SDs, ceiling and floor effects, and missingness were calculated for each raw item score and for the Upper Extremity and Mobility summary T-scores. Known groups comparisons were made for the physician-rated clinical severity item (split into two groups at the median) and the CHRIs physical health and mental health items (collapsed to three levels). The PROMIS physical functioning T-scores were compared using the Wilcoxon rank sum test for the clinical severity item and the Spearman correlation coefficient for the CHRIs physical and mental health items. For Spearman correlations, we considered correlations <0.30 as low, 0.30-0.60 as moderate, and >0.60 as high. A correlation of 0.40 has previously been used as evidence for convergent validity.[11, 89]

PROMIS physical functioning scores over time: We also explored changes in Upper Extremity and Mobility scale scores over time. Given the degenerative nature of many of the underlying medical conditions, we hypothesized that the scores would decrease over time. Time was treated as a categorical term with baseline as the reference. Repeated measures analysis with unstructured covariance was used to account for the correlation over time. Random intercepts and slopes were considered, but the Akaike information criterion indicated they were unnecessary.

All analyses were conducted in SAS version 9.2 (SAS Institute, Inc., Cary, NC); the alpha level was set at 0.05.

Chapter 3

Results of Understanding the Relationship Between Child Health-Related Quality of Life and Parent Emotional Functioning in Pediatric Hematopoietic Stem Cell Transplant

The sample included 258 parent and child dyads who completed the HRQL measures at 45 days. Most parents were mothers (84.5%) with a mean age of 39.7 (SD=6.9) years. The mean child age was 10.9 (SD=4.1) years and 49.6% were female (Table 3.1).

Table 3.1: Baseline parent, child, and disease characteristics

Parent Demographics	
Parent age in years, mean (SD)	39.7 (6.9)
Parent female, n (%)	218 (84.5%)
Parent education, n (%)	
High school graduate or less	79 (30.6%)
Some college or more	179 (69.4%)
Household income, n (%)	
<$40,000	74 (29.3%)
$40,000-$59,999	50 (19.8%)
$60,000-$79,999	36 (14.2%)
>$80,000	93 (36.8%)
Race/ethnicity, n (%)	
Non-Hispanic white	173 (67.6%)
Non-Hispanic non-white	30 (11.7%)
Hispanic	49 (19.4%)
Refused, unknown	4 (1.6%)
Child Demographics	
Child age in years, mean (SD)	10.9 (4.1)
Child female, n (%)	128 (49.6%)
Child Disease Characteristics	
Transplant type, n (%)	
Autologous	54 (20.9%)
Allogeneic, related	74 (28.7%)
Allogeneic, unrelated	130 (50.4%)
Causal malignancy, n (%)	195 (75.6%)
Duration of illness in months, median (25^{th} to 75^{th})	11.5 (5, 40)
Study, n (%)	
JTR	134 (51.9%)
HSCT-CHESS™, control	61 (23.6%)
HSCT-CHESS™, intervention	63 (24.4%)

By 45 days, 185 (71.7%) children had a complication (aGVHD ≥ grade 2 or systemic infection) and 6 children had died. We observed no differences between child and parent dyads who completed the 45-day assessments and those who did not (Table 3.2).

Table 3.2: Comparison of baseline characteristics between 45-day respondents and non-respondents

	Non-respondents, n=52	Respondents, n=258	p
Parent Characteristics			
Parent age in years, mean (SD)	40.6 (8.1)	39.7 (6.9)	0.46
Parent female, n (%)	42 (80.8%)	218 (84.5%)	0.51
Parent race/ethnicity, n (%)			0.82
Non-Hispanic white	38 (73.1%)	173 (67.6%)	
Non-Hispanic non-white	5 (9.6%)	30 (11.7%)	
Hispanic	8 (15.4%)	49 (19.4%)	
Refused, unknown	1 (1.9%)	4 (1.6%)	
Parent education, n (%)			0.78
High school graduate or less	17 (32.7%)	79 (30.6%)	
Some college or more	35 (67.3%	179 (69.4%)	
Child Characteristics			
Child age in years, mean (SD)	11.3 (3.6)	10.9 (4.1)	0.50
Child female, n (%)	29 (55.8%)	128 (49.6%)	0.42
Child Clinical Characteristics			
Transplant type, n (%)			0.18
Autologous	15 (28.9%)	54 (20.9%)	
Allogeneic, related	9 (17.3%)	74 (28.7%)	
Allogeneic, unrelated	28 (53.9%)	130 (50.4%)	
Causal malignancy, n (%)	42 (80.8%)	195 (75.6%)	0.42
Duration of illness in months, median (25^{th} to 75^{th})	11.5 (6, 43.5)	11.5 (5, 40)	0.38
Study, n (%)			0.34
JTR	29 (55.6%)	134 (51.9%)	
HSCT-CHESS™, control	15 (28.9%)	61 (23.6%)	
HSCT-CHESS™, intervention	8 (15.4%)	63 (24.4%)	

Scale properties and inter-scale correlations are presented in Table 3.3. The Cronbach's alpha for the parent-proxy reported domains ranged from 0.80 to 0.93, while the alpha coefficient for child reported domains ranged from 0.79 to 0.84. Parent-proxy raters reported their child's generic HRQL lower than child raters reported their own generic HRQL (all p-values from paired t-tests were <0.01), but there were no systematic difference in child HSCT-related worry scores by rater. Parent emotional functioning was more highly correlated with parent-proxy report of the child's HRQL than with child report of their HRQL, but all were significantly different than 0 ($p<0.05$). Of note, within rater the highest correlated domains were parent-proxy reported physical and emotional

functioning (r=0.59), parent-proxy reported emotional and role functioning (r=0.62), and child reported physical and emotional functioning (r=0.61). For child reported HSCT-related worry, there were moderate correlations with child reported physical (r=-0.30), emotional (r=-0.36), and role functioning (r=-0.32), but correlations of the parent-proxy reported domains were lower.

Table 3.3: HRQL domain properties and correlations by rater

Domain	Mean (SD)	Cronbach's α	Correlations[a]							
			Parent EF	Parent-Proxy PF	Parent-Proxy EF	Parent-Proxy RF	Parent-Proxy Worry	Child PF	Child EF	Child RF
Parent Emotional Functioning	56.1 (18.2)	0.86								
Parent-Proxy Report										
Physical Functioning	44.1 (32.8)	0.93	0.27							
Emotional Functioning	55.7 (20.8)	0.88	0.46	0.59						
Role Functioning	64.5 (26.6)	0.82	0.30	0.46	0.62					
HSCT-related Worry	25.8 (23.8)	0.80	-0.20	-0.15	-0.19	-0.17				
Child Report										
Physical Functioning	64.1 (25.7)	0.82	0.18	0.36	0.37	0.23	-0.21			
Emotional Functioning	69.3 (19.6)	0.84	0.25	0.38	0.57	0.38	-0.25	0.61		
Role Functioning	74.7 (24.3)	0.80	0.19	0.17	0.30	0.23	-0.19	0.47	0.51	
HSCT-related Worry	27.3 (25.7)	0.79	-0.17	-0.18	-0.15	-0.12	0.25	-0.30	-0.36	-0.32

[a] All correlations had $p<0.05$.

EF=emotional functioning; PF=physical functioning; RF=role functioning.

Linear Regression Models

Univariate linear regression models indicated that all domains of child HRQL, using both parent-proxy report and child report, were associated with parent emotional functioning (Table 3.4). For the generic child HRQL domains, higher scores (that is, better HRQL) were associated with higher (better) parent emotional functioning. Conversely, higher child HSCT-related worry scores were associated with lower parent emotional functioning. When all generic child HRQL domains were included in the same linear regression model, the child's emotional functioning was the only domain associated with the parent's emotional functioning for both parent-proxy and child report.

Table 3.4: Linear regression models for parent emotional functioning by rater

	Univariate [a]			Generic Child HRQL[b]			Multivariable[c]		
Domain	β (SE)	p	β'	β (SE)	p	β'	β (SE)	p	β'
Parent-Proxy Report									
Physical Functioning	0.15 (0.03)	<0.001	0.27	0.00 (0.04)	0.90	-0.01	-0.03 (0.04)	0.50	-0.05
Emotional Functioning	0.40 (0.05)	<0.001	0.46	0.39 (0.07)	<0.001	0.44	0.42 (0.07)	<0.001	0.48
Role Functioning	0.21 (0.04)	<0.001	0.30	0.02 (0.05)	0.67	0.03	0.00 (0.05)	0.98	0.00
HSCT-related Worry	-0.15 (0.05)	0.002	-0.20				-0.12 (0.04)	0.001	-0.15
Child Report									
Physical Functioning	0.13 (0.04)	0.004	0.18	0.02 (0.06)	0.72	0.03	0.04 (0.06)	0.47	0.06
Emotional Functioning	0.23 (0.06)	<0.001	0.25	0.18 (0.07)	0.02	0.19	0.21 (0.08)	0.006	0.23
Role Functioning	0.14 (0.05)	0.003	0.19	0.06 (0.05)	0.29	0.08	0.05 (0.05)	0.33	0.07
HSCT-related Worry	-0.12 (0.04)	0.008	-0.17				-0.02 (0.05)	0.63	-0.03

[a] Each domain fit in separate model.
[b] All generic HRQL domains in one model by rater.
[c] All domains in one model by rater, adjusted for child age.
β' indicates standardized β.

For the multivariable parent-proxy report model that included all child HRQL domains and also adjusted for child age, child emotional functioning (β=0.42, p<0.001) and child HSCT-related worry (β=-0.12, p=0.001) were significantly associated with parent emotional functioning. This parent-proxy report model accounted for 25% of the variability in parent emotional functioning. On the other hand, child HSCT-related worry was not significantly associated with parent emotional functioning in the multivariable child report model (β=-0.02, p=0.63), but child emotional functioning was significantly associated with parent emotional functioning (β=0.21, p=0.006). This child report model accounted for 11% of the variability in parent emotional functioning.

Structural Equation Models

In support of the MAR assumption, we found that no items had more than 3% missing data and no items appeared to have more missing data than others.

Confirmatory factor analysis: The initial CFA measurement models for both parent-proxy report and child report did not meet the acceptable fit criteria (Table 3.5). Accordingly, item covariances were added based on measurement indexes >10 provided that the item relationships had face validity (e.g., exercising moderately and exercising hard would be expected to covary). The revised measurement models for both parent-proxy and child report met fit criteria for RSMEA and SRMR, although the CFI and TLI were slightly lower than desired.

