8-9-2022 9:00 AM

Health-Related Quality of Life in Children with Spinal Muscular Atrophy

Tran M. Nguyen, *The University of Western Ontario*

Supervisor: Campbell, Craig, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

Abstract

Spinal Muscular Atrophy (SMA) is a genetic disorder characterized by weakness and muscle atrophy. Due to the chronic nature of SMA, it is important to understand the health-related quality of life among children affected by this disease. Participants were recruited from the Canadian Neuromuscular Disease Registry, where 45 families completed the Pediatric Quality of Life Inventory questionnaires. Results from the child self-report and parent proxy questionnaires were compared to those of healthy children and children with Duchenne Muscular Dystrophy. Agreement between parents and children was assessed using paired t-tests and intraclass correlation coefficients. Additionally, multivariable linear regressions were used to determine child and family characteristics associated with health-related quality of life outcomes. Higher levels of perceived fatigue were consistently associated with lower health-related quality of life outcomes. Based on the results, interventions to reduce fatigue could lead to improvement of health-related quality of life for children with Spinal Muscular Atrophy.

Keywords: Spinal muscular atrophy, cross-sectional study, health-related quality of life, fatigue, parent proxy, quality of life

Summary for Lay Audience

Spinal muscular atrophy is one of the most common fatal genetic childhood diseases. This motor nerve disorder causes weakening of the muscles. Due to the serious and long-term nature of spinal muscular atrophy, it is important for healthcare workers and researchers to try to understand and improve the health-related quality of life in children with this disease.

In this study, both children with spinal muscular atrophy and their parents filled out questionnaires asking about the child's health-related quality of life. We looked at whether scores from children with spinal muscular atrophy were different than scores from healthy children and children with another neuromuscular condition. We also assessed whether children and their parents had similar scores, and lastly, we looked at any social or clinical factors that may be related to a child's health-related quality of life.

The health-related quality of life scores of children with SMA were worse compared to those of healthy children in all domains, and worse in the physical domains compared children with another neuromuscular condition. The agreement between children and parent scores ranged from good to poor, with parents reporting lower scores in most topics compared to their children. Lastly, fatigue was the factor most associated to worse HRQL scores.

Acknowledgments

I would like to thank my thesis supervisor, Dr. Craig Campbell for all his guidance and support throughout my degree. His expertise and encouragement were instrumental to the completion of my project. I would also like to thank my supervisory committee, Dr. Kathy Speechley and Dr. Piotr Wilk for reviewing my drafts and providing me with their invaluable input.

Thank you to the members of the pediatric muscular team at Children's Hospital and members of the Canadian Neuromuscular Disease Registry for their coordination and contributions towards this project.

A sincere thank you to my friends and family for their support of my academic pursuits over the years. Lastly, I would like to express my gratitude towards the families who have participated in this study, their strength and optimism continue to motivate me.

Table of Contents

List of Tables

List of Appendices

List of Abbreviations

AUQEI- Autoquestionnnaire Qualite´ de Vie Enfant Image

CNDR- Canadian Neuromuscular Disease Registry

DMD- Duchenne's muscular dystrophy

EMA- European Medicines Agency

EQ-5D-Y- EuroQoL-5 Dimension-Youth

EQ-5D- 3L- EuroQoL-5 Dimension-three levels

FDA- Food and Drug Administration

HRQL- Health-related quality of life

HFMS- Hammersmith Functional Motor Scale

HUI- Health Utility Index

ICC- Intraclass correlation coefficient

NM- Neuromuscular

Peds QL- Pediatric quality of life

PRO- patient reported outcome

QoL-Quality of life

RCT- randomized clinical trial

SMA- Spinal Muscular Atrophy

SMN1- Survival motor neuron 1

TDM- Tailored Design method

WHO- World Health Organization

Chapter 1

1.0 Introduction and Research Objectives

1.1 Background

This chapter consists of a brief overview of spinal muscular atrophy (SMA), the constructs of quality of life (QoL) and health-related quality of life (HRQL), the measures used to assess HRQL in children and their parents/caregivers, and lastly the objectives and hypotheses of this study.

SMA is an autosomal recessive neurodegenerative disease, characterized by atrophy of the muscles and generalized weakness.(1) With an incidence of 1 in 6,000 to 1 in 10,000 live births per year, it is the most common cause of lower motor neuron disease and one of the most common fatal childhood genetic diseases.(2) The prevalence of the carrier state is approximately 1 in 54.(3, 4) Due to the serious and chronic nature of this neuromuscular (NM) disease, it is important to understand and improve HRQL in this population. Although there is no cure for SMA, new therapies such as gene therapy, have dramatically changed the clinical picture and ongoing medical advances have resulted in increased interest in SMA research, especially understanding function and outcomes from a patient perspective.

The goal of this study is to assess the HRQL of children with SMA from both the children's and parents' perspective. It is important to understand both perspectives, because there are circumstances in the context of SMA where the child is too young, or too ill to report on their own HRQL. It is also commonly the parents' perceptions of their child's HRQL that are used to inform their child's treatment decisions. Furthermore, there is still a limited understanding of the dynamic and relationship between the parent and child HRQL perspectives in chronic childhood diseases. In this study, we aimed to examine both the child reported and parent/caregiver proxy HRQL scores whenever possible and examine the extent of agreement between these two perspectives. Lastly, we aimed to explore associations of both the child reported and parent/caregiver proxy HRQL scores with clinical and family characteristics.

1.2 Spinal Muscular Atrophy

Individuals with SMA have insufficient levels of the survival motor neuron (SMN) protein due to the loss or mutation of the SMN1 gene on the chromosome 5q13. The lack of SMN protein leads to the loss of motor neurons with the downstream effect being muscle weakness. SMA is inherited in an autosomal recessive manner, meaning that the affected individual has two mutated genes, often inheriting one from each parent. If an individual only has one mutated gene, they are a carrier but are not affected by SMA or do not exhibit any symptoms.(1, 5) Two carriers have a 25% chance of having an affected child, and in 2% of patients with SMA, only one parent is a carrier, and a new mutation in the offspring results in SMA. A pseudogene called SMN2, differs from SMN1 by a single nucleotide in an intronic region adjacent to exon 7, resulting in an mRNA splicing phenomenon that excludes exon 7, and thus produces a protein that is unstable and not as functional. Only 10-20% of the SMN2 protein is fully functional, resulting in a spectrum of disease severity that is inversely correlated to the number of copies of SMN2.(3) The higher the SMN2 copy number, the milder the clinical phenotype. Therefore, type 1 SMA patients usually have no more than two copies, and the type 3 patients have four or more copies. (2)

The most common forms of SMA can be categorized into four different groups, based on the highest milestone achieved.(5) Type 1 (Werdnig-Hoffmann disease or infantile-onset SMA) is the most common type of SMA, accounting for approximately 50% of patients with SMA. Type 1 SMA is also the most severe type, with common symptoms including hypotonia (reduced muscle tone), diminished limb movements, lack of tendon reflexes, fasciculations, swallowing and feeding difficulties, and impaired breathing.(1) Children with type 1 SMA typically do not live past two years of age. Children with type 2 SMA (intermediate) usually do not present with their first symptoms until 6-18 months of age. They can sit without support but are unable to stand or walk unaided, and some may lose the ability to stay seated independently over time without treatment.(1) The progression of the disease is variable depending on the treatments received and the life expectancy is up to adolescence or early adulthood. Children with type 3 SMA (Kugelberg-Welander disease) develop symptoms after 18 months of age

and the symptoms can be very heterogenous. Children with type 3 SMA usually meet all their major motor milestones, such an independent walking. Considering the symptoms are heterogenous for type 3 SMA, some children may require wheelchair assistance, whereas others may be able to walk independently with minimal muscular weakness.(1) With appropriate medical care, most children with SMA type 3 have a normal lifespan. People with type 4 SMA develop symptoms in adolescence or adulthood and are fully ambulatory with mild motor impairment, and no reported respiratory or nutritional problems.(1) Similar to type 3 SMA, with appropriate management, most patients with SMA type 4 have a normal expectancy.

Genetic testing is widely available to detect deletions or mutations of the SMN1 gene. This test identifies at least 95% of SMA type 1, 2, and 3 and may also reveal if a person is a carrier of a defective gene that could be passed on to children.(5) The absence of the SMN1 exon 7 confirms the diagnosis, with 95% sensitivity and almost 100% specificity.(4) However, if the typical SMN mutations are not found, additional tests can also be performed. These additional tests include electromyography (which records the electrical activity of the muscles during contraction and at rest), nerve conduction studies (which measure the nerve's ability to send an electrical signal), muscle biopsy, and sequencing of the SMN1 gene or RNA qualifications. (4, 5)

There are currently a few therapies available for the treatment and management of SMA. Nusinersen is the first drug approved by the Food and Drug Administration (FDA) to treat children and adults with SMA. It is an antisense oligonucleotide drug that modulates pre-messenger RNA splicing of the SMN2 gene, increasing the production of functional SMN protein. The drug is administered by injection into the fluid surrounding the spinal cord. Multiple multicenter, double blind, sham-controlled trials comparing nusinersen to placebo (6) found that those with early or later onset SMA who received nusinersen had significant improvement in motor function, compared to the control group. (6-8)

In addition to drug therapy, gene therapy has also been used for SMA. This method uses an AAV9 viral vectors to replace SMN1.(4) Onasemnogene abeparovec-xioi (Zolgensma ™) is a gene therapy drug approved by the FDA in 2019. (9) This drug is

generally intended for children less than two years of age who have type 1 or infantile onset SMA. (9) The drug is administered by having a viral vector deliver a full functional SMN gene to the targeted motor neurons.(5, 10) If successful, this drug may improve the muscle movement and function, thus improving survival. (10) Lastly, in August 2020, the FDA approved the first orally administered drug, risdiplam (Evrysdi), to treat patients aged two months of age and older with SMA.(5, 11) EVRYSDI is a pre-mRNA splicing modifier of SMN2 designed to treat SMA. The drug increases the body's production of the SMN protein and sustains the amount of SMN protein in the body, which helps treat SMA.(11)

There are also other treatments aimed at managing the symptoms of SMA including physical therapy, occupational therapy, and rehabilitation. These therapies aim to improve posture, slow muscle weakness and atrophy. Stretching and strengthening exercises may help reduce contractures, increase range of motion, and keeps circulation flowing. Some individuals may also require additional therapy for speech and swallowing difficulties, as well as require assistive devices to improve and maintain their independence such as wheelchairs, braces, speech synthesizers etc.(5)

1.3 Health-Related Quality of Life

1.3.1 Quality of Life and Health-Related Quality of Life

QoL and HRQL are often used interchangeably in the literature, however they are actually distinct constructs.(12) The World Health Organization (WHO) defines QoL as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personals beliefs and their relationship to salient features of their environment."(13) This is in comparison to HRQL which focuses on the impact of illness and treatments on a person's life and does not pertain to aspects of life that are not influenced by healthcare intervention.(14, 15)

For the purpose of this study, we focus on HRQL. Although the definitions of HRQL vary greatly, there are two central themes found in most definitions. The first is that

HRQL is subjective and should be assessed from the patient's perspective, if possible. Secondly, HRQL is multidimensional and includes a broad range of outcomes.(16) HRQL includes patients' assessment of their current level of functioning and their satisfaction with it, compared to what they believe to be ideal.(17) Due to the interchangeable use of the QoL and HRQL terms in the existing literature, the term that most accurately describes the concept being measured will be used, regardless of whether authors may have mislabeled HRQL as QOL.

1.4 Health-Related Quality of Life Measurements

There are many reasons why measuring HRQL is important. First, in the context of the epidemiologic transition, health issues in the developed world have moved from predominantly infectious and short-term diseases to more long-term chronic diseases.(18) Since people are now living longer with chronic conditions, it is important to understand their perspective of disease by measuring their HRQL. Thus, HRQL questions have become an important component of public health surveillance and are generally considered valid indicators of unmet needs and intervention outcomes.(19) HRQL can also be foundational in the context of health economics and informing public policy for therapies. There is also growing interest to include HRQL outcomes in clinical trials as endpoints to evaluate changes in morbidity and medical interventions.(20, 21) Secondly**,** although physiologic measures provide information to health providers, those measures often poorly correlate with the patients' functional capacity.(14) HRQL may also vary greatly among people, and thus two people with the same diagnosis and physical functioning status may have vastly different HRQL scores.(14, 22) Third, the HRQL of an individual is not constant and may undergo different trajectories over time, which can impact the understanding of their condition and inform their treatment.(23) Lastly, the identification of factors contributing to HRQL that are modifiable can help both clinicians and researchers to improve management of a disorder(24)

Based on these reasons, clinicians and policymakers recognize the importance of measuring HRQL to have a more comprehensive understanding of the effects of chronic conditions, as well as to inform patient management and policy decisions.(14) Regarding the health regulatory pathways, HRQL is accepted as a key patient reported outcome (PRO)

by both the FDA and the European Medicines Agency (EMA). The EMA requires reports of improvement in HRQL to be supported by data collected from instruments validated for the corresponding condition. The FDA requires PRO instruments to assess and measure concepts of interest, and if one does not exist, the sponsor is required to develop a new instrument or modify an existing one.(25-27)

1.4.1 Health-Related Quality of Life in Children

The assessment of HRQL in children and adolescents with chronic illnesses has become increasingly important since children are living with these illnesses for a longer period of time.(20) When assessing HRQL in children specifically, it is important to take into consideration that children are embedded within multiple social contexts, such as their family, classroom, peer groups; each of these social settings may impact their HRQL.(16)

Studies show that children can begin reporting their own HRQL between the ages of four to six years.(28) Although children as young as four are able to provide information on concrete aspects of their health status such as pain and medication use (16), the more subjective domains such as emotional impact of disease are more appropriate for assessment by older children.(16)

1.4.2 Health-Related Quality of Life and Parent/Caregiver Proxy in Children

Similar to adults, older children are the best informants of their own HRQL. However, some children may be too young, too ill, or cognitively impaired to assess and report their own HRQL or they may not be able to understand the language in a questionnaire, hence a parent or caregiver proxy is sometimes necessary.(21) A parent/caregiver proxy is also important because it is commonly the parents' perceptions of their child's HRQL that are used in their child's healthcare decisions.

Previous research has shown a greater agreement between parents and children in HRQL measures when assessing observable functions such as physical functioning.(14) However, there is less agreement when measuring non-observable functions such as social or emotional HRQL.(14, 29) Even though agreement is higher in the physical

domain, proxy respondents still overestimate children's dysfunction, compared to how children rate their own functional limitations. Research also showed that agreement on HRQL is better between parents and chronically ill children, compared to parents and healthy children, but no differences were found across age, gender or disease groups.(29)

Overall, both the child and parent/caregiver proxy perspectives offer valuable information, and it has been recommended that HRQL assessments be collected from both viewpoints. (29-31)

1.5 Objectives and Hypotheses

Using a cross-sectional sample of children with SMA, the objectives of this study were:

1. To describe HRQL from the children's and parent/caregiver's perspectives. As a reference, HRQL of those with SMA were compared to published data on HRQL in similar-aged healthy children, and children with a chronic NM disease from the children's and parents' perspectives.
   Hypothesis: Children with SMA will have a lower HRQL compared to healthy children. Children with SMA will have similar HRQL compared to children with another chronic NM.
2. To examine the extent of agreement between the child reported and parent/caregiver proxy-reported HRQL among older children. Only older children (≥ 5 years) will be included in this analysis, given that children < 5 years were not asked to assess their own HRQL.
   Hypothesis: Children's self-assessments of their HRQL and the assessments from their parent/caregiver are more similar for physical domains than for emotional/social domains of HRQL.
3. To explore the associations of clinical and family characteristics to both the child reported and parent/caregiver proxy assessments of HRQL.
   Hypotheses:
   1. Children whose families have higher social economic status have better HRQL, as reported by both child and parent/caregiver, than children from families with lower socio-economic status.

2. Children who have a lower level of functioning (i.e., poorer ventilatory status, have scoliosis and are non-ambulatory) have poorer HRQL as reported by both child and parent/caregiver.
3. Children who are diagnosed with a more severe type of SMA have poorer HRQL, as reported by both child and parent/caregiver, compared to children who are diagnosed with a less severe type of SMA.

Chapter 2

2.0 Literature Review

A systematic literature review was performed to inform the study of HRQL in children with SMA. This chapter consists of the selection process and eligibility criteria for the literature review, the data extraction and analysis process, the results of the review, the discussion, and limitations of the included studies and lastly the conclusion. There were four main objectives from the literature review:

1. To identify the HRQL measures currently used in the SMA population.
2. To assess the studies that compared HRQL in the SMA population to healthy children and children with other conditions.
3. To assess the studies including both the parent/caregiver proxy and child reports and how they are correlated.
4. To identify the family and clinical characteristics associated with patients' HRQL scores as assessed by either the child and/or parent proxy.

The findings from the first and second objectives were used to evaluate the current landscape of HRQL in the SMA population and examine whether the level of HRQL in this population differs from levels in other populations. The findings from the third objective were used to identify the clinical and family characteristics to include in the multivariable regression. The results from the final objective of the review were used to contextualize the results of this study related to the agreement between the parent/caregiver proxy and child reported HRQL.

The literature review was conducted from inception to November 29, 2020, in MEDLINE, EMBASE and Cochrane CENTRAL. Search terms included "spinal muscular atrophy", "SMA", "Healthy related quality of life", "HRQL", "HRQOL", "Pediatric", or "Child". The full search strategy is located in **Appendix A**.

2.1 Study Selection and Eligibility Criteria

All study types including observational and clinical trials were included. Studies were eligible for inclusion if: 1) the study population included children (<18 years)

diagnosed with SMA (type 1, 2, 3 or 4) and/or their parent/caregiver proxy and 2) HRQL or QOL was assessed as an outcome in children with SMA, either as reported by the child and/or parent/caregiver proxy. Studies were excluded if they were non-English studies, measured HRQL in children with other diseases, or only included adults with SMA.

One researcher (T.N.) screened abstracts for eligibility. If there was an abstract and full-text publication of the same study meeting the inclusion criteria, the full-text publication was included, and the abstract was excluded. Any questions that were raised during the screening was resolved by a second researcher (C.C.).

2.2 Data extraction and analysis

Data were extracted into a Microsoft excel spreadsheet. The following study design characteristics were extracted: 1) trial design and participant characteristics (author, year of publication, country of publication, study design, age of participants and sample size); 2) the main objectives of the studies; 3) the measure/questionnaire used to assess the HRQL of the participants; 4) the main findings from the studies; and 5) the clinical or demographic factors correlated to HRQL scores.

2.3 Results

The search yielded 441 results and after removal of duplicate studies, 316 abstracts were screened, and 35 full text studies were selected for full-text review. Thirteen studies were excluded after full-text review (**Table 2-1**), leaving 21 included studies (**Table 2-2**). The main reasons for exclusion included: 1) the studies only assessing HRQL of the parent/caregiver and not of the child, 2) abstracts of full text studies that were already included, and 3) the study including children with different types of NM diseases.(32-52) The PRISMA diagram is located in **Appendix B.**

Included Studies

The 21 included studies were published between 2011 and 2020 and conducted in Australia, Brazil, Czech Republic, Chile, France, Germany, Spain, Italy, United Kingdom, and United States. Twelve of the included studies were cross sectional,(32-41, 45, 49) two were prospective longitudinal studies,(43, 48) one was a retrospective

study,(42) and six were randomized controlled trials(44, 46, 47, 50-52). Most of the studies (16/21) only included children and adolescent participants, with five studies also including adult participants.(32, 35, 37, 46, 50) There was a wide range of sample sizes, with nine to 478 participants. Eleven different HRQL instruments were identified in the literature review, which included: The Health Utilities Index 3 (HUI), EQ-5D-Y, EQ-5D-3L, EQ-5D-5L, Autoquestionnaire Qualite´ de Vie Enfant Image (Portuguese version) AUQEI, Short Form-36, PedsQL Neuromuscular module, PedsQL Generic Core module, Peds-QL family impact module, Peds-QL Fatigue module, and a Likert scale survey of six quality of life issues (**Table 2-3**). Most of the included studies provided general descriptions of the HRQL scores in patients with SMA. However, some studies performed additional stratified analyses. Thirteen studies compared the HRQL scores between subgroups by SMA type, treatment groups, age, respiratory support, and the use of a gastrostomy tube.(32-34, 36, 37, 39, 41-43, 46, 47, 50, 51) Five studies differentiated HRQL score to functional or fatigue scores.(32, 35, 50) Lastly, nineteen studies included a parent/caregiver proxy questionnaire, with five of those studies assessing the correlation and agreement between the child's scores and the parent/caregiver proxy scores (36-38, 43, 49); a detailed summary of each of the analyses are described below.(32-38, 41-52)

For the included studies, the clinical and family characteristics assessed and correlated to the HRQL scores included: SMA type, age, ventilation support, use of gastrostomy tube, fatigue scores, nusinersen use, functional measures, and treatment groups. Thirteen studies assessed the HRQL scores by different subgroups including SMA type, age, ventilation, ambulation, and treatment.(32-34, 36, 37, 39, 41-43, 46, 47, 50, 51) Five studies compared the PedsQL score by SMA type,(36, 37, 41-43) and two studies compared EQ-5D-Y scores by SMA type.(33, 39) Belter et al. compared HUI scores by SMA type, ventilation, and mobility. De Oliveira et al. compared AUQEI scores by SMA type. Vega et al. compared PedsQL scores by SMA type, age, ventilation, and Weaver et al. compared Peds QL scores by SMA type, and whether the patients received respiratory support, had a gastronomy tube, were prescribed nusinersen and had orthopedic interventions. Lastly, four studies compared PedsQL scores by the treatment groups the participants were assigned to in the randomized controlled trial (RCT).(46, 47, 50, 51)

Studies that compared HRQL in the SMA population to healthy children and children with other conditions

Five studies compared HRQL in children with SMA to healthy cohorts.(32, 39, 41, 45, 49) Lopez-Bastida et al., Vega et al., Belter et al., and Iannaccone et al. compared the scores of children with SMA to those of the general population, established from the literature.(32, 39, 41, 49) Bach et al. compared the HRQL of participants with SMA to their control group of healthy children.(45) Lopez-Bastida and Belter compared HRQL in children with SMA to those with other conditions.(32, 39) Lopez-Bastida et al. compared children with SMA to children with type 1 diabetes and Vega et al. 2020 compared patients with SMA to patients with Duchenne's muscular dystrophy (DMD).(39, 41)

In Lopez-Bastida et al., the estimated average EQ-5D social tariff score for patients was 0.16. The score is significantly lower compared to young healthy Spanish people between 16 and 20 years of age (0.987).(39) Additionally, the estimated average EQ-5D social tariff score for SMA caregivers was only 0.49 while that of the general population was 0.959. In Vega et al. 2020, the scores showed healthy peers reported a PedsQL of 81.34 +/- 15.2, compared to the overall HRQL of 51.92 +/- 17 for patients with SMA.(41) Iannacone et al. 2009 reported differences between the healthy children sample and children with SMA.(49) Children with SMA and their parents report statistically significant lower HRQL than healthy children. The greatest differences were in the Physical Functioning Scale for both the child self-report and parent proxy-report.

Regarding the comparison of HRQL of patients with SMA to those with other conditions, Lopez-Bastida et al. compared patients with SMA to patients with type 1 diabetes. They found the HRQL score for patients with SMA was significantly lower than for those with type 1 diabetes (0.16 to 0.94 respectively).(39) Lastly, Vega et al. 2020 compared patients with SMA to patients with DMD.(41) The study found children with DMD had a better HRQL compared to children with SMA in all PedsQL domains (total score, disease, communication, and family). The authors hypothesized this may be because DMD patients have greater independent mobility and verbal communication until more advanced stages of their disease.