Table 3.5: SEM performance and fit statistics by rater

	Model Chi-Square	CFI	TLI	AIC	RSMEA (90%CI)	SRMR
Parent-Proxy Report						
Measurement model	789.9 (df=289)***	0.874	0.859	17523.751	0.082 (0.075 0.089)	0.085
Measurement model + item-level covariance	510.8 (df=282)***	0.943	0.934	17258.722	0.056 (0.048 0.064)	0.058
Primary SEM with all paths	733.338 (df=285)***	0.887	0.872	17475.223	0.078 (0.071 0.085)	0.173
Primary SEM with significant paths	733.775 (df=287)***	0.888	0.873	17471.661	0.078 (0.071 0.085)	0.172
Primary SEM with significant paths and adjustment	797.669 (df=309)***	0.879	0.863	17460.757	0.078 (0.072 0.085)	0.165
Alternative SEM with all paths	510.837 (df=282)***	0.943	0.934	17258.722	0.056 (0.048 0.064)	0.058
Alternative SEM with significant paths	513.631 (df=286)***	0.943	0.935	17253.516	0.056 (0.048 0.063)	0.059
Alternative SEM with significant paths and adjustment	574.157 (df=310)***	0.935	0.926	17235.244	0.057 (0.050 0.065)	0.061
Child Report						
Measurement model	606.838 (df=289)***	0.888	0.874	18241.579	0.065 (0.058 0.073)	0.063
Measurement model + item-level covariance	463.329 (df=285)***	0.937	0.928	18106.07	0.049 (0.041 0.057)	0.056
Primary SEM with all paths	577.817 (df=288)***	0.897	0.884	18214.558	0.062 (0.055 0.070)	0.101
Primary SEM with significant paths	579.484 (df=290)***	0.898	0.885	18212.225	0.062 (0.055 0.070)	0.102
Primary SEM with significant paths and adjustment	621.061 (df=312)***	0.894	0.881	18148.858	0.062 (0.055 0.069)	0.088

Alternative SEM with all paths	463.329 (df=285)***	0.937	0.928	18106.07	0.049 (0.041 0.057)	0.056
Alternative SEM with significant paths	467.899 (df=289)***	0.937	0.929	18102.641	0.049 (0.041 0.057)	0.058
Alternative SEM with significant paths and adjustment	558.599 (df=313)***	0.916	0.905	18084.396	0.055 (0.048 0.063)	0.072

***p<0.001

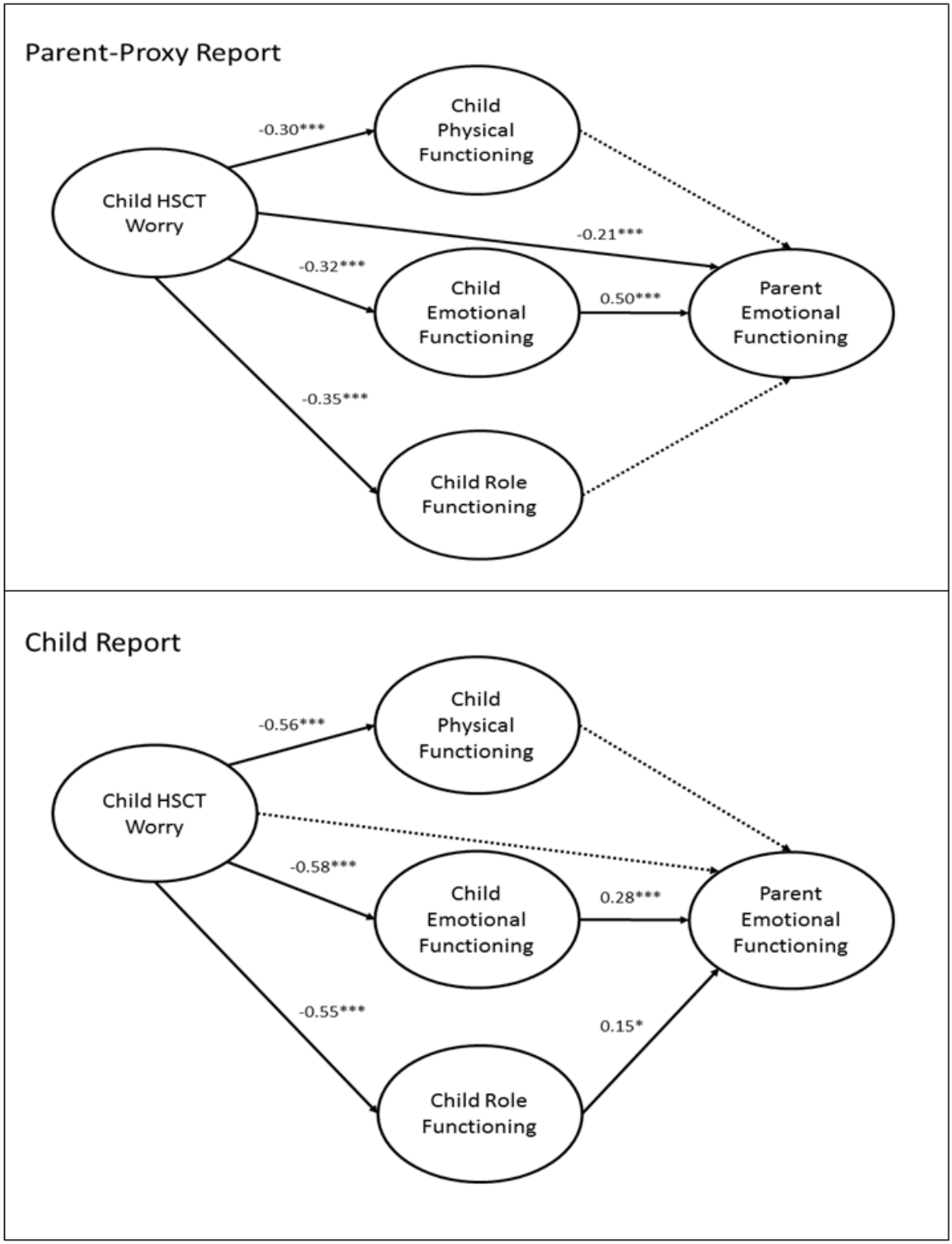
Primary SEM by rater: The primary SEM for parent-proxy report indicated statistically significant relationships between increased child HSCT-related worry and decreased child HRQL in the domains of physical, emotional, and role functioning (Table 3.6, Figure 3.1). Increased child HSCT-related worry was also associated with decreased parent emotional functioning. Child emotional functioning was the only generic child HRQL domain that was associated with parent emotional functioning. In addition to the direct effect that child HSCT-related worry had on parent emotional functioning, there was also an indirect effect through child emotional functioning. This parent-proxy report model explained 40% of the variability in parent emotional functioning. However, fit statistics for this model did not fall within the acceptable range (Table 3.5).

Table 3.6: Results from primary SEM assessing relationship between child HRQL and parent emotional functioning by rater

	Parent-Proxy Report		Child Report	
	Unstandardized Estimate (SE)	Standardized Estimate (SE)	Unstandardized Estimate (SE)	Standardized Estimate (SE)
Direct Effects				
Child worry → Child PF	-0.41 (0.10)***	-0.30 (0.07)***	-0.60 (0.11)***	-0.55 (0.06)***
Child worry → Child EF	-0.31 (0.08)***	-0.31 (0.07)***	-0.38 (0.07)***	-0.57 (0.06)***
Child worry → Child RF	-0.37 (0.09)***	-0.35 (0.08)***	-0.57 (0.10)***	-0.54 (0.06)***
Child worry → Parent EF	-0.18 (0.06)***	-0.21 (0.07)***	--	--
Child PF → Parent EF	--	--	--	--
Child EF → Parent EF	0.45 (0.07)***	0.50 (0.06)***	0.39 (0.14)***	0.28 (0.09)***
Child RF → Parent EF	--	--	0.13 (0.07)*	0.15 (0.08)*
Indirect Effects				
Child worry → Child PF → Parent EF	--	--	--	--
Child worry → Child EF → Parent EF	-0.14 (0.04)***	-0.16 (0.04)***	-0.15 (0.05)***	-0.16 (0.05)***
Child worry → Child RF → Parent EF	--	--	-0.07 (0.04)*	-0.08 (0.05)*

*p<0.1, **p<0.05, ***p<0.01
Models are adjusted for child age.
EF=emotional functioning; PF=physical functioning; RF=role functioning.

Figure 3.1: Primary SEM assessing relationship between child HRQL and parent emotional functioning by rater



*p<0.1, **p<0.05, ***p<0.01
Standardized estimates are reported. Models are adjusted for child age. Dashed lines indicate non-significant pathways that were removed from the model.

Similar to the parent-proxy report model, the child report model indicated statistically significant relationships between increased child HSCT-related worry and decreased child HRQL in the domains of physical, emotional, and role functioning (Table 3.6, Figure 3.1). Higher child emotional functioning was also significantly associated with higher parent emotional functioning. Unlike in the parent-proxy report model, child HSCT-related worry was not directly associated with parent emotional functioning, but was associated indirectly through child emotional functioning. This model also indicated a borderline relationship between higher child role functioning and higher parent emotional functioning. This child report model explained 12% of the variability in parent emotional functioning. However, the RSMEA was the only fit statistic for this model that fell within the acceptable range (Table 2.4).

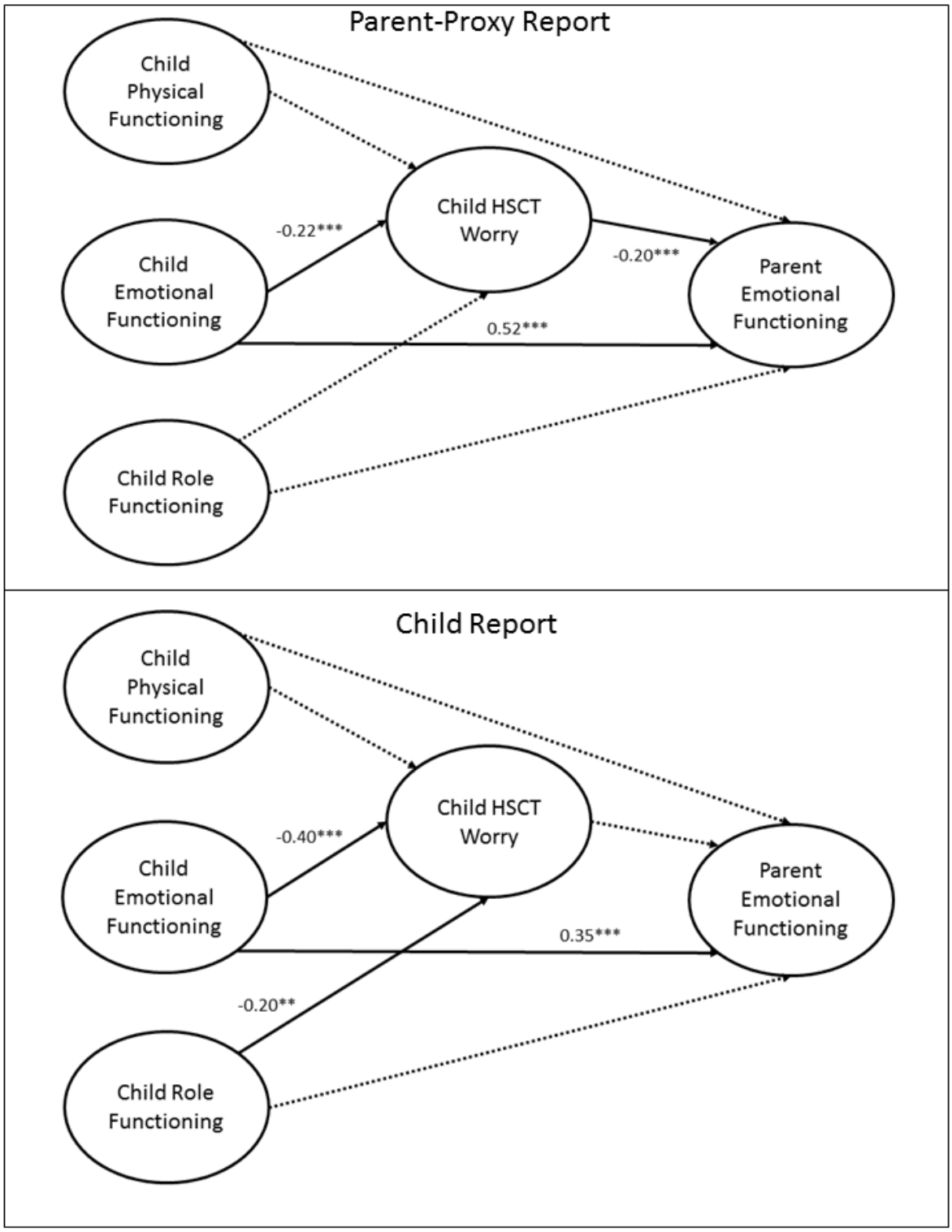
Alternative SEM by rater: The alternative SEM for parent-proxy report indicated a statistically significant relationship between increased child emotional functioning and decreased HSCT-related worry (Table 3.7, Figure 3.2). Child physical and role functioning were not associated with child HSCT-related worry. A relationship between increased child emotional functioning and increased parent emotional functioning was observed, as was an association between increased child HSCT-related worry and decreased parent emotional functioning. There was also an indirect relationship between child emotional functioning, child HSCT-related worry, and parent emotional functioning. This parent-proxy report model explained 37% of the variability in parent emotional functioning. This model had acceptable fit criteria for RSMEA and SRMR, but was slightly below the threshold for CFI and TLI.

Table 3.7: Results from alternative SEM assessing relationship between child HRQL and parent emotional functioning by rater

	Parent-Proxy Report		Child Report	
	Unstandardized Estimate (SE)	Standardized Estimate (SE)	Unstandardized Estimate (SE)	Standardized Estimate (SE)
Direct Effects				
Child PF → Child worry	--	--	--	--
Child EF → Child worry	-0.20 (0.07)***	-0.22 (0.07)***	-0.55 (0.16)***	-0.38 (0.09)***
Child RF → Child worry	--	--	-0.21 (0.09)**	-0.22 (0.09)**
Child PF → Parent EF	--	--	--	--
Child EF → Parent EF	0.45 (0.07)***	0.52 (0.05)***	0.47 (0.11)***	0.36 (0.06)***
Child RF → Parent EF	--	--	--	--
Child worry → Parent EF	-0.18 (0.06)***	-0.20 (0.07)***	--	--
Indirect Effects				
Child PF → Child worry → Parent EF	--	--	--	--
Child EF → Child worry → Parent EF	0.04 (0.02)**	0.04 (0.02)**	--	--
Child RF → Child worry → Parent EF	--	--	--	--

*p<0.1, **p<0.05, ***p<0.01
Modes are adjusted for child age.
EF=emotional functioning; PF=physical functioning; RF=role functioning.

Figure 3.2: Alternative SEM assessing relationship between child HRQL and parent emotional functioning by rater



*p<0.1, **p<0.05, ***p<0.01
Standardized estimates are reported. Models are adjusted for child age. Dashed lines indicate non-significant pathways that were removed from the model.

For the child report model, higher child emotional and role functioning were associated with significantly lower child HSCT-related worry (Table 3.7, Figure 3.2). Child emotional functioning was the only factor that was significantly associated with parent emotional functioning. This child report model explained 17% of the variability in parent emotional functioning. This model had acceptable fit criteria for RSMEA and SRMR, but was slightly below the threshold for CFI and TLI.

Sensitivity Analyses

The interaction terms for child age and each of the child HRQL domains in the parent-proxy and child report linear regression models were not statistically significant (all p-values >0.1). Similarly, the interaction terms for complications and each of the child HRQL domains in the parent-proxy and child report linear regression models were not statistically significant (all p-values >0.2).

Chapter 4

Results of Predicting Healthcare Utilization for Children with Respiratory Insufficiency Using Parent-Proxy Ratings of Children's Health-Related Quality of Life

HRQL measures were completed by 120 parents. Median child age was 7 years and 46% were female (Table 4.1). More than half of children (58%) had both private and public insurance. The most common diagnosis was SMA type 2 (22%) and 43% of children had artificial respiratory and ventilator support. Median clinical severity was 6.5 (possible range: 1-10). The mean parent age was 40 years and most were mothers (82%). The median global HRQL score was 65 (25^{th}-75^{th} percentile: 45, 80) and the median general health score was 50 (25^{th}-75^{th} percentile: 25, 50).

Table 4.1: Baseline child, disease, and family characteristics, n=120

Child Characteristics	
Child age in years, median (25^{th}-75^{th} percentile)	7 (3, 13)
Child female, n (%)	55 (45.8%)
Race/ethnicity, n (%)	
Asian	7 (5.8%)
Non-Hispanic black	6 (5.0%)
Hispanic	5 (4.2%)
Non-Hispanic white	93 (77.5%)
Other/Unknown	9 (7.5%)
Insurance status, n (%)	
Private and public	70 (58.3%)
Private only	21 (17.5%)
Public only	29 (24.2%)
Disease Characteristics	
Diagnostic category, n (%)	
Acquired injury	14 (11.7%)
Anomalies	11 (9.2%)
Chronic lung disease	14 (11.7%)
Congenital heart disease	8 (6.7%)
Dystrophies	17 (14.2%)
SMA type 1	8 (6.7%)
SMA type 2	26 (21.7%)
SMA type 3	6 (5.0%)
Other	16 (13.3%)
Respiratory support, n (%)	
Artificial	6 (5.0%)
Artificial + ventilator	51 (42.5%)
Non-invasive	32 (26.7%)
None	31 (25.8%)
Physician-rated clinical severity, median (25^{th}-75^{th} percentile)	6.5 (4, 7)

Family Characteristics	
Parent female, n (%)	97 (18.5%)
Parent age in years, mean (SD)	40.3 (8.4)
Parent education, n (%)	
<High school	4 (3.6%)
High school graduate	17 (15.2%)
Some college	29 (25.9%)
≥College graduate	62 (55.4%)

There were no differences in child age, child gender, clinical severity, diagnosis, or respiratory support between respondents and non-respondents (Table 4.2).

Table 4.2: Comparison of baseline characteristics between respondents and non-respondents

	Non-Respondents, n=76	Respondents, n=120	p
Child age in years, median (25^{th}-75^{th})	6.0 (1, 12)	5 (1, 12)	0.61
Child female, n (%)	33 (43.4%)	55 (45.8%)	0.74
Clinical severity, median (25^{th}-75^{th})	6 (3, 8)	6.5 (4, 7)	0.16
Diagnosis, n (%)			0.87
Acquired	14 (18.4%)	21 (17.5%)	
Congenital	62 (81.6%)	99 (82.5%)	
Respiratory support, n (%)			0.36
Artificial	8 (10.5%)	6 (5.0%)	
Artificial + ventilator	26 (34.2%)	61 (42.5%)	
Non-invasive	19 (25.0%)	32 (26.7%)	
None	23 (30.3%)	31 (61.2%)	

Healthcare Utilization

Twelve children, eight of whom had died, were not eligible for utilization for at least 5 of 6 months in the hospital billing data following their HRQL assessment, so they were excluded from healthcare utilization analyses. Those who died tended to have lower general health scores, higher clinical severity, and higher 1-month healthcare utilization (Table 4.3).

Table 4.3: Comparison of children included in analysis and those excluded due to death

	Included in analysis, n=108	Excluded due to death, n=8
Global HRQL, mean (SD)	62.7 (25.3)	67.9 (25.0)
General health, mean (SD)	48.1 (26.0)	31.3 (25.9)
Clinical severity, mean (SD)	5.7 (2.1)	8.8 (1.2)
Any 1-month utilization, n (%)	36 (33.3%)	3 (37.5%)

In the 6 months following the HRQL assessment, 75% of patients had any healthcare utilization and 32% had any hospitalization. The median number of total healthcare days was 2.5 (25^{th} to 75^{th} percentile: 0.5, 8) (Table 4.4).

Table 4.4: Summary of days of healthcare utilization, n=108[a]

	Median (25^{th}-75^{th} percentile)	Non-0 Median (25^{th}-75^{th} percentile)	Min	Max
Outpatient/ED days	2 (0, 4)	3 (2, 5)	0	27
Inpatient days	0 (0, 2.5)	4 (3, 11)	0	53
Total days	2.5 (0.5, 8)	5 (2, 9)	0	55

[a] Restricted to those with HRQL data and eligible for utilization within billing data for at least 5 months.

In the 1 month following the baseline HRQL assessment, 34% of patients had any healthcare utilization and 11% had any hospitalization (Table 4.5). In the 3 months following the baseline HRQL assessment, 61% of patients had any healthcare utilization and 24% had any hospitalization.

Table 4.5: Summary of healthcare contact days using alternative time windows following HRQL assessment

	Median (25^{th}-75^{th} percentile)	Non-0 Median (25^{th}-75^{th} percentile)	Min	Max
1-month window, n=119				
Outpatient/ED days	0 (0, 1)	1 (1, 2)	0	6
Inpatient days	0 (0, 0)	3 (2, 6)	0	15
Total days	0 (0, 1)	2 (1, 4)	0	15
3-month window, n=115				
Outpatient/ED days	1 (0, 2)	2 (1, 4)	0	21
Inpatient days	0 (0, 0)	4 (2, 10)	0	45
Total days	1 (0, 5)	3.5 (1, 6)	0	47

Table 4.6 summarizes healthcare utilization by categorical global HQRL, general health and clinical severity. In nearly all cases, those with worse HRQL, general health, and clinical severity had higher proportions of any healthcare utilization and any hospitalization. Similarly, the number of total healthcare days and inpatient days were generally higher in the worse categories.

Table 4.6: Healthcare utilization by categories of HRQL and clinical severity, n=108[a]

	n	Any Utilization, n (%)	Total Days		Any Hospitalization, n (%)	Inpatient Days	
			Median (25-75th percentile)	Non-0 Median (25-75th percentile)		Median (25-75th percentile)	Non-0 Median (25-75th percentile)
Global HRQL[b]							
Poor/fair	29	25 (86.2%)	9 (2, 17)	10 (3, 17)	15 (51.7%)	1 (0, 11)	11 (4, 13)
Good	37	30 (81.1%)	2 (1, 5)	3.5 (2, 6)	8 (21.6%)	0 (0, 0)	2.5 (2, 12.5)
V good/excellent	42	26 (61.9%)	1 (0, 7)	5 (2, 8)	12 (28.6%)	0 (0, 2)	4 (2.5, 7)
General health[b]							
Poor/fair	34	27 (79.4%)	8 (2, 16)	10 (4, 17)	15 (44.1%)	0 (0, 11)	11 (4, 18)
Good	46	35 (76.1%)	2 (1, 7)	3 (2, 8)	15 (32.6%)	0 (0, 2)	3 (2, 7)
V good/excellent	28	19 (67.9%)	1 (0, 3.5)	2 (1, 6)	5 (17.9%)	0 (0, 0)	3 (2, 4)
Clinical severity[c]							
Most	21	16 (76.2%)	5 (1, 9)	5.5 (2.5, 10)	10 (47.6%)	0 (0, 4)	5.5 (2, 11)
Moderately	44	32 (72.3%)	3 (1, 9)	6.5 (2, 10)	14 (31.8%)	0 (0, 3.5)	7.5 (4, 20)
Least	43	31 (72.1%)	2 (0, 6)	3 (1, 8)	11 (25.6%)	0 (0, 1)	4 (2, 9)

[a] Restricted to those with HRQL data and eligible for utilization within billing data for at least 5 months.
[b] Poor/fair <50 points; good ≥50 and <75 points; very (v) good/excellent ≥75 points.
[c] Least severe ≤5 points; moderately severe >5 and ≤7 points; most severe >7 points.

Modeling total healthcare days: Unadjusted results indicated that global HRQL, general health, and clinical severity were associated with total healthcare days (Table 4.7). In the model including global HRQL and clinical severity, the effects of global HRQL remained, while the effects of clinical severity were attenuated. After further adjusting for years enrolled in the CAPE Program and child age, the effects of global HRQL strengthened, while there was no change in the effect of clinical severity. Having poor/fair global HRQL was associated with 3.7 times more total healthcare days compared with having very good/excellent global HRQL ($p<0.001$).

Table 4.7: Global HRQL and general health models for total healthcare days

	Unadjusted model		Adjusted model 1[a]		Adjusted model 2[b]	
	Rate Ratio (95% CI)	p	Rate Ratio (95% CI)	p	Rate Ratio (95% CI)	p
Global HRQL model[c]						
Global HRQL						
Poor/fair	3.5 (1.9, 6.4)	<0.001	3.1 (1.7, 5.8)	<0.001	3.7 (1.9, 7.2)	<0.001
Good	1.5 (0.8, 2.6)	0.21	1.4 (0.8, 2.5)	0.26	1.6 (0.9, 2.8)	0.15
V good/excellent (ref)						
Clinical severity						
Most	1.5 (0.7, 3.1)	0.27	1.1 (0.6, 2.3)	0.75	1.1 (0.5, 2.1)	0.89
Moderately	2.5 (1.4, 4.5)	0.001	1.6 (1.0, 2.9)	0.08	1.6 (0.9, 2.8)	0.12
Least (ref)						
General health model[c]						
General health						
Poor/fair	3.4 (1.8, 6.6)	<0.001	3.4 (1.7, 6.5)	<0.001	3.3 (1.7, 6.6)	<0.001
Good	1.4 (0.7, 2.6)	0.34	1.5 (0.8, 2.9)	0.19	1.5 (0.8, 2.9)	0.19
V good/excellent (ref)						
Clinical severity						
Most	1.5 (0.7, 3.1)	0.27	1.2 (0.6, 2.5)	0.54	1.2 (0.6, 2.3)	0.67
Moderately	2.5 (1.4, 4.5)	0.001	1.9 (1.1, 3.4)	0.02	1.8 (1.0, 3.2)	0.05
Least (ref)						

[a] Adjusted model 1 adjusts for physician-rated clinical severity.
[b] Adjusted model 2 adjusts for physician-rated clinical severity, years enrolled in the CAPE Program, and child age
[c] Poor/fair <50 points; good ≥50 and <75 points; very (v) good/excellent ≥75 point. Least severe ≤5 points; moderately severe >5 and ≤7 points; most severe >7 points.