In conclusion, the included studies show that children with SMA have a significantly lower HRQL compared to healthy children. It also appears that children with SMA have a lower HRQL compared to children with other chronic conditions such as type 1 diabetes and DMD.

Studies including both the parent/caregiver proxy and child reports and how they are correlated

Most of the included studies reported on HQOL scores from a parent/caregiver proxy (19/21). In four of the studies, the questionnaires were completed by the parent/caregiver proxy if the child was too young and did not meet the age requirements or were too highly dependent on their parents.(32, 33, 37, 41) Five of the studies assessed the correlation and agreement between the child and parent/caregiver proxy scores.(36-38, 43, 49)

In literature assessing the QoL in children, it is common for parents to act as a proxy for their child if the child is unable to answer due to their age or disability.(21, 53) The goal of a parent proxy-report is for the parents to assess what they believe are their child's own perceptions and feelings.(54) Four studies assessed only the parent proxy-report,(32, 33, 44, 45) where the parent or caregiver completed the questionnaire on behalf of their child. Compared to fourteen studies that included parallel child self-report and parent proxy-report.(35-39, 41-43, 47-52) However, only five of these studies assessed the correlation and agreement between the child and parent proxy-reports.(36-38, 43, 49)

Klug 2016 and Kocova 2014 did not note any significant differences in the child self-report compared to the parent proxy HRQL.(37, 38) Klug et al. 2016 stated there were no significant differences in the self and proxy evaluation of HRQL in patients with SMA II or III ($p > 0.05$).(37) Comparisons of the individual questions showed good agreement between the responses of the child and parent. There were only statistically significant differences for two questions between the child and parent proxy.(38)

Alternatively, when Frognia et al. 2018 compared child and parents PedsQL scores, a moderate or large discrepancy was found in five of the 51 families included in

the study.(36) Weaver et al. 2020 compared the child self-report and parent proxy by using a linear mixed effects model with family ID as the random effect.(43) They found the child reported better HRQL compared to the parent proxy. Lastly, Iannaccone et al. 2009 reported moderate intraclass correlation coefficient (ICCs) between the parent and child with the PedsQL questionnaires. The greatest overall agreement was found in the PedsQL Total Generic Core module and "about my NM disease" module.(49) Overall, there were mixed results regarding the differences between the self and proxy parent HRQL reports. When assessing the agreement between the parent/caregiver and child HRQL scores, it is important to note that children who are able to report their own HRQL may be older, less cognitively impaired and less ill compared to children who are not able to report their own HRQL.

Family and clinical characteristics associated with patients' HRQL scores as assessed by either the child and/or parent proxy

SMA Type

Some types of SMA can be very severe, leading to muscle weakness that may result in respiratory, swallowing, and back muscle weakness. This in turn causes issues for patients that may require ventilation support, a gastrostomy tube, or result in loss of ambulation. When the PedsQL scores was assessed by SMA type, children with less severe SMA types appeared to have better HRQL compared to those with more severe SMA types. One study assessed the HRQL reported by families and patients and found only four out of 42 parents of children with SMA type 2, and three out of nine parents of children with SMA type 3 reported scores >80 in PedsQL.(36) In another study,189 patients/parents assessed the HRQL of patients with SMA, with 52% of respondents being a parent proxy and 48% of the respondents being the patient. The study found patients with SMA type 3 assessed their disease-specific HRQL as fairly high (self-reported), while patients with SMA type 1 had poorer proxy-assessed HRQL (69 vs. 34 on a scale with 0 = min. and 100 = max.; $p < 0.001$). There were no significant differences in the self or proxy evaluations of HRQL in SMA 2 and 3.(37) In one study, the authors retrospectively studied electronic medical records of 80 SMA patients, with the aim of assessing the correlation between the reported HRQL using the PedsQL 4.0

Generic Core module and PedsQL 3.0 NM module and the SMA type. A repeated measures linear model was used to examine the PedsQL scores. All children with all three types of SMA and their parents reported decreased scores on the PedsQL Generic Core Scales and PedsQL NM module, with the most decreased scores among patients with SMA type 1.(42) Weaver et al also reported significant differences using parent proxy PedsQL Family Impact module with SMA types 1 and 2 in key functioning domains (physical, emotional, social), family relations, family functioning, and parent HRQL scales (all adjusted $p < .03$). For the PedsQL Neuromuscular module, the communication domain was significantly different according to the SMA type for child report, whereas the communication, family resources, and total score were significantly different according to SMA type for the proxy-report.(43)

Two studies compared the EQ-5D-Y scores by SMA type. With an EQ-5D score of 0 equivalent to death and 1 meaning perfect health, the average self-reported score of patients with SMA in one study was 0.115, with children with SMA type 3 reporting the highest score (SMA type 1 = 0.104, SMA type 2 = 0.067).(33) For the overall EQ-5D VAS score, with 0 being the worst health you can imagine and 100 being the best health you can imagine, the average self-reported score of patients with SMA was 66.24 (SMA type 1= 59.25, SMA type 2= 67.46, SMA type 3 = 66.11).(33) In the other study, the HRQL scores of the patients with SMA and their caregivers were assessed (time trade off -TTO- social tariff, as well as the VAS).(39) The patients with SMA self-reported an EQ-5D social tariff score of 0.16 (max. of 1), while the self-reported EQ-5D VAS was 54.1. However, when considering only patients with SMA type 2, the mean self-reported EQ-5D social tariff decreased significantly, obtaining a score equal to -0.012.

In contrast, two other studies found no differences in QoL and HRQL scores when comparing children with different types of SMA.(34, 41) In an assessment of QoL with the AUQEI Portuguese version, no differences were found when comparing self-reported scores from children with different SMA types. In the other study, the PedsQL NM score which consists of the disease, communication, and family domains were assessed in children with SMA type 1, 2, and 3. The parent proxy communication domain score was lower in patients with SMA type 1 compared to SMA type 2 and 3, but not in

the other PedsQL NM domains.(41) The total parent proxy PedsQL NM score was 46.5 for patients with SMA type 1 and 56.3 for patients with SMA types 2-3.

In summary, most of the included studies found an inverse relationship between HRQL and the severity of SMA type, except for the study by De Oliviera and Vega. However, the results found in that study may be explained by the different type of questionnaire (AUQEI) used to assess HRQL.

Age

Two studies assessed whether the HRQL score differed according to the age of the child with SMA.(35, 41) One study assessed whether the parent proxy-reported PedsQL scores differed between children > 6 years and children ≤ 6 years and did not find a significant difference.(41) Another study assessed whether an association between age and perceived fatigue, for both child self-report and parent proxy-reports, was present and also did not find a significant difference.(35)

Fatigue

To examine perceived fatigue, Belter et al. used the PROMIS fatigue SF parent proxy instrument and found the scores in those with SMA were worse compared to the general population and there did not appear to be a trend of scores varying by SMA type or functional status.(32) Montes et al. conducted a randomized, controlled trial measuring the effects of exercise on various outcomes, including fatigue as a secondary outcome. (50) They used the PedsQL multidimensional fatigue score and noted, while both children and parents reported good HRQL overall (83, 86.5 – on a scale of 0–100), the children reported slightly lower levels of fatigue than their parents (85,74 – on a scale of 0–100).(50) Lastly, Dunaway et al. assessed fatigue using the PedsQL Multidimensional fatigue score and the Fatigue Severity Score.(35) The results showed that all participants with SMA reported perceived fatigue, and the child report of perceived fatigue was similar to the parent proxy. They also found that perceived fatigue was similar between participants with SMA type 2 and 3 (PedsQL Fatigue score: 70.2% vs. 73.4%) and was not associated with function, HRQL, or fatigability in ambulatory patients with SMA.

(35) There were also no associations between age and ambulatory status and perceived fatigue, with all correlations having alpha levels of $p > 0.05$.

Overall, the studies assessing perceived fatigue in the SMA population all agreed that fatigue scores in this population were worse compared to the general population.(32, 35, 50) Two studies also noted perceived fatigue was not affected by the SMA type and functional status, although the studies used different measures (PROMIS fatigue SF and PedsQL Fatigue).(32, 35) There were discrepancies regarding whether the perceived fatigue scores were similar between self and parent proxy-reports.

Nusinersen

As previously mentioned, Nusinersen is a medication that is used to treat SMA where it is administered by injection into the fluid surrounding the spinal cord.(6) Three studies assessed whether the use of Nusinersen affects the HRQL.(43, 44, 47)

Both Chiriboga et al. and Weaver et al. did not find a significant difference in the PedsQL score between those on Nusinersen compared to placebo. Chiriboga et al. found a slight improvement for the PedsQL Generic Core scales for the 9 mg group at day 85 compared to baseline for both child self-reported and parent proxy-report.(47) Similarly, a slight improvement for the Peds QL NM was observed for baseline compared to the 9 mg group with the change being greater for patient self-report compared to the parent report, however neither were significant. No meaningful changes in the HRQL scores were seen in other dose groups.(47) Weaver et al. noted both child and proxy-report HRQL scores were better for children receiving nusinersen compared to children on placebo, although this was not statistically significant.(43) Alternatively, the family impact scales, and parental HRQL were both better for families of children not receiving nusinersen.

Montes et al. assessed PedsQL parent proxy scores in a nusinersen treatment group compared to placebo. The PedsQL Generic Core total score improved from baseline for children treated with nusinersen, with a mean change score of 2.3 (-1.08, 5.72), whereas the PedsQL NM score stabilized over time -0.2 (-3.79, 3.49).(44)

In summary, results from the included studies show mixed results in HRQL of those taking nusinersen compared to those not taking nusinersen.

Ventilation Support

Weaver et al. found that ventilation support impacted both child self-report and parent proxy-report of HRQL.(43) On the PedsQL NM module, QoL was rated better by self-report for children without positive pressure ventilation support (68.2 vs. 55.9, P= 0.97) than by proxy-report (61.8 vs. 50.5, P = 0.029).

Gastrostomy Tube

Weaver et al. showed that the self-reported HRQL from the PedsQL NM module score was significantly better for children without a gastronomy tube compared to those who were gastronomy tube fed (68.2 vs. 48, P = 0.041). The parental proxy score of the child's HRQL for those without the gastronomy tube also appeared to be better (61.3 vs. 41.6, P =0.001).(43)

Functional Measures

Five studies assessed the correlation between clinical measurements and HRQL scores.(34-36, 50, 51) Frongia assessed the correlation between the PedsQL with functional scales such as the Egen Klassifikation 2 (EK2), Hammersmith Functional Motor Scale Expanded (HSMSE) and RULM. (36) Their results showed that regardless of the functional motor outcome, children and adolescents with SMA, as well as their parents, have a perception of relatively good HRQL. Dunaway compared PedsQL and short form scores with fatigue and function scores, which showed the Peds QL NM child and parent report did not correlate to the function tests (Hammersmith or six-minute walk test) (all correlations had alpha levels of $p > 0.05$). They also found no association between ambulatory status and perceived fatigue.(35) De Oliveria compared AUQEI child reported scores to functional status (measured by Hammersmith functional score), and no significant difference was found when comparing QoL to the functional score.(34) Finally, Swoboda et al. found the parent proxy HRQL scores did not improve as the modified Hammersmith Functional Motor Scale (MHFMS) improved, but there was

evidence of deterioration in HRQL as the Hammersmith score declined.(51) Therefore, none of the studies found a significant relationship between functional status and HRQL of patients with SMA.

Treatment Groups

Four RCTs assessed HRQL as a secondary outcome using PedsQL. Three of the studies used both the child self-reported and parent proxy PedsQL scores according to their intervention group.(46, 50, 51) All three studies were randomized, placebo-controlled trials, assessing various interventions such as olesoxime, exercise, or l-carnitine and valproic acid. One study assessed the child self-reported and parent proxy PedsQL score according to the different dose groups of the nusinersen drug (1 mg, 3 mg, 6 mg, 9 mg).(47) None of the studies found a significant difference in the PedsQL score between the treatment and control, or dose groups.