In the model including general health and clinical severity, the effects of general health remained, while the effects of clinical severity were slightly attenuated, but still significant. Adjusting for years enrolled in the CAPE Program and child age did not change these results. Having poor/fair general health was associated with 3.3 times more total healthcare days compared with having very good/excellent general health ($p<0.001$). Compared with those with the lowest clinical severity, those with moderate clinical severity had 1.8 times more total healthcare days ($p=0.05$).

Modeling inpatient days: Unadjusted results indicated that global HRQL, general health, and clinical severity were associated with inpatient days (Table 4.8). In the model including global HRQL and clinical severity, the effects of both were slightly attenuated. Further adjustment for years enrolled in the CAPE Program and child age resulted in larger effects for global HRQL. Those with poor/fair global HRQL had 6.3 times more inpatient days than those with very good/excellent global HRQL ($p=0.01$).

Table 4.8: Global HRQL and general health models for inpatient days

	Unadjusted model		Adjusted model 1[a]		Adjusted model 2[b]	
	Rate Ratio (95% CI)	p	Rate Ratio (95% CI)	p	Rate Ratio (95% CI)	p
Global HRQL model[c]						
Global HRQL						
Poor/fair	4.9 (1.4, 16.9)	0.01	4.0 (1.1, 13.9)	0.03	6.3 (1.5, 27.0)	0.01
Good	1.5 (0.5, 4.7)	0.53	1.2 (0.4, 4.0)	0.76	1.8 (0.5, 6.7)	0.37
V good/excellent (ref)						
Clinical severity						
Most	2.2 (0.5, 9.1)	0.28	1.5 (0.4, 6.1)	0.56	1.2 (0.3, 5.3)	0.79
Moderately	4.1 (1.3, 12.6)	0.01	2.4 (0.8, 7.2)	0.14	2.0 (0.6, 7.4)	0.29
Least (ref)						
General health model[c]						
General health						
Poor/fair	8.3 (2.2, 31.4)	0.002	7.1 (1.9, 27.0)	0.004	7.9 (1.9, 32.3)	0.004
Good	2.4 (0.7, 8.5)	0.18	2.4 (0.7, 8.5)	0.18	2.3 (0.6, 8.3)	0.22
V good/excellent (ref)						
Clinical severity						
Most	2.2 (0.5, 9.1)	0.28	1.8 (0.4, 7.0)	0.42	1.7 (0.4, 6.5)	0.47
Moderately	4.1 (1.3, 12.6)	0.01	2.7 (0.9, 8.0)	0.09	2.4 (0.7, 8.0)	0.14
Least (ref)						

[a] Adjusted model 1 adjusts for physician-rated clinical severity

[b] Adjusted model 2 adjusts for physician-rated clinical severity, years enrolled in the CAPE Program, and child age

[c] Poor/fair <50 points; good ≥50 and <75 points; very (v) good/excellent ≥75 point. Least severe ≤5 points; moderately severe >5 and ≤7 points; most severe >7 points.

In the model including general health and clinical severity, the effects of both were slightly attenuated. Adjusting for years enrolled in the CAPE Program and child age strengthened the relationship between general health and inpatient days. Those with poor/fair general health had 7.9 times more inpatient days than those with very good/excellent general health (p=0.004).

Chapter 5

Results of Leveraging Pediatric PROMIS Item Banks to Assess Physical Functioning in Children at Risk for Severe Functional Loss

The custom Upper Extremity and Mobility short forms were completed by 57 parent-proxy raters. The mean child age was 12 years (SD=6) and nearly half were female (Table 5.1). SMA was the most common diagnosis (35%) and the median clinical severity was 6 (possible range 1 to 10). Most patients had some degree of respiratory support; 40% had artificial respiratory and ventilator support, while 32% had non-invasive respiratory support. The mean parent age was 44 years (SD=8), most were female (83%), and most were college graduates (63%).

Table 5.1: Baseline child, disease, and family characteristics, n=57

Child Characteristics	
Child age in years, mean (SD)	12.4 (6.2)
Child female, n (%)	28 (49.1%)
Race/ethnicity, n (%)	
White, non-Hispanic	42 (73.7%)
Asian	6 (10.5%)
Black, non-Hispanic	3 (5.3%)
Hispanic/Latino	3 (5.3%)
Unknown	3 (5.3%)
Disease Characteristics	
Diagnosis, n (%)	
Acquired injury	6 (10.5%)
Anomalies (All)	4 (7.0%)
Chronic lung disease	4 (7.0%)
Dystrophies	12 (21.1%)
SMA (Types 1, 2, 3)	20 (35.1%)
Other	11 (19.3%)
Respiratory support, n (%)	
Artificial	3 (5.3%)
Artificial + ventilator	23 (40.4%)
Non-invasive	18 (31.6%)
None	13 (22.8%)
Physician-rated clinical severity, median (25^{th}-75^{th} percentile)	6.0 (4.0-7.0)
Family Characteristics	
Parent female, n (%)	47 (82.5%)
Parent age in years, mean (SD)	43.7 (7.8)
Parent education, n (%)	
<High school	2 (3.7%)
High school graduate	6 (11.1%)
Some college	12 (22.2%)
≥College graduate	34 (63.0%)

We found that children of respondents (n=57) and non-respondents (n=139) were similar in child gender, child age, diagnosis, and respiratory support (Table 5.2). However, children of non-respondents were significantly younger than children of respondents ($p<0.001$), representing the fact that the parent-proxy physical functioning custom short forms were only valid for use among children aged five years and older.

Table 5.2: Comparison of baseline characteristics between respondents and non-respondents

	Non-respondents, n=139	Respondents, n=57	p
Child age in years, median (25^{th}-75^{th} percentile)	3 (1, 11)	11 (6, 14)	<0.001
Child female, n (%)	60 (43.2%)	28 (49.1%)	0.53
Clinical severity, median (25^{th}-75^{th} percentile)	6 (3, 8)	6 (4, 7)	0.95
Diagnosis, n (%)			0.63
Acquired	26 (18.7%)	9 (15.8%)	
Congenital	113 (81.3%)	48 (84.2%)	
Respiratory support, n (%)			0.59
Artificial	11 (7.9%)	3 (5.3%)	
Artificial + ventilator	54 (38.9%)	23 (40.4%)	
Non-invasive	33 (23.7%)	19 (31.6%)	
None	41 (29.5%)	13 (22.8%)	

PROMIS physical functioning

The mean Upper Extremity T-score was 21.4 (SD=12.6) and the mean Mobility T-score was 22.0 (SD=11.1) (Table 5.3). There were <2% missing data for any item. For the Upper Extremity scale, 26.3% scored at the measurement floor, while 15.8% scored at the measurement floor for the Mobility scale. The percentage of parents endorsing the most severe response option (i.e., “not able to do”) varied by item. For example, among the Upper Extremity items, 30% answered that the child could not move their hands or fingers, while 67% reported that the child could not pull a shirt over his/her head. Among

the Mobility items, 27% of parents reported that the child could not turn his/her head all the way to the side, while 68% could not get up from a regular toilet.

Table 5.3: Raw item scores and Upper Extremity and Mobility T-scores

	N	Mean (SD)	Median (25^{th}-75^{th} percentile)	Min, Max	% Floor	% Ceiling
Upper Extremity						
T-score	57	21.4 (12.6)	16.9 (11.5, 22.5)	11.5, 52.5	26.3	10.5
Pull shirt over head	57	1.0 (1.6)	0 (0, 2)	0, 4	66.7	15.8
Put on shoes	57	0.8 (1.5)	0 (0, 0)	0, 4	75.4	14.0
Use key to unlock door	57	0.8 (1.6)	0 (0, 1)	0, 4	73.7	17.5
Zip up clothes	57	0.9 (1.6)	0 (0, 1)	0, 4	70.2	17.5
Put toothpaste on toothbrush	57	1.0 (1.6)	0 (0, 2)	0, 4	64.9	19.3
Put on clothes without help	57	0.9 (1.5)	0 (0, 1)	0, 4	71.9	15.8
Put on socks without help	57	0.8 (1.4)	0 (0, 2)	0, 4	71.9	10.5
Open clothing drawers	57	1.2 (1.7)	0 (0, 3)	0, 4	61.4	21.1
Hold a full cup	57	1.5 (1.8)	0 (0, 4)	0, 4	54.4	28.1
Use a mouse or touch pad[a]	56	1.8 (1.4)	3 (0, 3)	0, 3	32.1	51.8
Wash face with cloth[b]	57	0.6 (0.8)	0 (0, 1)	0, 2	66.7	22.8
Move hands or fingers[a]	57	1.8 (1.3)	2 (0, 3)	0, 3	29.8	49.1
Write with pen or pencil[a]	57	1.5 (1.4)	1 (0, 3)	0, 3	38.6	38.6
Mobility						
T-score	57	22.0 (11.1)	16.7 (14.5, 29.7)	12.8, 54.7	15.8	5.3
Get up from the floor	57	0.9 (1.4)	0 (0, 2)	0, 4	68.4	10.5
Move legs	57	1.9 (1.6)	2 (0, 4)	0, 4	26.3	26.3
Stand up without help	57	1.2 (1.7)	0 (0, 3)	0, 4	66.7	21.1
Walk up stairs without holding on	57	0.5 (1.1)	0 (0, 0)	0, 4	79.0	5.3
Get into bed	56	1.0 (1.7)	0 (0, 2.5)	0, 4	71.4	19.6
Walk across room	57	1.2 (1.8)	0 (0, 4)	0, 4	66.7	26.3
Bend over to pick something up	57	0.9 (1.5)	0 (0, 2)	0, 4	71.9	12.3
Walk more than one block	57	0.6 (1.3)	0 (0, 0)	0, 4	75.4	8.8
Get up from regular toilet	57	1.1 (1.7)	0 (0, 3)	0, 4	68.4	21.1
Get down on knees without holding on	57	0.6 (1.3)	0 (0, 0)	0, 4	80.7	7.0
Turn head all the way to the side	56	2.2 (1.6)	3 (0, 4)	0, 4	26.8	32.1