2.4 Discussion and Limitations of Previous Studies

The current literature is a useful starting point to assess the QoL and HRQL in children with SMA. There were a few notable points of agreement among the included studies in the literature review. First, the included studies did not find a difference in HRQL for nusinersen use, ventilation support, or functional score status. Although the studies agreed on these points, only two small studies assessed the relationship between nusinersen and HRQL, and the ventilation studies focused more on the HRQL of the parents as opposed to the HRQL of the children. Secondly, most of the studies agreed the HRQL of patients were impaired across all PedsQL modules and patients with SMA have lower HRQL scores compared to healthy children. Lastly, the studies found an inverse relationship between HRQL scores and the severity of SMA.

There were also some important points of disagreement across the included studies. First, findings were inconsistent regarding the agreement between the child's HRQL score and the parent proxy HRQL score. Some studies did not note any significant differences in the child self-report compared to the parent proxy HRQL, however some studies reported the child self-reported QoL was higher compared to scores reported by

the parent proxies. Secondly, data regarding fatigue in the SMA population and its association with HRQL were scarce and inconsistent. There were discrepancies between whether the perceived fatigue scores were similar between self and parent proxy-reports and, although two studies assessed associations between age and ambulatory status and perceived fatigue scores, they used different fatigue measurements (PROMIS fatigue and PedsQL Fatigue). None of the studies assessed an association between HRQL scores and fatigue scores.

There were some consistent shortcomings of the studies identified in this literature review. The first challenge is the interchangeability of the HRQL and QOL terminology in the published literature. Although some studies use the term QOL, the measurement that is used in the study is actually assessing HRQL. There needs to be a consistent terminology adopted and linked clearly to the construct of HRQL that is distinct from QOL. Secondly, although some studies compared HRQL scores by clinical factors such as age, SMA type, ventilation status etc. there was a lack of studies using a multivariable regression to assess the relationship between independent variables of various types and HRQL in children with SMA. Lastly, all the studies were cross-sectional studies, which limits the ability to make longitudinal observations and assess HRQL temporality related to disease factors and make casual inferences.

2.5 Conclusion

Given the current discrepancies and limitations in the literature regarding the HRQL of children with SMA, further comprehensive studies are required to examine the HRQL in both the children self-report and parent proxy-reports using validated questionnaires. Such studies would allow clinicians and researchers to gain more insight into the factors associated with HRQL in children with SMA and identify potential risk factors related to low HRQL and intervene, hopefully resulting in better outcomes for children with SMA. The current discrepancies and limitations found in the literature review helped guide the main objectives of my project.

Table 2-1 Systematic Literature review: Table of Excluded Studies

Study	Reason for exclusion
1. Benini F, Salamon E, Divisic A, Maghini I, Agosto C. Acknowledging Limits: Statistics and the Child's Quality of Life in Spinal Muscular Atrophy. *Journal of Paediatrics and Child Health*. 01 Jun 2020;56(6):995-996.	Letter to the editor, not a study
2. Brown L, Hoffman K, Krosschell K, et al. REGISTRIES, CARE, QUALITY OF LIFE, MANAGEMENT OF NMD: P.341 Use of the assessment of caregiver experience with neuromuscular disease (ACEND with SMA) - a caregiver experience from a single center. *Neuromuscular Disorders*. October 2020;30 (Supplement 1): S145-S146.	Only assessed caregiver scores on ASCEND
3. Dunaway S, Montes J, Kramer S, Podwika B, Rao A, De Vivo D. Perceived fatigue and physiological fatigue in spinal muscular atrophy (SMA): Are they related? *Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN*. 2014;82(10 SUPPL. 1)	This is an abstract of an included study
4. Johnson NB, Paradis AD, Naoshy S, Montes J, Krasinski DC. Impact of Caregiver Experience and Hrqol in Later-Onset Spinal Muscular Atrophy (Sma): Results from the Phase 3 Cherish Trial. *Value in Health Regional Issues*. October 2019;19 (Supplement): S76.	Only assesses the HRQL of caregivers
5. Johnson NB, Paradis AD, Naoshy S, Wong J, Montes J, Krasinski DC. Evaluation of nusinersen on impact of caregiver experience and hrqol in later-onset spinal muscular atrophy (SMA): Results from the phase 3 cherish trial. *Neurology Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN*. 2020;94(15 Supplement)	Only assesses the HRQL of caregivers
6. Kaltsa A, Hantzara V, Barbaresou C, Tsipou H, Kolaitis G. Impact of neuromuscular diseases upon health-related quality of life of children and adolescents: A Greek cross-sectional study. *European Child and Adolescent Psychiatry*. June 2011;20(1): S206-S207.	Includes children with all different types of neuromuscular diseases (Duchenne Muscular Dystrophy, Becker Muscular Dystrophy and type II Spinal Muscular Atrophy)
7. Lloyd AJ, Thompson R, Gallop K, Teynor M. Estimation of the quality-of-life benefits associated with treatment for spinal muscular atrophy. *ClinicoEconomics and Outcomes Research*. 2019; 11:615-622.	This is an economic study where experts estimated quality of life weights or utilities for different SMA states
8. Sakai S, Maki M, Sakai N, Sudoh A, Kato M, Saitoh S. Questionnaire survey conducted on the parents of patients with spinal muscular atrophy type 1 in Japan regarding switch devices, language development, upper extremity function and QOL. [Japanese]. *No To Hattatsu*. November 2012;44(6):465-471.	Only assesses the HRQL of caregivers
9. Scott C, Swoboda KJ, Kissel JT. Comparing child and parent-proxy responses regarding function and	Included the full text manuscript already (SMA CARNIVAL TRIAL PART II: a prospective,

assessment of quality of life: report from SMA CARNI-VAL clinical trial. 2009:58, Abstract no: ORM-F&S-07.	single-armed trial of L-carnitine and valproic acid in ambulatory children with spinal muscular atrophy)
10. von Gontard A, Rudnik-Schoneborn S, Zerres K. Stress and coping in parents of children and adolescents with spinal muscular atrophy. *Klinische Padiatrie*. 2012;224(4):247-51.	Only assesses the stress and coping of caregivers
11. Voos M, Polido G, Barbosa A, Favero F, Caromano F. Visual, cognitive and motor skills in children with type I spinal muscle atrophy. *Neuromuscular Disorders*. October 2015;25(2): S196.	Main outcomes assess the visual, cognitive, and motor skills in children with type 1 SMA. No usable HRQL data
12. Love D, Hicks R, Wei Y, Zapata Aldana E, Almobarak S, Campbell C. P.218Utility based health related quality of life in children and adolescents with spinal muscular atrophy. *Neuromuscular Disorders*. October 2019;29 (Supplement 1): S130.	This abstract is using data from the same survey used in this thesis (Timepoint 1)
13. Lopez Bastida J, Pena-Longobardo LM, Aranda-Reneo I, et al. Pro44 the Economic Impact and Health-Related Quality of Life of Spinal Muscular Atrophy (Sma). An Analysis across Three European Countries. *Value in Health*. November 2019;22 (Supplement 3): S848-S849.	This is an abstract of an included study
14. Iannaccone ST, American Spinal Muscular Atrophy Randomized Trials G. Outcome measures for pediatric spinal muscular atrophy. Multicenter Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Validation Study. Archives of Neurology. 2002;59(9):1445-50.	The full patient population of this publication is published in “reliability of 4 outcome measures in pediatric spinal muscular atrophy”

Table 2-2 Systematic Literature Review: Table of Included Studies

	Study	Study Design	HRQL measure(s)	Sample size (N)	Objective(s)
1	Belter L et al 2020	Cross sectional	HUI3	478	The survey assesses HRQL, loss of work productivity and fatigue using the HUI, WPAI and the PROMIS fatigue SF
2	Chambers et al 2020	Cross sectional cohort	EQ-5D-Y and CarerQoL (for parents)	40	To quantify the economic and health related quality of life burden incurred by households with a child affected by SMA
3	De Oliveira et al 2011	Cross sectional cohort	AUQEI Portuguese version	33	To determine the level of quality of life in a cohort of SMA children and adolescents and study its relation to motor ability.
4	Dunaway et al 2019	Cross sectional cohort	PedsQL NM, PedsQL Fatigue scale and short form-36	32	To assess the relationship of perceived fatigue to fatigability, function, and quality of life in SMA in children and adults with SMA and their caregivers
5	Frongia et al 2018	Cross sectional cohort	PedsQL Generic Core	51	To describe the correlation between the functional motor status with the perceived quality of life by families and patients
6	Klug et al 2016	Cross sectional cohort	PedsQL NM	189	This study aimed at analyzing the economic burden and disease specific HRQL of patients with SMA in Germany (children and adults)
7	Kocova et al 2014	Cross sectional cohort	PedsQL NM	35	To improve the care for children with spinal muscular atrophy in the Czech Republic, we created a survey to obtain the baseline information about their quality of life and compared the data with equivalent data from the United States
8	Lopez-Bastida J et al 2017	Cross sectional cohort	EQ-5D- 3L (for proxy caregivers)	81	The aim of this study was to determine the economic burden and HRQL of patients (children/adolescents) with SMA and their caregivers in Spain
9	Pena-Longobardo LM et al 2020	Cross sectional	EQ-5D-3L for patients and 5Q-5D-5L for caregivers	86	This study aimed to estimate the economic impact and health related quality of life of patients with SMA in three European countries (France, Germany, and the UK)
10	Kissel JT et al 2011	RCT	PedsQL Generic Core	33	The primary objective was to assess the safety, tolerability, and efficacy of a combined regimen of oral VPA and carnitine in SMA patients 2–17 years of age
11	Vega P et al 2020	Cross sectional	Peds-QL NM	38	To characterize QoL in a sample of Chilean children and adolescents with SMA
12	Wagner S et al 2020	Retrospective study	Peds-QL NM and Peds QL Generic Core	80	The aim of the study is to compare HRQL among patients with different types of SMA

13	Weaver MS et al 2020	Prospective, longitudinal, crossover survey	Peds-QL NM, Peds-QL Family impact module	58	To report on the quality of life and family experience for children with SMA with attentiveness to patient and proxy concordance and to stratify quality of life reports by SMA type and medical interventions
14	Bach JR et al 2003	Cross sectional	Likert scale survey of QoL	54	To compare healthcare professionals' assessment of the quality of life of spinal muscular atrophy type 1 children with that of the care providers for the children
15	Bertini E et al 2017	RCT	Peds-QL NM	160	Investigated the safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 SMA
16	Chiriboga CA et al 2016	RCT	PedsQL Generic Core and NM	28	To examine the safety, tolerability and PK of nusinersen in patients with childhood SMA
17	Iannaccone ST et al 2003	Prospective study	Peds NM	34	To demonstrate that 4 outcome measures are reliable for use in clinical trials in patients with SMA
18	Iannaccone ST et al 2009	Cross sectional	PedsQL Generic Core and NM	176	The aim of the study was to investigate the feasibility, reliability, and validity of the PedsQL NM and the PedsQL generic core module in children with SMA
19	Montes J et al 2014	RCT	PedsQL NM and PedsQL Fatigue scale	9	To assess the effects of exercise on measures of function, strength, and exercise capacity in ambulatory SMA patients.
20	Montes J et al 2020	RCT	Peds-QL Generic Core and Peds-QL NM	63	ACSCEND and PedsQL generic core and neuromuscular module were administered to caregivers of children in the CHERISH and SHINE to assess the effects of longer-term treatment with nusinersen on caregiver impact and HRQL
21	Swoboda KJ et al 2010	RCT	PedsQL Generic Core	61	To assess potential benefit for improving motor function in a young non-ambulatory cohort of children with SMA in a randomized double-blind placebo controlled clinical trial

Table 2-3 Quality of Life Instruments Identified in Literature Review

Instrument	Included Domains	Studies
Health Utilities Index 3 (HUI3)	• Vision • Hearing • Speech • Ambulation • Dexterity • Emotion • Cognition • Pain	Belter et al 2020
EQ-5D-Y	• Mobility • Looking after myself • Doing usual activities • Having pain or discomfort • Feeling worried, sad, or unhappy	Chambers et al 2020
Auto questionnnaire Qualite´ de Vie Enfant Image (Portuguese version) AUQEI	• Family factors • Social factors • Activities • Health • Body functions • Separation	De Oliveira et al 2011
Short Form-36	• Physical functioning • Physical role • Pain • General health • Vitality • Social function • Emotional role • Mental health	Dunaway et al 2019
PedsQL Neuromuscular Module	• Neuromuscular disease • Communication • Family resources	Dunaway et al 2019 Klug et al 2016 Kocova et al 2014 Vega et al 2020 Wagner et al 2020 Weaver et al 2020 Montes et al 2014 Bertini et al 2017 Chiriboga et al 2016 Iannaccone et al 2003 Iannaccone et al 2009 Montes et al 2020
EQ-5D- 3L	• Mobility • Self-care • Usual activities • Pain/discomfort	Lopez-Bastida et al 2017 Pena-Longobardo et al 2020

	• Anxiety/depression	
EQ-5D-5L	• Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression	Pena-Longobardo et al 2020
PedsQL Generic Core Module	• Physical functioning • Emotional functioning • Social functioning • School functioning	Frongia et al 2018 Wagner et al 2020 Montes et al 2020 Chiriboga et al 2016 Iannaccone et al 2009 Swoboda et al 2010 Kissel et al 2011
Peds-QL Family Impact Module	• Physical functioning • Emotional functioning • Social functioning • Cognitive functioning • Communication • Worry • Daily activities • Family relationships	Weaver et al 2020
Peds-QL Fatigue Module	• General fatigue • Sleep/rest fatigue • Cognitive fatigue	Montes et al 2014 Dunaway et al 2019
Likert scale survey of QoL	No Domains	Bach et al 2003

Chapter 3

3.0 Methods

3.1 Data Source

This chapter gives an overview of the source of the study data, ethics approval, the eligibility criteria, data collection procedures, an overview of the measures collected in the questionnaires, and lastly the statistical analyses used to address the objectives.

Study participants were recruited through the Canadian Neuromuscular Disease Registry (CNDR), a Canada-wide clinic-based registry of people diagnosed with a NM disease. The CNDR collects demographic and medical information on patients in Canada, with the goal of improving the understanding of NM therapies and accelerating the development of effective therapies.(55, 56) The CNDR consists of 36 clinical sites in 15 academic centers across Canada. To date, 4310 patients have been recruited from the 10 provinces and 3 territories across Canada. Patients are usually consented to participate through affiliated clinics across Canada, or in some cases, can self-register through the National office.(55) To be eligible for inclusion into the CNDR, the patient must have a confirmed diagnosis of a NM disease and provide informed consent.(56) When patients or their parent/caregiver (if patients are < 18 years) register for the CNDR, they are notified of clinical trials they or their child may qualify for, new scientific advancements, therapy access, and any survey-based research studies.(57)

There are currently 229 SMA patients in the registry, accounting for 5.3% of the total participants in the CNDR. Fifty-four percent (N=125) of those SMA patients are pediatric. Based on published prevalence estimates, the CNDR currently has an ascertainment of 38.1% of adult and pediatric SMA patients in Canada.(55) The CNDR supports different types of projects including clinical trial feasibility and planning, trial notifications, survey and questionnaire-based studies, data analysis, and other informational mail-outs.(55) Previous studies published from the CNDR database include clinical outcomes in DMD,(58) the relationship between QoL and HRQL in males with DMD,(59) fatigue in children with DMD,(60) and a multi-source approach to determine SMA incidence and research ready populations,(61) to name a few.

3.2 Ethics

The ethics approval for the study was obtained from both Western University's Health Sciences Research Ethics Board and approval was given by the CNDR research advisory committee.

3.3 Eligibility

All 77 parent/caregivers of a child diagnosed with SMA, along with their affected child between the ages of 0 and 18 years, who consented to being a part of the CNDR and indicated they were interested in research opportunities were contacted. The inclusion and exclusion criteria for the study are listed below.

Inclusion criteria:

1. Patients with a confirmed genetic diagnosis of SMA
2. Enrollment in the CNDR and the parent has indicated interest in research studies
3. The availability of the parent or caregiver to complete a parent proxy questionnaire

Exclusion criteria:

1. The presence of comorbidities unrelated to SMA
2. The inability to adhere to the study protocol, due to cognitive impairment or lack of language skills required to complete the questionnaire
3. Patients involved in any long-term study with Nusinersen

3.4 Data Collection

The CNDR mailed out a Letter of Information (**Appendix C**), assent form (**Appendix C**), set of questionnaires, and a token of appreciation ($10.00 gift card) to all eligible parent/guardians in the database who had a child diagnosed with SMA and indicated they were interested in participating in research. Overall, there were a total of 77 eligible families who met the inclusion criteria, out of 125 patients in the registry. To protect their confidentiality, a unique study number was generated by the CNDR staff and added to the questionnaire prior to being sent out, with only the CNDR national staff able

to link questionnaire responses to identifying information and not our local research team.

Questionnaire packages were compiled in London, Ontario and sent to the national office of the CNDR to be mailed out in August 2018. The questionnaire booklets for both the child and parent/guardians were distributed according to the ages of the child. Only children who were five and older were sent their own questionnaires to complete (N = 63); if the child was younger than five years of age (N = 14) they were not sent their own questionnaires. All parents, regardless of child's age, were sent parent/caregiver version of the questionnaire.

Therefore, only the responses related to the group of older children (≥ 5 years) will be used to examine the agreement between the child reported and parent/caregiver proxy HRQL scores. The parent and child were instructed to independently complete the questionnaires.

The questionnaire booklets were categorized into five different categories, based on child's age. Although the content of the in the questionnaires is assessed all the same concepts, the language for each of the age groups was modified to be age appropriate.

The age groups included:

1. Infant questionnaire (Only parent/caregiver proxy questionnaire) (N= 1)
2. Toddler questionnaire (2-4 years) (Only parent/caregiver proxy questionnaire) (N = 13)
3. Young child questionnaire (5-7 years) (child self-report and parent/caregiver proxy questionnaires) (N = 12)
4. Child questionnaire (8-12 years) (child self-report and parent/caregiver proxy questionnaires) (N = 26)
5. Teen questionnaire (13-18 years) (child self-report and parent/caregiver proxy questionnaires) (N = 25)

The parent/guardian was asked to complete the questionnaires about their child, without consulting their child. The child was asked to independently complete their own

questionnaire. If the child was unable to independently complete their questionnaire, the parents were instructed to read the questions to their child verbatim and not guide the child when answering their question. The full instructions for both the parents and child are located in the **APPENDIX D-F**. Implied consent and assent were assumed if the parents mailed back the questionnaires.

A modified Dillman's Tailored Design method (TDM) was used when designing the survey methodology. This method was implemented to maximize the response rate of the participants. Based on the principles of TDM, a reminder postcard was mailed out to all families one week after the initial questionnaires were mailed (**Appendix G**). Finally, a month after the initial mail-out another reminder package (minus the token of appreciation) was sent to those families who still did not respond (**Appendix H**). A member of the CNDR or the CNDR coordinator from the clinic where the participant was enrolled followed-up by telephone, for the participants who did not respond (**Appendix I**).

Questionnaires were initially returned to the CNDR office at the University of Calgary, Alberta, Canada. The questionnaires were then forwarded from Calgary to Children's Hospital in London, Ontario where the information from the questionnaires was entered into REDCap and exported into SAS for data analysis. Data verification was performed, where data from 50% of the questionnaires were double checked for accuracy in REDCap.

3.5 Measures

Children with SMA and their parents completed the PedsQL questionnaires that assessed child HRQL (**Table 3-1**). Children completed the PedsQL 4.0 Generic Core module, PedsQL 3.0 NM module, and PedsQL 3.0 Fatigue module. Parents completed the PedsQL 4.0 Generic Core module, PedsQL 3.0 NM module, and the PedsQL 3.0 Fatigue module. In addition, the parents also answered questions regarding family and the child's clinical characteristics. The measures are described in detail below.

Pediatric Quality of Life (PedsQL) Questionnaire

The PedsQL questionnaire was used to measure the HRQL of the children with SMA in the current study. It is a HRQL instrument designed for both children and adolescents and integrating generic core scales with disease specific scales into one instrument.(62, 63) It is a reliable and valid measure to assess the HRQL in both healthy children, as well as those with acute and chronic conditions, including SMA.(48, 49, 63-68) The PedsQL 1.0 was originally derived from the Pediatric Cancer database and utilized non-categorically.(69) However, the PedsQL has developed over the years to the 2.0 and 3.0 versions to include additional constructs, a more sensitive scaling range, and a wider range for patient and parent proxy-report.

The PedsQL measures both the patients' and parents' perceptions of the patients' HRQL as defined in terms of the impact of disease and treatment on an individual's physical, psychological, and social functioning, and disease treatment/specific symptoms.(69) There are different versions of the PedsQL questionnaire depending on the age of the child. The three different versions include: the young child questionnaire, child questionnaire, and teenager questionnaire. The forms are similar, however the questionnaires for the younger children are more simply worded.(69) The parent questionnaire is the same as the child/adolescent questionnaire, but in third person tense (Varni et al. 1999).(69) Each specific PedsQL module contains different domains with their own questions and each question is measured on a five-point Likert scale from 0-4 (0=never, 1=almost never, 2=sometimes, 3=often, 4=almost always). All the questions are reverse scored and linearly transformed into a scale out of 100, where 0=100, 1=75, 2=50, 3=25, 4=0. Therefore, lower scores indicate a worse HRQL, and higher scores indicate a better HRQL. If more than 50% of the items in the scale are missing, the scale scores are not to be calculated.

This study used the generic core module, the NM module, and the fatigue module for both children and parent proxy. Each PedsQL module is further explained in detail below and an example of the questionnaires can be found in the **Appendices J-M.**

PedsQL 4.0 Generic Core Module

The PedsQL 4.0 Generic Core module is a multidimensional child self-report and parent proxy-report, developed to be integrated with the PedsQL disease specific modules (**Appendix J**).(62, 63) This module was designed to assess the differences between healthy children and pediatric patient with both acute or chronic health conditions.(63) It has been used on over 35,000 healthy children and children with a variety of pediatric health conditions.(49) The child self-report includes different forms designed for children ages 5-7 years, 8-12 years, and 13-18 years.(63) The parent proxy-reports include forms designed for parents with children from ages 2-4 years (toddler), 5-7 years (young child), 8-12 (child), and 13-18 (adolescent). The items for each of the age forms are almost identical, with the minor differences due to the appropriate language for that age category. For the toddler age range (2-4 years) there is no self-report form for the child, due to the developmental limitations' children under 5 years of age. The young child report is scored on a 3-point Likert scale (0=Not at all, 2=Sometimes, 4= A lot) for ease of interpretation and the rest are scored on a 5-point Likert scale (0= never, 4=almost always). The generic core module consists of 23 items, divided into four separate categories including physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items).

The PedsQL 4.0 Generic Core module can be scored a couple of different ways in addition to the overall and domain scores. The psychosocial health summary score can be derived from the sum of the emotional, social, and school functioning scales, and the physical summary score is equivalent to the physical functioning score.

PedsQL 3.0 Neuromuscular Module

The PedsQL 3.0 NM module was developed to assess the HRQL in children with NM disorders including SMA (**Appendix K**).(49) Similar to the generic core module, the NM module also reports parallel child self-report formats for ages 5-7 years, 8-12 years, and 13-18 years and parent/caregiver report formats for ages 2-4 years, 5-7 years, 8-12 years, and 13-18 years.(49) The NM module was developed using the authors' research and clinical experiences with NM disorders including SMA and DMD, along with other

chronic pediatric conditions. The authors used the same methodology used to develop other Peds QL disease specific modules (i.e., arthritis, cancer, diabetes etc.).(49) The PedsQL 3.0 NM module consists of 25 items, divided into three different categories including about my NM disease (17 items), communication (3 items), and family resources (5 items). The young child report only consists of the 17 items "About my NM disease scale" and does not contain the "Communication" and "About our family resources" scales since the authors found the coefficient alphas on these two scales to be in the unacceptable range for children 5-7 years.(49) The parent report for ages 2-18 years includes all 3 dimensions and all 25 items. The PedsQL 3.0 NM can be scored either by dimension or the overall score.