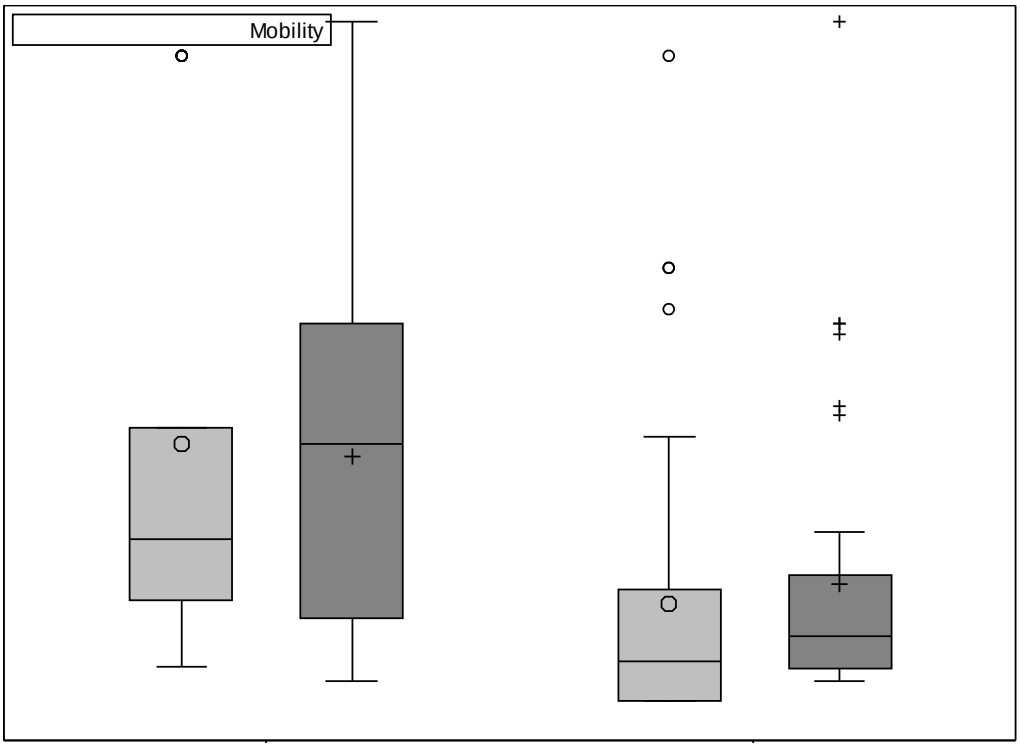
Used a wheelchair[c]	56	1.2 (1.6)	0 (0, 2.5)	0, 4	57.1	17.9
Used a walker, cane, or crutches[c]	57	3.7 (0.9)	4 (4, 4)	0, 4	5.3	89.5

[a] Response levels “with a lot of trouble” and “not able to do” collapsed per PROMIS scoring algorithm.
[b] Response levels “with some trouble,” “with a lot of trouble,” and “not able to do” collapsed per PROMIS scoring algorithm.
[c] Not used in Mobility T-score because item did not perform well.

With regards to assistive devices, more than half reported that their child always used a wheelchair to get around. Nearly 90% reported that their child never used a walker, cane, or crutches to get around, but this likely reflects their inability to use these devices rather than their ability to walk. As such, the two items on assistive devices were excluded from the Mobility scoring algorithm (resulting in an 11-item scale).

When physician-rated clinical severity was split at its median of 6, the median Upper Extremity T-score for the less severe group was significantly higher (21.8; 25^{th}-75^{th} percentile: 17.9, 28.9; Figure 5.1) than the T-score in the more severe group (14.1; 25^{th}-75^{th} percentile: 11.5, 18.6; $p<0.001$). Similarly, the median Mobility T-score for the less severe group was significantly higher (27.8; 25^{th}-75^{th} percentile: 16.7, 35.5) than the T-score in the more severe group (15.6; 25^{th}-75^{th} percentile: 13.6, 19.5; $p=0.004$).

Figure 5.1: Boxplots of PROMIS physical functioning T-scores by clinical severity item[a]

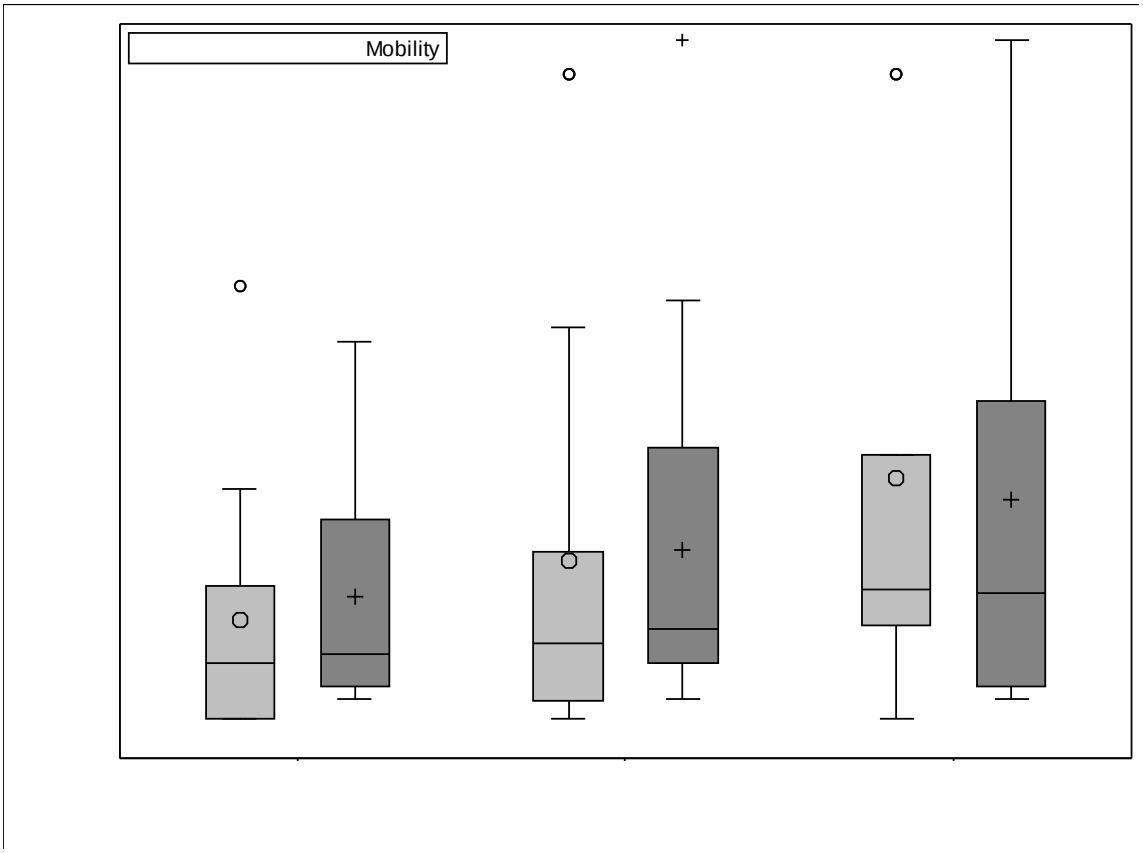


[a] Clinical severity was split into two groups at its median of 6
P<0.001 when comparing Upper Extremity T-scores; p=0.004 when comparing Mobility T-scores.
Note: the line within the box represents the median; the circle or plus sign within the box represents the mean; the length of the box represents the interquartile range; the length of the whiskers represents the distance between the box and the observation that is less than 1.5 times the interquartile range; the points outside the whiskers represent outliers.

Both Upper Extremity and Mobility T-scores were slightly higher in the subgroups defined by better CHRIs physical health item scores (Figure 5.2; r=0.28 [p=0.04], r=0.15 [p=0.26], respectively), although the Spearman correlations were low. Upper Extremity and Mobility T-scores also were slightly higher among those with better CHRIs mental health item scores (Figure 5.3; r=0.35 [p=0.008], r=0.21 [p=0.12], respectively), although the Spearman correlations were low to moderate. Figure 5.2 shows that the relationship between Upper Extremity and Mobility T-scores appeared more linear for the physical

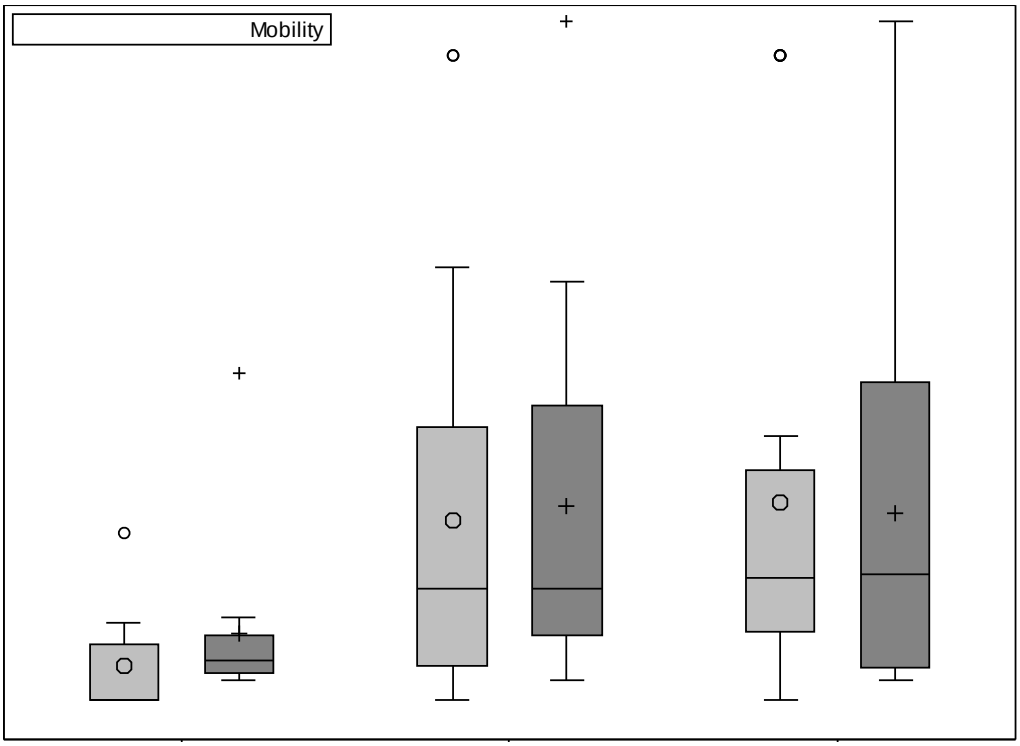
health item (T-scores were progressively higher for those scoring good and very good/excellent compared with poor/fair). In contrast, Figure 5.3 shows that the Upper Extremity and Mobility T-scores were higher for those scoring good on the mental health item compared with poor/fair, but there was little difference between good and very good/excellent.

Figure 5.2: Boxplots of PROMIS physical functioning T-scores by CHRIs physical health item score



Spearman correlation for Upper Extremity: r=0.28 (p=0.04); Spearman correlation for Mobility: r=0.15 (p=0.26).
Note: the line within the box represents the median; the circle or plus sign within the box represents the mean; the length of the box represents the interquartile range; the length of the whiskers represents the distance between the box and the observation that is less than 1.5 times the interquartile range; the points outside the whiskers represent outliers.

Figure 5.3: Boxplots of PROMIS physical functioning T-scores by CHRIs mental health item score



Spearman correlation for Upper Extremity: r=0.35 (p=0.008); Spearman correlation for Mobility: r=0.21 (p=0.12).
Note: the line within the box represents the median; the circle or plus sign within the box represents the mean; the length of the box represents the interquartile range; the length of the whiskers represents the distance between the box and the observation that is less than 1.5 times the interquartile range; the points outside the whiskers represent outliers.

CHRIs physical functioning

For each CHRIs physical functioning item, more than 60% of the 45 parents reported that their child's functioning was "not applicable" (Table 5.4). Furthermore, 53% reported "not applicable" for all five items. Based on the number of "not applicable" responses, CHRIs physical functioning domain scores could only be calculated for 14 children. The mean score in these 14 children (55.1, SD=33.9) were not representative of all children in the sample because scores could not be calculated for those with lower levels of physical functioning. When the "not applicable" option was scored as the same as "a

whole lot," the mean physical functioning score for the 45 children was 16.4 (SD=27.0) with 60% scoring at the floor.

Table 5.4: CHRIs item response distributions for parent-proxy rated physical functioning, n=45

During the past week, how much has not feeling well, or problems with health, gotten in the way when your child wants to do each of the following?	Not applicable	Not at all	A little	Some	A lot	A whole lot
Exercise hard (like running fast, biking up hill), n (%)	35 (77.8%)	5 (11.1%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	2 (4.4%)
Exercise moderately (like playing softball or swimming for fun), n (%)	30 (66.7%)	5 (11.1%)	2 (4.4%)	2 (4.4%)	4 (8.9%)	2 (4.4%)
Walk a few blocks (around school, at the mall), n (%)	30 (66.7%)	3 (6.7%)	1 (2.2%)	2 (4.4%)	6 (13.3%)	3 (6.7%)
Lift, carry or climb (like carrying school books or climbing stairs), n (%)	30 (68.2%)	2 (4.6%)	3 (6.8%)	5 (9.1%)	3 (6.8%)	2 (4.6%)
Work around the house (like making the bed, picking up your room or taking out the trash), n (%)	28 (62.2%)	3 (6.7%)	1 (2.2%)	3 (6.7%)	4 (8.9%)	6 (13.3%)

PROMIS physical functioning scores over time

Among parents completing the short forms at more than one time period (Table 5.5), there was no indication of changing scores over time for Upper Extremity (Type 3 Test p=0.61), but Mobility scores were lower in the 6+ months following baseline (Type 3 Test p<0.001).