PedsQL 3.0 Fatigue Module

Lastly, the PedsQL 3.0 Multidimensional Fatigue module is a generic symptom-specific instrument measure child and parent perceptions of fatigue in pediatric patients (**Appendix M**).(67, 70) The multidimensional constructs were derived from literature reviews of both the adult and pediatric populations and incorporated into the PedsQL measurement model. (70) Similar to the Generic core and NM modules, the Fatigue module comprises the child self-report and parent proxy-report formats. The parent proxy-reports are parallel to the child self-report forms and are designed to assess the parent's perceptions of their child's fatigue. (70) The parent proxy-report also includes the toddler age range (2-4 years), which does not include a self-report form due to the developmental limitations of the child.(70) The PedsQL 3.0 Fatigue module is composed of 18 items, categorized into three dimensions including general fatigue (6 items), sleep/rest fatigue (6 items), and cognitive fatigue (6 items). The PedsQL 3.0 Fatigue module can be scored either by dimension or the overall score. Items were marked on a 3-point scale from 0-4 (0= Not at all, 2 = sometimes, 4= a lot) for the young child report for ease of interpretation, and items were marked on a 5-point Likert scale from 0-4 for the other child and parent proxy-reports.

Clinical Information

Additional clinical information was assessed in the parent questionnaires (**Appendix N**). The information included the SMA type, ambulatory status (yes or no), scoliosis status (yes or no), use of assisted ventilation (none, tracheostomy/ventilation, non-invasive bilevel positive airway pressure (Bi-PAP) machine, other), and medications the child is currently receiving (i.e., Nusinersen/Spinraza, salbutamol, valproate, gabapentin, nutritional supplements, and any other medications/supplements or investigational products).

Family Characteristics

The child and family characteristics and sociodemographic information were also collected in the parent questionnaire (**Appendix N**). The socio-demographics information included the parent's highest level of education, current work status, current marital status, partner's work status, total yearly household income and main sources of income.

Clinical Expertise

Given that the sample size was relatively small and there was limited pre-existing literature on what to base variable selection on for regression modelling, it was felt a clinical perspective would be important to inform the selection of variables. A meeting was held with five neurologists (CC, MH, CS, HM, KS) with experience treating children with SMA. A list of the clinical and family demographic factors collected from our questionnaire, along with the results from the literature review were presented to them. Based on this information, the clinicians were asked to rank these characteristics in terms of importance to patients' HRQL. Overall, the top factors selected included: family income, fatigue, ventilation status, and ambulatory status. This meeting was helpful to determine the variables the clinicians believed to be most associated with a child's HRQL, based on their clinical experience. This information was then used to confirm the variables that should be included in the final regression models.

The clinicians thought annual family income was important because it determines whether the families can afford general life expenses that may improve the patients

HRQL. The clinicians included fatigue because it has been significantly associated with other pediatric NM conditions, such as DMD. Lastly, ventilation status and ambulatory status were included as a marker of the patient's disease severity and independence.

SMA type was not included because the diagnosis of the SMA type is dependent on the child's best motor status, which is usually determined early in life after it is relatively constant. Therefore, children with type 1 SMA who survive infancy, children with type 2 SMA and type 3 SMA who lose ambulation, are all similar enough that other factors such as lung function and ambulation are the major differentiating disease severity factors. Furthermore, it is becoming less important given the disease modifying therapies now available which are changing the trajectory of the disease. Lastly, nusinersen use was also not included because the clinicians felt that regardless of treatment with nusinersen, it is less important than the impact it had on the motor function, such as ambulation and breathing.

3.6 Statistical Analyses

Statistical Analyses were performed with SAS software version 9.4. A two-sided p value of less than 0.05 was considered statistically significant for all tests. Below are the statistical approaches used to assess the three objectives of this thesis.

Objective 1: To describe the HRQL in children with SMA from the children' and parents' perspective

The mean, median, standard deviation, and range of child reported and parent/caregiver proxy-reported HRQL scores for children with SMA were computed for the total score and sub-scores for the following PedsQL modules: 1) PedsQL 4.0 Generic Core module (sub scores include: physical, psychosocial, emotional, social, school); 2) PedsQL 3.0 NM module (sub scores include: NM disease, communication, family resources); and 3) PedsQL 3.0 Fatigue module (sub scores include: general fatigue, sleep/rest fatigue, cognitive fatigue).

As a reference, the self-reported and proxy-reported HRQL scores of children with SMA were compared to similar-aged healthy children and children with

another chronic NM disease (Duchenne Muscular Dystrophy), along with their parent/caregiver proxy scores using published data. Unpaired t-tests were performed between the child reported and parent/caregiver proxy-reported scores of children with SMA, to the child reported and parent/caregiver proxy-reported scores of similar-aged healthy children and children with DMD.

Objective 2: To examine the agreement between child reported and parent/caregiver proxy scores in older children with SMA

To examine the agreement between the child reported (≥ 5 years) and parent/caregiver proxy scores. Paired t-tests and ICC analyses were performed to examine differences between the child self-reported and parent/caregiver proxy scores. This was computed for both the total score and sub scores of the following PedsQL modules: 1) PedsQL 4.0 Generic Core module (sub scores include: physical, psychosocial, emotional, social, school); 2) PedsQL 3.0 NM module (sub scores include: NM disease, communication, family resources), and 3) PedsQL 3.0 Fatigue module (sub scores include: general fatigue, sleep/rest fatigue, cognitive fatigue).

Objective 3: To explore associations between both the child reported and parent/caregiver proxy HRQL scores to clinical and family characteristics in younger and older children with SMA

To explore the association between the child reported and parent/caregiver proxy HRQL scores (PedsQL 4.0 Generic Core module and PedsQL 3.0 NM module) with the clinical and family characteristics in children with SMA. Due to the small sample size and exploratory nature of this objective, a combination of a literature review, clinical expertise, and bivariate analyses were used to determine the variables to include in the final regression models. For a variable to be included in the final regression model, it would have to be 1) assessed as significantly associated to the child reported and parent/caregiver proxy HRQL scores based on the bivariate analysis and 2)

identified as relevant in either the literature review or informed by the meeting of clinical experts.

Bivariate analyses were performed to assess associations between clinical and family characteristics and child reported and parent/caregiver proxy-reported PedsQL 4.0 Generic Core and PedsQL 3.0 NM module scores. For dichotomous variables (ambulatory status, scoliosis status, use of approved medications, and use of non-approved medications), unpaired two-sample t-tests or non-parametric Wilcoxon Rank Sum tests were computed to assess for differences in the PedsQL 4.0 Generic Core and PedsQL 3.0 NM scores between categories. The Wilcoxon Rank Sum tests were used if $n<30$ in one of the categories, or if the PedsQL score violated the normality assumption. For categorical variables of more than two categories (SMA type, ventilation support, parental education, parental work status, parental marital status, and total household income), one-way ANOVA or a non-parametric Kruskal-Wallis tests were used. The Kruskal-Wallis tests were used instead of the one-way ANOVA when $n<30$ in one or more categories, or when the PedsQL score violated the normality assumption. The distributions of continuous variables were assessed using graphical methods such as the normal quantile-quantile plots, box and whisker plots, and histograms. Statistical analyses for normality were also performed using the Shapiro-Wilk test of normality.

The relationships among the continuous variables (age, PedsQL 3.0 Fatigue module) and the PedsQL 4.0 Generic Core and PedsQL 3.0 NM module scores were first visually assessed using scatter plots. Pairwise comparisons between the continuous variables and the PedsQL scores were examined with Pearson's correlation coefficient (r) for normally distributed data, or Spearman's rank correlation coefficient (p) for non-normally distributed data. Multivariable linear regression analyses were used to explore the associations of the clinical and family characteristics to both the child reported and parent/caregiver proxy-reported scores PedsQL scores. For a variable to be included in the final multivariable linear regression, it had to be considered

significant ($p < 0.10$) based on the bivariate analysis and suggested in either the clinician assessment or literature review as relevant (**Table 4-9**).

Table 3-1 Child and Parent QoL and HRQL Measures

Questionnaire	Sections	Single item or multidisciplinary	Parent and/or child	Items
PedsQL 4.0 Generic Core	Physical functioning, Emotional functioning, Social functioning, and School functioning	Multidisciplinary	Both	23 items
PedsQL 3.0 Neuromuscular Module	About my neuromuscular disease, Communication, Family resources	Multidisciplinary	Both	25 items
PedsQL Fatigue Module	General fatigue, Sleep/Rest Fatigue, Cognitive Fatigue	Multidisciplinary	Both	18 items
PedsQL 2.0 Family Impact Module	Physical functioning, Emotional functioning, Social functioning, Cognitive functioning, Communication, Worry, Daily activities, Family relationships	Multidisciplinary	Parent	36 items

Chapter 4

4.0 Results

4.1 Sample Descriptive Statistics

The initial part of this chapter provides a description of the clinical and demographic characteristics of the sample, reports information regarding missing data, and includes an assessment of the responder and non-responder characteristics. The second part of this chapter reports on the results pertaining to the three objectives of the thesis.

Seventy-seven eligible families were identified from the CNDR and sent questionnaires in 2018. Of these, 46 eligible families returned their completed questionnaires, resulting in an overall response rate of 59.7% (46/77). One of the responder families was subsequently excluded due to an ineligible diagnosis (distal SMA), leaving 45 included families (**Appendix O**). Both the parent and child questionnaires were completed in 33 families and 12 families completed the parent questionnaire. For the 12 families that only completed the parent questionnaire, eight of the children were too young (< 5 years) to complete their own questionnaires and four children chose not to return their questionnaires. Univariate analyses were used to examine characteristics of the sample (mean, median, and standard deviation (SD) for continuous variables and frequencies for categorical variables).

The children's clinical and demographic characteristics are presented in **Table 4-1** The mean age of the patients with SMA was 9.9 years (SD 4.8) with eight (17.8%) categorized as "toddler", seven (15.6%) categorized as "young child", 16 (35.6%) as "child", and 14 (31.1%) as "teen". There were 10 (22.2%) children with type 1 SMA, 27 children (60.0%) with type 2 SMA, seven children (15.6%) with type 3 SMA, and one child (3.8%) with type 4 SMA. Eight (17.8%) respondents were ambulatory and 22 (48.9%) were taking Nusinersen.

The demographic characteristics of the parents/caregivers of the children are presented in **Table 4-2**. The mean age of parent respondents was 40.8 years (SD 10.1). The majority of parent/proxy questionnaires were completed by the mother ([34/45] 75.6%), where

most of the parents were married ([40/45] 88.9 %) and living with their spouse ([43/45] 95.6%).

4.2 Missing Data

The percent missing for each question in the PedsQL questionnaires ranged from 2% to 9% for the child reported scores, and 2% to 22% for the parent/caregiver proxy scores. The main reason for the high missing percentage in parent/caregiver proxy scores were due to the missed questions regarding running or walking in the PedsQL Generic Core module. These questions may have been left blank since the child may not have been ambulatory and the question may not have pertained to them. Unfortunately, the questionnaire design does not have a 'not applicable' response, so for this study while we assume it is left blank due to a high number of children not walking, we have described it here as potentially missing data.

Computation of the PedsQL domain scores requires that at least half of the questions must be completed to be considered not missing. The percentage of missing domains scores ranged from 4% to 13% for parent/caregiver proxy and was 3% for the child reported questionnaire. Similar to above, the domains with a higher missing percentage were in the physical domain of the PedsQL Generic Core module, where the questions may not have pertained to the child.

Lastly, there was minimal missing data from the questions on family and clinical characteristics.

4.3 Comparison of Responders and Non-Responders

Aggregate information about the non-respondents was obtained from the CNDR database. Bivariate analyses such as an independent t-test, chi square test of independence (t- and X^2), and fisher's exact test of independence were performed to determine whether non-respondents differed from respondents, regarding their clinical and demographic characteristics. Clinical characteristics of non-respondents were not statistically significantly different from the respondents in any of the domains (**Table 4-**

1). The non-responder information was taken from the patient's registry database, whereas the responder information was taken from the respondents' questionnaires.

4.4 Objective 1 Results: To describe the HRQL scores in children with SMA from the children' and parents' perspective

Child self-report

The child reported PedsQL 4.0 Generic Core (sub scores include: physical, psychosocial, emotional, social, school), the PedsQL 3.0 NM module (sub scores include: NM disease, communication, family resources), and the PedsQL Fatigue module (sub scores include: general fatigue, sleep/rest fatigue, cognitive fatigue) mean, median, SDs, and ranges are presented in **Table 4-3**. The PedsQL scores for the physical domain scores were the lowest and the fatigue total, fatigue domain scores, and emotional domain scores were the highest.

PedsQL scores from similar-aged healthy children and children with DMD were used as a reference (**Table 4-4**).(59, 60, 63) Un-paired t-tests were conducted to assess the differences between the scores from similar-aged healthy children and children with SMA. The healthy child self-reported sample consisted of 209 to 401 (depending on the questionnaire) participants who were assessed in either physicians' offices during check-ups or by telephone. Compared to the similar-aged healthy children, children with SMA reported significantly lower scores for the total PedsQL 4.0 Generic Core module ($p < 0.001$), the PedsQL 4.0 Generic physical summary score ($p < 0.001$), the PedsQL 4.0 Generic psychosocial summary score ($P < 0.001$), the PedsQL 4.0 Generic social summary score ($P < 0.001$), the PedsQL 4.0 Generic school summary score ($P = 0.006$), the total PedsQL 3.0 Fatigue module ($P = 0.004$) and the PedsQL General Fatigue summary score ($P = 0.001$). However, there were no significant differences between the similar-aged healthy children and children with SMA for the PedsQL 4.0 Generic emotional summary score, PedsQL 3.0 Fatigue sleep/rest fatigue and PedsQL 3.0 cognitive fatigue summary scores (**Table 4-4**).

Un-paired t-tests were also conducted to assess the differences between the scores from similar-aged children with DMD and children with SMA. Children with SMA were compared to children with DMD because it is another common degenerative neuromuscular disorder in children. The DMD child self-reported sample consisted of 64 to 83 (depending on the questionnaire) participants, who were also recruited from the CNDR as part of a different study. Compared to children with DMD, children with SMA reported similar PedsQL 4.0 Generic Core, PedsQL 3.0 NM, and PedsQL 3.0 Fatigue scores. However, children with DMD did report significantly higher PedsQL Generic physical summary score (P = 0.004), PedsQL 3.0 total NM score (P = 0.04), and about my NM disease summary score (P = 0.009) (**Table 4-4**).

Parent proxy-report

The parent proxy-reported PedsQL 4.0 Generic Core (sub scores include: physical, psychosocial, emotional, social, school), the PedsQL 3.0 NM module (sub scores include: NM disease, communication, family resources), and the PedsQL Fatigue module (sub scores include: general fatigue, sleep/rest fatigue, cognitive fatigue) mean scores, SDs, and ranges are presented in **Table 4-3**. The PedsQL scores for the physical domain were the lowest while the total fatigue and sleep/rest and cognitive fatigue domain scores, and emotional domain scores were the highest.

Un-paired t-tests were conducted to assess the differences between parent proxy scores from similar-aged healthy children and parent proxy scores from children with SMA. The parent proxy sample of healthy children consisted of 259 to 718 (depending on the questionnaire) participants who were assessed in either physicians' offices during check-ups or by telephone. Compared to parents with similar-aged healthy children, parents of children with SMA reported significantly lower scores in all domains of the PedsQL 4.0 Generic Core module (P < 0.001), and all domains of the PedsQL 3.0 Fatigue module, including the PedsQL 3.0 Total fatigue module (P < 0.001), PedsQL 3.0 Fatigue general summary score (P < 0.001), PedsQL 3.0 Fatigue sleep/rest summary score (P < 0.001), and the PedsQL 3.0 Fatigue cognitive fatigue summary score (P = 0.042). (**Table 4-5**). (59, 60, 63) Un-paired t-tests were also conducted to assess the differences between the parent proxy scores from similar-aged children with DMD and children with SMA. The

parent proxy sample of children with DMD consisted of 69 to 96 (depending on the questionnaire) participants who were also recruited from the CNDR. Parents of children with DMD reported significantly higher scores in the PedsQL 3.0 NM total score, "About My NM Disease" ($P < 0.001$) and "About Our Family Resources" ($P < 0.001$) summary scores. This is in comparison to parents of children with SMA who reported significantly higher PedsQL 4.0 Generic emotional summary score ($P = 0.008$), Generic social summary score ($P = 0.026$), Generic psychosocial summary score ($P = 0.008$), and PedsQL 3.0 Fatigue cognitive summary score ($P = 0.001$) compared to the parents of children with DMD (**Table 4-5**).

Objective 2 Results: To examine the agreement between child reported and parent/caregiver proxy scores in children with SMA

Paired t-tests were conducted to compare parent proxy and child reported (≥ 5 years) PedsQL scores for the PedsQL 4.0 Generic Core module, PedsQL 3.0 Fatigue module, and PedsQL 3.0 NM module (**Table 4-6**). The parent proxy consistently rated the PedsQL scores lower compared to the child report for most of the PedsQL 4.0 Generic and PedsQL 3.0 NM modules, however not all results were statistically significant. The parent proxy-reported scores were significantly lower for the PedsQL 3.0 NM total module ($P = < 0.001$), "about my neuromuscular disorder" summary score ($P = 0.001$), and "about our family resources" summary score ($P < 0.001$). For the PedsQL 4.0 Fatigue module, the parent proxy scores were significantly lower for the "general fatigue" summary score ($P = 0.03$) and significantly higher for the "cognitive fatigue" ($P = 0.01$) summary score (**Table 4-6**).

The ICC between the parent proxy and child reported (≥ 5 years) PedsQL scores for the PedsQL 4.0 Generic Core module, PedsQL 3.0 Fatigue module, and the PedsQL 3.0 NM module were calculated using a two-way random model (2,1).(71) The ICCs were compared to the guidelines established by Koo 2016 et al. to determine whether the correlations were considered: "poor", "moderate", "good", or "excellent". (72) The guidelines state that when the reliability coefficient is below 0.50, this is indicative of "poor" reliability. When it is between 0.50 and 0.75 the reliability is "moderate", between

0.75 and 0.90 the reliability is “good”, and when it is above 0.90 the reliability is considered “excellent” (**Table 4-7**).

PedsQL: Generic Core Module

The ICC between the child self-report and parent proxy scores were considered “poor” for the physical, social, and school summary scores. The ICC was reported as “moderate” for the generic core total score, psychosocial summary score and emotional summary score. (**Table 4-7**).

PedsQL: Fatigue Module

The ICC between the child self-report and parent proxy scores were considered “good” for the total fatigue module score and cognitive fatigue summary score. The ICC was considered “moderate” for both the general fatigue and sleep/rest fatigue summary scores (**Table 4-7**).

PedsQL: Neuromuscular Module

The ICC between the child self-report and parent proxy scores were considered “moderate” for the about my neuromuscular disease summary score. The ICC was considered “poor” for the total NM score, communication summary score, and family resources summary score (**Table 4-7)**.

Objective 3 Results: To explore associations between both the child reported and parent/caregiver proxy HRQL scores to clinical and family characteristics in children with SMA

Bivariate Analysis

This section reports on the associations between both the clinical and family characteristics collected in the questionnaires, to the child self-reported and parent/caregiver proxy HRQL scores. The following clinical and family characteristics were collected and assessed through bivariate analysis: age, SMA type, ambulatory status, ventilation support, scoliosis, approved medications, not approved medications,

parental work status, parental educational status, parental marital status, and total yearly household income.

Age

Age was assessed as both a continuous and a categorical variable. Age was not found significantly associated with any child or parent/caregiver proxy PedsQL score when assessed either as a continuous or categorical variable.

SMA Type

SMA type was assessed as a categorical variable (type 1, type 2, type 3, and type 4) and was significantly associated with the child reported PedsQL 4.0 Generic physical summary score ($\chi^2 = 6.70$; P = 0.08). SMA type was also significantly associated with the parent/caregiver reported ($\chi^2 = 7.52$; P = 0.06) PedsQL 3.0 NM total score.

Ambulatory Status

Ambulatory status was significantly associated with PedsQL 4.0 Generic physical summary score for the child report (Z = 2.68; P = 0.01). Ambulatory status was also significantly associated with the PedsQL 3.0 NM total score for the parent/caregiver proxy-report (Z = 2.34; P = 0.02).

Ventilation Support

Ventilation support was assessed as a categorical variable (none, Bi-PAP, tracheostomy, other). It was significantly associated with parent/caregiver proxy PedsQL 3.0 NM total score ($\chi^2 = 10.60$; P = 0.005).

Scoliosis

Scoliosis was not considered significantly associated with any child or parent/caregiver reported PedsQL 4.0 Generic total score, PedsQL 4.0 Generic sub-scores, or the PedsQL 3.0 NM module total score.

Approved Medications

Approved medications were not considered significantly associated with any child reported PedsQL 4.0 Generic total score, PedsQL 4.0 Generic sub-scores, or the PedsQL 3.0 NM total score. However, it was significantly associated with the parent/caregiver proxy-reported PedsQL 3.0 NM total score ($Z = -2.02$, $P = 0.05$).

Non-Approved Medications

Non-approved medications were not significantly associated with any child or parent/caregiver reported PedsQL 4.0 Generic total score, PedsQL 4.0 Generic sub-scores, or the PedsQL 3.0 NM total score.

PedsQL Fatigue Module

The PedsQL 3.0 Fatigue module score was significantly associated with all the child and parent/caregiver reported PedsQL 4.0 Generic total score (child [0.65, $P < 0.001$]; parent [0.51, $P < 0.001$]), Generic 4.0 psychosocial summary score (child [0.75, $P < 0.001$]; parent [0.66, $P < 0.001$]), and the PedsQL 3.0 NM module total score (child [0.61, $P < 0.001$]; parent [0.49, $P < 0.001$]).

Parental Education

Parental education was assessed as a categorical variable (high school or less, vocational, college or university). Education was not significantly associated to any of the child or parent/caregiver reported PedsQL scores.

Parental Work Status

Parental work status was assessed as a categorical variable (not working due to my child's health, not working for "other" reasons, working full-time, working part-time, stay-at-home parent, student, retired). Parental work status was not significantly associated any of the child reported or parent/caregiver proxy PedsQL scores.

Parental Marital Status

Parental marital status was assessed as a categorical variable (married, living common law, widowed, separated, divorced, single). Parental marital status was not significantly associated caregiver proxy PedsQL scores.

Total Household Income

Total household income was assessed as a categorical variable (>$20,000, $20,000-$39,999, $40,000-$59,999$60,000-$79,999, $80,000-$99,999, $100,000 or more, undisclosed). Total household income was not significantly associated with any of the parent/caregiver reported PedsQL scores.

Summary

Due to the small sample size and exploratory nature of this objective, the correlates included in the regression model were determined based on a combination of a literature review (**Table 4-8**), clinical expertise (**Section 3.8**), and bivariate analyses. The following covariates were included in the regression model predicting the child self-reported and parent proxy-reported scores: PedsQL 3.0 Fatigue score (continuous), ventilation (categorical), ambulation (binary), and SMA type (categorical) (**Table 4-9**). Each of these covariates was assessed as significantly associated to the child reported and parent/caregiver proxy HRQL scores based on the bivariate analysis and either the literature review or clinical expertise.