Table 5.5: Upper Extremity and Mobility T-scores over time, n=57

		Upper Extremity		Mobility	
Time	N	Mean (SD)	Median (25^{th}, 75^{th})	Mean (SD)	Median (25^{th}, 75^{th})
Baseline	11	23.9 (13.5)	19.3 (13.7, 36.4)	22.0 (8.1)	19.5 (14.5, 29.7)
6 Months	29	23.2 (14.8)	16.4 (14.4, 23.7)	21.9 (13.4)	16.7 (13.6, 19.5)
12 Months	38	22.0 (13.2)	17.9 (12.1, 23.3)	22.8 (11.8)	16.7 (14.5, 30.2)
18 Months	27	21.5 (12.9)	17.5 (12.1, 24.9)	21.7 (11.9)	16.7 (12.8, 30.7)

Chapter 6

Discussion

6.1 Understanding the Relationship Between Child Health-Related Quality of Life and Parent Emotional Functioning in Pediatric Hematopoietic Stem Cell Transplant

Among children who are 45 days post-HSCT, the relationship between child HRQL and parent emotional functioning is complex. Across all generic domains of child HRQL, parent-proxy report of child HRQL was lower than child report. Results from the parent-proxy report multivariable linear regression model indicated that child emotional functioning and child HSCT-related worry were associated with parent emotional functioning. On the other hand, only child emotional functioning was associated with parent emotional functioning in the child report multivariable linear regression model. The alternative conceptual model, which placed generic child HRQL before child HSCT-related worry in relation to parent emotional functioning, met more of the model fit criteria (e.g., RSMEA, SRMR) than the primary model, which placed child HSCT-related worry first. Interestingly, the pathways differed slightly by parent-proxy and child report. These analyses point to the relationship between child emotional functioning, child HSCT-related worry, and parent emotional functioning.

The primary conceptual model linked child HSCT-related worry to generic child HRQL and then to parent emotional functioning. The alternative model had generic child HRQL leading to child HSCT-related worry and then to parent emotional functioning. Both the primary and alternative conceptual models were developed based on the Wilson and Cleary framework,[104] where factors resulting from the disease, such as symptoms or complications, precede functioning and HRQL. Fit statistics for the alternative models were slightly better and AIC values were lower than for the primary models for both parent-proxy and child report, indicating that generic child HRQL may fit better before

child HSCT-related worry. This alternative model conceptualization supports the idea that complications impact child HRQL and functioning, which then affect child HSCT-related worry, and then parent emotional functioning. That is, the child's complications may affect their functioning, which then causes the child to worry about further complications or adverse effects of their treatment. We did not find as much support for the idea that complications affect the child's HSCT-related worry and then lead to decreased child HRQL and functioning.

For both parent-proxy and child report, child HSCT-related worry was significantly associated with generic child HRQL for all domains in the primary model. In the alternative model, child emotional functioning was associated with child HSCT-related worry for both raters. For parent-proxy report, child emotional functioning was the only generic child HRQL domain associated with child HSCT-related worry, while child role functioning was also associated with child HSCT-related worry for child report. For both the primary and alternative models, direct associations between child HSCT-related worry and parent emotional functioning were only observed for parent report. Similar findings were seen in the linear regression models. Interestingly, our prior research indicates that complications may have the largest effect on the domain of child physical functioning.[70] While this current analysis does not address the same question directly, we saw higher associations between child emotional functioning and child HSCT-related worry, rather than between child physical functioning and child HSCT-related worry. However, it should be noted that child emotional and physical functioning were strongly correlated with each other, which could partially explain our observed relationship between child emotional functioning and child HSCT-related worry. Alternatively, the domains of child emotional functioning and worrying about future disease may be more closely linked than child physical functioning and worry. With regards to differences in

child HRQL by rater, parent-proxy report of generic child HRQL was lower than child report, but there was no systematic difference in child HSCT-related worry by rater. For all models, estimates were larger in magnitude for the relationships between child HSCT-related worry and generic child HRQL for child report than for parent-proxy report. On the other hand, for all associations of child HRQL with parent emotional functioning, the estimates were larger for parent report. This could be the result of shared variance that occurs when the same rater provides information about multiple constructs.

Ideally, HRQL ratings should be provided directly from the patient. However, there are situations when using proxy (i.e., parent) report or using both proxy report and child report may be necessary, such as when the child is too young, too sick, or has developmental, cognitive or functional limitations. Prior research on parent-proxy and child raters has found that a variety of factors influence agreement between the two, including HRQL domain, disease severity, child age, and parent emotional functioning. Domains such as physical functioning, which are more observable, tend to have higher parent and child agreement than non-observable domains such as emotional functioning (also referred to as "beneath the skin").[22, 67, 70] Generally, there is higher agreement between parent-proxy and child raters for sick as compared with healthy children.[23] This refers to the idea of a shared reality that parents and children experience when the child faces a serious illness, which is in contrast to the divergent realities among parents and healthy children as the child grows older and becomes more independent. Interestingly, among children undergoing HSCT, prior research shows that larger rater disagreement was observed when the child experienced severe clinical complications, such as systemic infection[70] or severe aGVHD versus milder complications, which could reflect different perspectives each rater places on the relationship between the complication and the child's HRQL. This difference in perspectives refers to information and criterion

variance where each rater has different access to information (information variance) and/or places different value on information (criterion variance). For example, the clinician may explain post-HSCT complications and their future implications more thoroughly to the parent caregiver than to the child, particularly when the child is young. However, sensitivity analyses indicated that complications did not modify the relationships between the child HRQL domains and parent emotional functioning in the linear regression models.

Also observed from prior research among the HSCT population were higher levels of agreement between parent-proxy and child raters among older children, which could be partially explained by older children having better access and understanding of information about their health;[70] and this may be appropriate. Due to the documented differences in parent-proxy and child report of HRQL by child age, we adjusted for age in the linear regression and SEM analyses. We did not specifically explore whether child age was associated with child HRQL or parent HRQL, but sensitivity analyses did indicate that child age was not an effect modifier of the relationships between the child HRQL domains and parent emotional functioning in the linear regression analysis. Interestingly, we also found that adjusting for child age did not appreciably change the results or model fit.

Differences in parent and child agreement have also been observed by levels of parent emotional functioning.[70] Parents with psychological distress may perceive their child's HRQL as lower,[64] even though the child may not perceive their own HRQL as lower. However, this relationship is complicated by the fact that children of parents with lower emotional functioning may actually experience decreased HRQL themselves as the result of their parent's distress. Both linear regression models and SEMs indicated

stronger associations between parent-proxy report of child HRQL and parent emotional functioning as compared with child report of their own HRQL and parent emotional functioning. This could be explained by several factors. First, the parent's perception of child HRQL likely affects parent emotional functioning directly. Parents witnessing their child's decreased HRQL and emotional distress may experience emotional distress themselves as a result. Alternatively, parent emotional functioning may influence how the parent perceives their child's HRQL. This would also be a type of shared variance.

Multivariable linear regression models and SEMs were both used to explore the complex relationships between child HSCT-related worry, generic child HRQL, and parent emotional functioning. Within the linear regression framework, variables are assumed to be measured without error, which may be untenable. However, SEM uses latent variables to remove measurement error. SEM also allows variables to be treated as both dependent and independent variables in the same model; we can explore direct and indirect pathways between different factors. Each analytic technique allows adjustment for potential confounders of the relationships, such as child age. Linear regression allows for a more accessible, albeit simplified, examination of the relationships between these factors. Assessment of fit and model assumptions (e.g., linearity, homogeneity of variance) is generally straightforward in linear regression as are the required modifications to deal with violations (e.g., transformation). On the other hand, conducting SEM is more complex and modifications to improve model fit are not as straightforward. For example, important factors may be missing from the SEM, but they may not have been collected, particularly when conducting secondary analyses. However, less acceptable model fit does provide information about whether the underlying conceptual model is appropriate. Our analyses showed that the alternative model, which placed generic child HRQL before child HSCT-related worry in relation to parent emotional

functioning, had better fit statistics than the primary model that placed child HSCT-related worry first.

These findings have several implications for supporting child recipients of HSCT and their parent caregivers. Foremost, as demonstrated here, and in prior research, the child's illness and their resulting HRQL affects the parent's emotional functioning,[91] which may then affect the parent's ability to function as a caregiver in optimizing their child's health outcomes.[71, 72] We have previously found a strong link between parent emotional functioning and clinically meaningful levels of emotional distress as measured by clinical evaluation using structured diagnostic interviews.[79] Intermittently assessing the child's HRQL throughout the HSCT course could provide the clinical team with information about either low levels of HRQL or decreasing levels of HRQL, which may be a marker of impending complications or deteriorating health status that could warrant clinical intervention. Also, acknowledging that complications resulting from HSCT can affect child HSCT-related worry, child HRQL, and parent emotional functioning, children and parents may need to be provided with psychosocial support to help them cope with these challenges. Although we do not know how much clinical information the children in this study were provided, the presence of child HSCT-related worry, and observed differences between child and parent-proxy report, highlight the issue of whether and how clinical information is shared with the child, and how this varies by child age and developmental stage.

We acknowledge this study's limitations. Unfortunately, the SEMs did not reach all of the desired model fit statistics, particularly for the primary model. There are several plausible explanations. First, the conceptual model may not fully explain the relationships between the different factors. However, we did find that the alternative model was a better fit to

the data. Second, key factors that are necessary to better explain the relationships, such as measures of the child's symptoms, the parent's coping patterns, social support, or resilience, may be missing. Although we collected data on many of these constructs, this was a secondary analysis so we did not have data on the same measures in each study. We did have complete HRQL data as that was related to the primary outcome of each study. This is one of the challenges of evaluating a conceptual model with SEM as a secondary analysis of an existing dataset as opposed to designing a study specifically for evaluating a conceptual model. Third, determining the direction of these relationships may not be possible, and we may need to accept that their interrelatedness is complex. This analysis is not meant to establish a causal relationship between child HRQL and parent emotional functioning, but to better understand potential pathways. Another limitation is that we focused only on a cross-sectional assessment at 45 days. This period was selected because of the magnitude of clinical complications and also the large number of participants still enrolled in the study. Although we have longitudinal data from these studies, we chose to analyze a single time point because we wanted to understand the relationship between child HRQL and parent emotional functioning while they were both influenced by similar factors (i.e., clinical complications), as opposed to exploring the relationship between child HRQL at baseline and parent emotional functioning 45 days later when the child's HRQL may have changed from baseline levels.

Despite these limitations, this study highlights the complex relationships between child HSCT-related worry, generic child HRQL, and parent emotional functioning within the context of pediatric HSCT, and especially the domains relating to child worry and child and parent emotional functioning. Next steps may be to design a study that would collect primary data that correspond to all factors in the conceptual model, such as symptom

scales. The post-HSCT period can be challenging for children and their parent caregivers, especially when the child experiences complications from their treatment. In order to optimize the child's outcomes, the parent caregiver must be an active and engaged caregiver, which can be difficult in the face of psychological distress. Therefore, providing psychosocial support for children and their families may be necessary for ensuring the mental and physical health of the child and their parent caregiver.

6.2 Predicting Healthcare Utilization for Children with Respiratory Insufficiency Using Parent-Proxy Ratings of Children's Health-Related Quality of Life

This study demonstrated that parent-proxy report of child global HRQL and general health were associated with future healthcare utilization, including total healthcare days and inpatient days, among children with CRI. These effects remained after adjusting for clinical severity, years enrolled in the CAPE Program, and child age. The extent of outpatient and inpatient resource utilization in this cohort relative to the general pediatric population illustrates the need to predict and intervene in order to optimize health outcomes, improve quality, and reduce healthcare costs. A brief measure of HRQL, such as the CHRIs global HRQL scale and the general health item, is minimally burdensome to families and may be a valuable screening tool.

Prior studies have demonstrated the predictive value of HRQL with respect to clinical outcomes and healthcare utilization,[13, 24, 28, 41, 43, 49, 66, 84, 86, 90, 103] although only a few focus on children. A study of 317 children aged 2-18 years enrolled in a Medicaid managed care plan found that parent-proxy reported HRQL explained more variation in healthcare costs after 6, 12, and 24 months than chronic condition status alone.[86] Furthermore, these investigators identified a high-risk group of children with increased healthcare cost by combining information from HRQL and chronic condition status, suggesting that these children would be candidates for additional care coordination. A study of children with inflammatory bowel disease found that child and parent-proxy reported HRQL predicted the number of disease-related hospital admissions, gastroenterology clinic visits, ED visits, psychology clinic visits, phone contacts, and pain management referrals over the next 12 months, controlling for demographic and disease parameters.[84] Our results

similarly found that parent-proxy report of child HRQL can predict future healthcare utilization.

In addition to examining the relationship between parent-proxy reported HRQL and healthcare utilization, we also explored the relationship between physician-rated clinical severity and healthcare utilization. As expected, those with higher clinical severity had more healthcare utilization in unadjusted analyses. However, we found that the effects of clinical severity were attenuated after adjustment for HRQL, time enrolled in the CAPE Program, and child age. In contrast, the effects of HRQL remained after adjustment for the other factors, demonstrating that HRQL may be a better predictor of future healthcare utilization than clinical severity. Further, parent-proxy report has the advantage of not requiring ongoing clinician involvement, so HRQL assessments could be completed during a clinical encounter or remotely between visits, and HRQL assessments could be repeated at appropriate intervals as part of regular clinical care.[25] Of interest, although we found that more children with the highest clinical severity had contact with the healthcare system (i.e., any healthcare utilization) than children with moderate clinical severity, child with moderate clinical severity had more total healthcare utilization days. This could be explained by several factors. First, there could be a handful of high utilizers with long hospitalizations in the moderate severity group that are driving these findings. Second, some children in the most severe group may be receiving palliative care and therefore do not have as much utilization for acute events. Alternatively, this clinical severity measure may not be the best tool for identifying children at risk for future healthcare utilization.

A primary goal of identifying patients at risk for acute events would be to augment lower cost services designed to keep the child at home with stable functioning, and shift care

away from costly services, such as ED visits or unplanned, acute care hospital admissions. Formal care coordination through medical homes or similar models, such as care provided by the CAPE Program, may be one method for improving health outcomes and decreasing unnecessary or preventable healthcare utilization.[36, 40, 57] A randomized trial of an enhanced medical home for high-risk children with chronic illnesses showed that comprehensive care decreased serious illnesses, ED visits, hospitalizations, intensive care unit (ICU) admissions, and hospital days.[57] This enhanced medical home provided coordinated and comprehensive care that included 24-hour access to primary care clinicians, easy access to subspecialists, and timely follow-up care.

The population of children enrolled in the CAPE Program and participating in this study was already receiving care as part of an integrated, home-based care program. However, the use of a prediction model that includes a marker, such as HRQL, could help identify families in need of interventions to improve child functioning and limit costlier healthcare utilization. This is clearly a high-risk group, as illustrated by the percentage with any hospitalizations (32%) and the mortality rate (6%) over a 6-month period. Routine screening with HRQL measures could identify low scores or decreasing score over time, prompting program staff to intervene with a home visit or clinic visit to troubleshoot before the child requires an unscheduled ED visit or hospitalization. Proactive evaluation would, ideally, shift healthcare utilization away from the inpatient setting to the outpatient or home setting, while also decreasing the angst and cost associated with a reactive, acute care encounter.

Given that the parent is usually the driver of the healthcare utilization in severely ill children, we relied on parent-proxy report for predicting future healthcare utilization. When collecting HRQL on pediatric populations, it is often recommended that both child

and parent-proxy raters be included as each may have different perspectives,[67, 70] referred to as information variance. However, the children in this study were distinct as their underlying illnesses often require constant care or monitoring. Parents serving as around-the-clock caregivers may have greater insight into their child's HRQL than parents of healthy children who become more independent with age. This distinction from healthy children also justifies the inclusion of the wide age range of children in this study (30 days to 22 years). In addition, developmental, cognitive, and functional limitations of many of the children in the current study precluded the use of child report.

We acknowledge the study's limitations. Healthcare utilization was captured from a single institution resulting in possible underestimation. However, given the complexity of these patients, and the fact that they were enrolled in an integrated, home-based care program at Boston Children's Hospital, the majority of their utilization occurred at this facility as confirmed by a review of claims data from two of the larger payers *(unpublished).* Further, while enrollment rates in the study were high, a portion of CAPE Program families did not participate in the HRQL study. Although we found no differences in child age, child gender, clinical severity, diagnosis, or respiratory support by participation status, there could be differences across other factors that would impact generalizability.

Conclusion

Children with CRI are at risk for developing severe acute illnesses that can result in unscheduled and costly services, such as inpatient stays that typically require ICU-level care. We found that parent-proxy HRQL scores were associated with future healthcare utilization among these children, including total healthcare days and inpatient days. Use of HRQL, alone or in combination with clinical severity, may help to identify children and

families who would be appropriate targets for earlier intervention, thereby improving outcomes, patient and family experience, and shifting care to less costly services. A minimally burdensome screener, such as the CHRIs global HRQL score and the general health item, has a higher likelihood of completion in families with significant care demands, and may reveal additional social, emotional, and access issues that represent drivers of healthcare utilization.

6.3 Leveraging Pediatric PROMIS Item Banks to Assess Physical Functioning in Children at Risk for Severe Functional Loss

Custom parent-proxy PROMIS short forms for Upper Extremity and Mobility were created and administered to 57 parents of children with CRI, secondary to a variety of medical disorders, including neuromuscular illnesses. The creation of these custom short forms was made possible by the previously validated parent-proxy PROMIS item banks and scoring based on IRT models. Mean T-scores confirmed that physical functioning in this sample was severely affected, with scores nearly three standard deviations below the PROMIS pediatric calibration population mean. Even among children in the lower severity group, mean T-scores were at least two standard deviations below the calibration population. Preliminary psychometric properties demonstrated that there were multiple items in the PROMIS banks that targeted lower levels of functioning and the potential of the two custom short forms to more accurately measure physical functioning in those at risk for lower levels of functioning. However, there were some participants still scoring at the floor of the scale despite our targeting items at the lower end of functioning.

The custom short forms demonstrated known groups validity with patients with worse clinical severity having lower Upper Extremity and Mobility T-scores, as expected. There were low to moderate Spearman correlations between the Upper Extremity and Mobility T-scores and the CHRIS-General items for physical and mental health. Given our hypothesis that the physical functioning scores would be more highly correlated for the physical health item than the mental health item, we were surprised to find that the strength of the correlation was higher for the mental health item. However, the figures demonstrated a linear relationship in the Upper Extremity and Mobility T-scores for

better physical health item scores, while the Upper Extremity and Mobility T-scores showed a threshold effect for mental health item scores of good or very good/excellent compared with poor/fair. This may imply that HRQL within the domain of mental health is most severely impacted for those with the worst physical functioning. Additionally, the use of parent-proxy report, rather than child report, may also explain the stronger relationship with mental health than physical health. That is, the parent may project assumptions about the child's mental health, based on observations about the child's inability to do many of the physical functioning items. Interestingly, we could assess item ordering and whether asking the physical functioning items before the single mental health item results in lower mental health scores. Future qualitative work with parents may help to better understand this relationship.

With a mean of 50 in the PROMIS pediatric calibration population, the range of possible T-scores for each custom short form (11.5 to 52.5 for Upper Extremity; 12.8 to 54.7 for Mobility) demonstrated that the items targeted the lower range of physical functioning. Additionally, the custom PROMIS short forms were able to capture differences at the lower end of physical functioning. However, there is evidence that some participants still scored at the floor of the scales. For the Upper Extremity scale, 26% scored at the measurement floor and for five out of 13 items more than 70% of parent-proxy raters scored their child at the lowest response category. Similarly, 16% scored at the floor for the Mobility scale and for five of the 11 items more than 70% of parent-proxy raters scored their child at the lowest response category. The persistence of children at the measurement floor indicates that for those at the lowest levels of physical functioning, these specific items are not sufficient for distinguishing between their levels of functioning. To address this, additional items at the lowest end of the scale may need to be developed[74] or "borrowed" from other scales, such as the Pediatric Neuro-QoL,[47] to

supplement the existing item bank. The floor effect also suggests that it may be more appropriate to ask a screening question(s) for each scale to establish whether it is necessary to continue probing with the physical functioning questions. Additionally, further analysis with larger sample sizes using IRT is needed to address the potential local dependence among some of the items near the lower end of the scale. Local dependence occurs when items in a scale are related to each other and indicates that some items could be removed.

The current study describes the development of custom PROMIS short forms targeted to a population of children with CRI and resulting decreased physical functioning. CATs, which tailor items to administer based on one's responses to previous items, are another powerful tool that could be used to measure physical functioning in this population. However, the goal of existing CATs, based on the PROMIS item banks, is to arrive at a T-score with a certain level of precision for the majority of respondents.[81] To be useful in patients with severe functional loss, the existing item bank may need to be enriched with additional items at the lower end of the scale, as indicated by the percentage of children scoring at the measurement floor on the custom short forms.

The two questions about assistive devices included as part of the Mobility short form proved to be inadequate in this population of children who are heavily reliant on these devices. For some children, self-propelled or electric wheelchairs are introduced to help overcome weakness, prevent fatigue, and preserve participation in role activities (e.g., school attendance). In contrast, for children with severe perinatal injury or abrupt spinal injury, "wheelchairs" often resemble more of a stroller or stretcher for transport and still require assistance from a caregiver. Within our sample, more than half of children used a wheelchair almost always while less than 20% never required a wheelchair. In

contrast, 90% of children never used a walker, cane, or crutches. In a general population, never using these devices indicates good physical functioning. However, in this population, never using these devices most likely represents an inability to use them. Further modification of assistive devices questions are needed for use in this population with attention paid to types of devices needed, similar to the work that has been done with adults requiring assistive devices.[2, 3] In addition, the evolution of new adaptive equipment, including eye gaze technology, exoskeletons and bionics, will require further considerations for questions about devices or supports. Eye gaze technology, for example, greatly enhances a person's ability to manipulate the environment, but may not alter their physical functioning.

Within clinical practice, the physical functioning short forms can provide the medical team with additional information about how the child's medical condition is affecting their functioning. Parents or children could also complete the forms between clinic visits to allow for remote monitoring of the child's medical condition that could signal deterioration requiring clinical intervention. This remote data collection would not be possible for the clinical measures that require clinician involvement.[9, 50, 52, 63, 88] Given the different expected rates of disease progression based on the underlying diagnosis,[53, 83] collecting physical functioning scores over time could provide useful information. Declining scores could indicate the need for medical or surgical intervention. Scores could also be used to assess the effectiveness of new treatments, such as gene-targeted therapies in SMA, or assess functional outcomes that may be more meaningful to the child and family than results of clinical tests, such as nerve conduction, electromyographs, and serum protein analyses.

Future studies that include both clinical assessment and self- (or parent-proxy) reported HRQL are necessary to better understand the relationship between these measures and to further establish validity of the custom PROMIS short forms. For example, the Pediatric Evaluation of Disability Inventory-Computer Adaptive Test (PEDI-CAT) is a parent-completed measure that includes domains on daily activities, mobility, social/cognitive functioning, and responsibility.[20] Unlike some other generic HRQL tools, the PEDI-CAT contains items that capture a range of functional levels, including the lower end of mobility.[35] However, the PEDI-CAT is not web-based so it cannot be completed remotely between clinic visits. Future studies are planned to compare mobility scores from the PEDI-CAT and the custom PROMIS short forms to better understand the validity of the short forms.

The items within each of the custom short forms also provide information that can help to allocate needed services. For example, children requiring help getting dressed, getting into bed, and using the toilet typically require around-the-clock care. Adding a home health aide or extending home nursing hours may help address some of these needs, and remove some of the burden on the parent caregiver. In addition, parent caregivers of children requiring near constant care may require additional emotional support.[45, 100, 105] Further, questions about using a mouse or touch pad recognize the role technology can play in improving communication and independence within this population. If children indicate that they are capable of using a mouse or touchpad, self-report of these short forms and other HRQL measures may be possible. Similarly, additional items about eye gaze technology could also help us to better understand communication abilities and which children are capable of providing self-report with assistance.

When testing the hypothesis that physical functioning scores would deteriorate over time, there was some indication that Upper Extremity scores were stable over the 18-month follow-up period, while there was some deterioration in the Mobility scores over time. However, these results should be taken with caution since there are different expected rates of disease progression based on the underlying diagnosis[53, 83] and only a subset of participants completed the short forms at more than one time period. In addition, reasons for missing later assessments may be related to the child's medical condition and physical functioning, so there may be non-ignorable missingness (i.e., those with lower scores may have dropped out or died making overall scores seem stable over time).

We acknowledge the study's limitations. First, this is a relatively small sample of parent-proxy respondents. However, the goal was to explore scores and preliminary psychometric properties and validity of these two custom short forms rather than to generalize findings to a larger population. Second, this is a heterogeneous sample with various underlying diagnoses with different effects on physical functioning and different physical functioning trajectories. Given that these diagnoses are relatively rare within an institution, and are often cared for together in multi-disciplinary clinics, the heterogeneous sample reflects the clinical reality of these diagnoses. However, a larger sample is needed to better explore differences within and across diagnoses. Third, due to the developmental, cognitive, and functional limitations in this sample, we relied on parent-proxy report rather than child report. Future research is needed to understand differences in parent-proxy report and child report, where possible, particularly among those children who could complete self-report measures with communication aids. These differences by rater may help explain the stronger relationship between physical functioning and mental health than between physical functioning and physical health.

Fourth, we did not have any objective measures of physical functioning in this population, such as disease-specific clinical assessments, with which to validate the parent-proxy report of the child's physical functioning.

Conclusion

In conclusion, we found that children with CRI due to neuromuscular illnesses had low mean Upper Extremity and Mobility T-scores, compared with the PROMIS pediatric calibration norms. There was evidence of known groups validity, especially compared with physician-rated clinical severity. However, floor effects still existed for some participants and items about assistive devices did not perform well in this group. Additional data collection is planned to further test the psychometric properties and validity of the custom PROMIS short forms in larger patient cohorts using IRT and adding additional items that may help discriminate at the very low end of physical functioning.

6.4 Overall

In this dissertation, we sought to understand the impact of complex pediatric medical disorders, such as CRI and conditions requiring HSCT, on the child and the parent, using patient-reported outcomes. We accomplished this by completing the following three research projects: (1) assessing the relationship between child HRQL and parent emotional functioning among children undergoing HSCT; (2) determining if the child's HRQL predicts future healthcare utilization among children with CRI; and (3) developing custom physical functioning short forms and exploring scale scores and preliminary psychometric properties and validity among children with CRI who are at risk for decreased physical functioning.

The use of parent-proxy report played an important role in each of these dissertation projects. Ideally, HRQL ratings should be provided directly from the patient. However, in some cases parent-proxy report or using both parent-proxy and child report may be necessary, such as when the child is too young, too sick, or has developmental, cognitive, or functional limitations. In fact, when the child is ill, it is often recommended that both child/adolescent and parent raters be included as each may have different perspectives.[67, 70] For the HSCT population, we obtained child HRQL scores from parent-proxy and child raters, which allowed for comparisons of the results between the two different raters. On the other hand, for the CRI population, we had to rely on parent-proxy report only because of the development, cognitive, and functional limitations that made collecting self-reported data from the child not possible for most cases. As observed in previous research,[22, 67, 70] we also observed differences in HRQL scores between parent-proxy and child raters in the HSCT population, with parents rating their child's HRQL lower. Factors that may influence these differences include HRQL domain, disease severity, child age, and parent emotional functioning. Domains such as physical

functioning, which are more observable, tend to have higher agreement between parent-proxy and child report than non-observable domains. This also supports our decision to use parent-proxy report for assessing the properties of the custom physical functioning short forms. Typically, there is higher agreement between parent-proxy and child raters for sick as compared with healthy children.[23] Parents serving as around-the-clock caregivers may have greater insights into their child's HRQL (referred to as shared reality) than parents of healthy children who become more independent with age. This applies to both the HSCT population and the CRI populations included in this dissertation research. Higher levels of agreement between parent-proxy and child report are often observed among older children, which could be partially explained by older children having better access and understanding to information about their health.[70] Finally, parent emotional functioning may affect differences in child HRQL scores by rater. Parents with low emotional functioning may perceive their child's HRQL as lower than the child perceives their own HRQL. This is independent from the fact that children of parents with decreased emotional functioning may actually rate their HRQL lower than children of parents with higher emotional functioning.

Information and criterion variance are the constructs that underlie most of the differences observed between parent-proxy and child raters. Information variance refers to differences in access to information. For example, the clinician may more thoroughly explain the child's medical condition to the parent caregiver than to the child, particularly when the child is young. Conversely, the child likely has more access to information about how they are doing in school (role functioning) or how they are feeling (emotional functioning). Criterion variance refers to how each rater appraises the current state against a previous or future state or ideal state. For example, a parent might compare

the child's functioning to their functioning before the illness or what the parent may hope for in the child's future.

Common across all of these dissertation projects and the different disease areas is the important role of the parent caregiver in helping to optimize the child's health outcomes. Technological advances in medicine have extended survival for many conditions that were previously fatal in childhood and allowed care to shift from the inpatient setting to outpatient or community settings. This places newfound demands on the parent caregiver. As proposed in the Chronic Care Model,[99] improved outcomes can be achieved through productive interactions between an informed, activated patient (or parent caregiver) and a prepared and proactive practice team. Self-activation, and the related construct of self-efficacy, are defined as having the ability and self-confidence to accomplish a desired goal,[4] and are key ingredients in patients' (or parents') ability to follow medical recommendations and manage their health. Higher levels of activation have been shown to be associated with improved clinical outcomes,[33, 44] while lower activation is associated with less patient involvement and worse clinical outcomes. Decreased parental emotional functioning as a result of the child's medical condition or treatment demands can make it difficult for the parent to maintain activation on behalf of their child. Therefore, providing them with psychosocial support, as needed, can help the parent caregiver meet the medical demands of their child.

As survival has improved among previously fatal childhood medical conditions, there are also important implications to consider as the child ages into adulthood and may take a larger role in the management of their own health. For certain degenerative medical conditions, the child may never be able to attain independence and will continue to rely on a caregiver. However, for survivors of pediatric HSCT, patients will need to become

activated on behalf of themselves. Unfortunately, the late effects of HSCT may be seen throughout the life of the survivor, and it is recommended that they receive guideline-driven survivorship care, based on assessed risk (e.g., neurocognitive testing, echocardiogram). Therefore, the survivor of pediatric HSCT will be required to learn about an illness they experienced as a child and may not have fully understood at the time. Achieving and maintaining activation will be required for appropriate self-management of their medical condition. In addition, survivors may continue to experience decreased HRQL,[19, 87] which should be considered by clinicians as it may indicate the need for clinical or psychosocial intervention.

This dissertation research has several limitations and strengths. These projects included a heterogeneous group of children ranging in age from 1 month to 22 years with a variety of underlying clinical conditions. However, these children share in common the experience of complex medical conditions and reliance on parent caregivers. To account for some of this heterogeneity, analyses adjusted for child age and disease-related factors where appropriate. The sample size for the CRI projects, especially the evaluation of the physical functioning short forms, was relatively small. However, given the rarity of these medical conditions, and compared with other investigations that have studied this population, our sample size was larger than most.[8, 51, 100] Although patients with CRI were recruited from a single center, this center is one of the few in New England that has an established, integrated care program to treat these patients and its catchment includes most patients in the region. On the other hand, the sample size for the HSCT study was large and represents transplant centers located across the US. When studying complex pediatric medical conditions, many of which are rare, amassing a large sample size can be difficult. In some cases, this may require combining different rare disorders together. Although this may cause heterogeneity, it also expands

generalizability to the broader population of children with complex medical conditions. Given the developmental, cognitive, and functional limitations in the CRI population, we had to rely on parent-proxy report only. As previously discussed, there are differences in parent-proxy and child report of child HRQL, but agreement between raters tends to be higher in children with chronic conditions, as compared with healthy children, and in more observable domains of HRQL, such as physical functioning. Fortunately we were able to include both parent-proxy and child report in the HSCT population, which allowed for the comparisons of conceptual models using different raters of child HRQL.

Clinical implications

Each of these projects provides valuable information that can be used in clinical practice to improve the care and health outcomes for children with complex medical conditions and their families. As shown in Project 1, child HSCT-related worry, child emotional functioning, and parent emotional functioning are all interrelated within the pediatric HSCT setting. Therefore, providing psychosocial support to at-risk children and parent caregivers can help improve their emotional functioning, and also better enable the parent caregiver to be an activated participant in caring for their child. In Project 2, we showed that child HRQL was associated with future healthcare utilization among children with CRI, even after adjustment for clinical severity. Therefore, clinicians should consider the use of HRQL measures, either at clinic visits ("point-of-care") or between clinic visits, as a marker for future health outcomes. There have been recommendations to treat HRQL as another vital sign collected at each healthcare encounter.[25] As such, Boston Children's Hospital CAPE Program has already started collecting information on child HRQL and parent emotional functioning at home visits among children with CRI. The two-paged form takes less than five minutes to complete and parents have been very receptive in completing it. Answers to the questions have been able to spark

discussion between the parent caregiver and clinical team and have also allowed the social worker to discuss psychosocial issues with the parent. We have also looked for decreasing scores over time as an indication that health status may be declining and clinical intervention may be needed. As shown in Project 3, physical functioning among children with CRI was substantially lower than the general population. Scores to specific items on the custom short forms (e.g., about eating or bathing) could be used to identify where additional nursing hours would help the child with activities of daily living. Decreasing physical functioning scores over time could also identify when certain medical or surgical interventions are required. In summary, all of the HRQL measures used in these projects could be used to give the clinician a more complete and nuanced understanding of the child's well-being and functioning and how it impacts the family.

Future research recommendations

Results of these projects have identified several areas for future research.

1. To better understand the role of activation among parents caring for severely sick children and which factors affect activation. Maintaining activation or increasing activation levels will allow parent caregivers to optimize their child's health outcomes.
2. To better understand the role of self-activation among survivors of pediatric HSCT as they transition into adulthood. This will be necessary if they are to become responsible for their own health care.
3. To determine how to best use HRQL scores to predict future healthcare utilization. This may include collecting HRQL at multiple time periods and calculating change scores.

4. To develop additional items for the custom physical functioning short forms, especially with regards to items about assistive devices, and collect additional data in order to perform additional psychometric analyses.
5. To focus on methods for electronically collecting patient-reported measures, particularly using computer adaptive testing, where appropriate.

Conclusions

In conclusion, this dissertation used patient-reported outcomes, specifically HRQL, to demonstrate the impact of complex pediatric medical disorders on the child and parent caregiver. Three distinct projects addressed different facets of this complex care paradigm including examining interrelationships between parent and child HRQL using SEM, determining how child HRQL could predict future healthcare utilization, and assessing the psychometric properties of custom physical functioning short forms. Better understanding the HRQL among these children will allow for improvements in care delivery and supports for the children and their families, which aligns with national calls for the "triple aim" of health care improvement efforts through improved outcomes, reduced costs, and better quality of care.[5]

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