As previously shown above in the results section, all the variables (fatigue score, ventilation status, and ambulatory status) the clinicians selected were significantly associated ($P < 0.10$) to at least one of the PedsQL 4.0 Generic total score, PedsQL 4.0 Generic Core physical summary score, PedsQL 4.0 Generic Core psychosocial summary socre, or PedsQL 3.0 NM total score in the bivariate analysis.

The assumptions of a linear regression of linearity and normality were met and the test for collinearity was not significant for the multivariable regression models.

Regression Analysis

Multivariable linear regressions were performed on HRQL outcomes in both child self-report and parent proxy-reports. The HRQL outcomes include the PedsQL 4.0 Generic Core total score, PedsQL 4.0 Generic physical summary score, PedsQL 4.0 Generic psychosocial summary score, and PedsQL 3.0 NM module total score.

Parent report

PedsQL 4.0 Generic Core Total

Fatigue and SMA type were significantly associated with the PedsQL 4.0 Generic Core total score, with an R^2 of 0.48. On average, a one unit increase in the fatigue score was associated with a 0.34 increase in the PedsQL 4.0 Generic module score (P = 0.005). Therefore, a better fatigue score (less fatigue) is associated with a better Generic module score (higher HRQL) (**Table 4-10**).

PedsQL 4.0 Generic Core Physical Summary Score

None of the variables was significantly associated with the PedsQL 4.0 Generic Core physical summary score (**Table 4-10**), with an R^2 of 0.22.

PedsQL 4.0 Generic Core Psychosocial Summary Score

Fatigue and SMA type were significantly associated with the PedsQL 4.0 Generic Core psychosocial summary score. On average, a one unit increase in the fatigue score was associated with a 0.50 increase in the PedsQL 4.0 Generic psychosocial module score (P < 0.0001). Therefore, a better fatigue score is associated with a better psychosocial score. The R^2 for this model was 0.56 (**Table 4-10**).

PedsQL 3.0 Neuromuscular Total

Fatigue and ventilation are both significantly associated with PedsQL 3.0 NM total score. On average, a one unit increase in the fatigue score was associated with a 0.56 increase in the PedsQL 3.0 NM total score (P = 0.0001). Therefore, a better fatigue score is

associated with a better neuromuscular score. Those on non-invasive Bi-PAP ventilation have on average a 11.03 lower PedsQL 3.0 NM score, compared to those not on any ventilation (P = 0.03) (**Table 4-10**). The R^2 for this model was 0.59.

Child report

PedsQL 4.0 Generic Core Total

Fatigue and SMA type are significantly associated with the PedsQL 4.0 Generic Core total score. On average, a one unit increase in the fatigue score was associated with a 0.46 increase in the PedsQL 4.0 Generic module score (P = 0.0004), therefore a better fatigue score (less fatigue) is associated with a better generic score (better HRQL). (**Table 4-11**). The R^2 for this model was 0.67.

PedsQL 4.0 Generic Core Physical Summary Score

Ambulation and SMA type were significantly associated with the PedsQL 4.0 Generic Core psychical summary score. On average, ambulatory patients have a PedsQL 4.0 Generic Core physical summary score of 25.62 higher than non-ambulatory patients (P = 0.02), (**Table 4-11)**. The R^2 for this model was 0.67.

PedsQL 4.0 Generic Core Psychosocial Summary Score

Only fatigue was significantly associated with the PedsQL 4.0 Generic Core psychosocial summary score. On average, a one unit increase in the fatigue score was associated with a 0.71 increase in the PedsQL 4.0 Generic psychosocial summary score (P < 0.0001) (**Table 4-11)**. Therefore, a better fatigue score is associated to a better psychosocial score. The R^2 for this model was 0.63.

PedsQL 3.0 Neuromuscular Total

Fatigue and ventilation were significantly associated with the PedsQL 3.0 NM total score. On average, a one unit increase in the fatigue score was associated with a 0.56 increase in the PedsQL 3.0 NM total score (P = 0.0007), therefore a better fatigue score is associated with a better NM score. Additionally, those with a tracheostomy have on average a 36.54

lower PedsQL 3.0 NM score, compared to those not on any ventilation (P = 0.01) (**Table 4-11**). The R^2 for this model was 0.60.

Regression results summary

The factor most consistently associated with HRQL outcomes was fatigue for both the child self-report and parent proxy-report. Fatigue was significantly associated with the PedsQL 4.0 Generic Core total score and psychosocial summary score, and the PedsQL 3.0 NM module total score.

SMA type was associated with the PedsQL 4.0 Generic total and physical summary scores for child reported HRQL scores, and SMA type was associated with the PedsQL 4.0 Generic total and psychosocial summary scores for parent reported scores. Ventilation was significantly associated with the PedsQL 3.0 NM total score for both parent/caregiver proxy and child self-reports. Lastly, ambulation was significantly associated with the child self-reported PedsQL 4.0 Generic physical summary score.

Table 4-1 Respondent vs. Non-respondent Demographic and Clinical Characteristics of Child with SMA

Variables	Responders (N = 45) N (%)	Non-responders (N = 32) N (%)	Significance (P value)
Age (years, SD)	9.9 (4.8)	11.6 (4.9)	P = 0.14
SMA type (%) Type 1 Type 2 Type 3 Type 4	 10 (22.2) 27 (60.0) 7 (15.6) 1 (2.2)	 10 (31.3) 16 (50.0) 6 (18.8) 0 (0.0)	 P=0.70 (Fischer's exact test)
Ambulant (%)	8 (17.8)	8 (25.0)	P = 0.57 (chi-square)
Nusinersen (approved medication) use (%)	22 (48.9)	16 (50.0)	P= 0.18 (chi-square)
Ventilation use (%) None Tracheostomy Non-invasive Bi-PAP	 22 (48.9) 3 (6.7) 20 (44.4)	 14 (43.8) 3 (9.4) 15 (46.9)	 P= 0.83 (Fisher's exact test)
FVC at last exam (%, SD)	73.67 (33.4)	61.76 (32.9)	P = 0.13

Table 4-2 Characteristics of Respondent Families

Variables	Responders (N = 45) N (%)
Age of parent respondents (years, SD)	40.8 (10.1)
Female parent	34 (75.6)
Biological parent	42 (93.3)
Married	40 (88.9)
Living with Spouse	43 (95.6)
Parents highest level of education	
Less than secondary school	1 (2.2)
Secondary school diploma or equivalent	4 (8.9)
Some postsecondary education	1 (2.2)
Apprenticeship or trade's certificate or diploma	3 (6.7)
College, CEGEP or other non-university certificate or diploma	8 (17.8) 17 (37.8)
Bachelor's Degree	4 (8.8)
Master's Degree	6 (13.3)
Professional Degree	1 (2.2)
Not reported/Missing	
Parent's work status	
Full-time	23 (51.1)
Part-time	9 (0.2)
Stay-at home parent	3 (6.7)
Not working due to my child's health	7 (15.6)
Not working for other reasons	3 (6.7)
Household income	
$20,000-$29,000	2 (4.4)
$30,000-$39,000	4 (8.9)
$40,000-$49,000	1 (2.2)
$50,000-$59,000	1 (2.2)
$60,000-$69,000	3 (6.7)
$70,000-$79,000	1 (2.2)
$80,000-$89,000	5 (11.1)
$90,000-$99,000	1 (2.2)
$100,000-$149,000	5 (11.1)
≥$150,000	16 (35.6)
Prefer not to disclose	5 (11.1)
Not reported/Missing	1 (2.2)

Table 4-3 PedsQL Scores of Children vs. Parent-Proxy

Module	Parent (N)	Parent Scores (All Ages) Mean (SD) Median [Range]	Child (N)	Child Scores Mean (SD) Median [Range]
PedsQL 4.0 Generic Core Module				
Total Score	42	54.48 (13.85) 52.17 [27.78-100]	33	57.35 (13.83) 56.52 [35.71-100]
Physical Health Summary Score	39	34.48 (26.50) 25.00 [0.00-100]	32	31.63 (18.47) 26.56 [6.25-100]
Psychosocial Health Summary Score	42	64.67 (13.03) 65.00 [45-100]	33	70.41 (15.66) 71.67 [40-100]
Emotional Summary Score	43	71.16 (18.09) 70.00 [35-100]	33	74.85 (18.31) 70.00 [40-100]
Social Summary Score	42	57.98 (17.43) 57.50 [30-100]	33	66.52 (17.57) 60.00 [30-100]
School Summary Score	39	61.41 (19.70) 60.00 [15-100]	33	68.33 (18.10) 70.00 [30-100]
PedsQL 4.0 Neuromuscular Module				
Total Score	43	54.19 (17.70) 53.00 [17-100]	33	65.77 (16.04) 67.00 [31.25-100]
About my Neuromuscular Disease	43	54.51 (19.76) 55.88 [13.24-100]	33	63.38 (17.91) 66.18 [27.94-100]
Communication	43	61.05 (27.68) 66.67 [0-100]	28	72.32 (24.43) 75.00 [0-100]
About our Family Resources	43	48.95 (22.77) 50.00 [0-100]	28	73.57 (20.68) 77.50 [35-100]
PedsQL 4.0 Fatigue Module				
Total Score	44	75.50 (15.45) 73.61 [33.33-100.00]	33	74.86 (15.12) 72.22 [44.44-100]
General Fatigue	44	67.42 (20.75) 66.67	33	74.74 (17.50) 75.00

		[12.5-100]		[33.33-100]
Sleep/Rest Fatigue	44	76.33 (14.92) 75.00 [33.33-100]	33	73.23 (16.86) 75.00 [37.5-100]
Cognitive Fatigue	44	82.77 (17.87) 89.58 [50.00-100]	33	76.26 (21.76) 75.00 [20.83-100]
PedsQL 2.0 Family Impact Module				
Total Score	45	48.84 (18.35) 46.53 [4.17-86.81]	-	-
Parent HRQL Summary Score	45	49.66 (20.88) 48.75 [1.25-96.25]	-	-
Family functioning Summary Score	45	48.96 (23.10) 53.13 [3.13-100]	-	-
Physical score	45	49.07 (22.52) 50.00 [4.17-100]	-	-
Emotional Score	45	48.31 (25.81) 45.00 [0-100]	-	-
Social Score	45	43.33 (24.66) 43.75 [0-100]	-	-
Cognitive Score	45	56.78 (25.41) 55.00 [0-100]	-	-
Communication Score	45	50.93 (23.98) 50.00 [8.33-100]	-	-
Worry Score	45	44.11 (21.93) 50.00 [0-95]	-	-
Daily Score	45	32.96 (25.87) 33.33 [0-100]	-	-
Family Relationships Score	45	58.56 (25.01) 60.00 [0-100]	-	-

Table 4-4 Mean self-reported PedsQL score in children with SMA, children with DMD, and healthy children

	N	SMA Mean (SD) (Current study sample)	N	DMD (Wei et al 2016, El-Aloul et al 2019)(59, 60) Mean (SD)	N	Healthy (Varni et al 2001)(63) Mean (SD)	SMA and Healthy Comparison Mean Difference (MD) 95% CI Standard Error (SE) P-Value	SMA and DMD comparison Mean Difference (MD) 95% CI Standard Error (SE) P-Value
Generic Core Total Score	32	57.35 (13.83) [35.71-100]	82	58.3 (15.5)	401	83.0 (14.8)	-25.65 (-30.95, -20.35) [2.71] P < 0.001	-0.95 (-7.10, 5.20) [3.14] P = 0.76
Physical summary	32	31.63 (18.47) [6.25-100]	82	45.3 (23.8)	400	84.4 (17.3)	-52.77 (-59.03, -46.51) [3.19] P < 0.001	-13.67 (-22.84, -4.50) [4.68] P = 0.004
Psychosocial summary	33	70.41 (15.66) [40-100]	83	65.4 (15.5)	399	82.4 (15.5)	-11.99 (-17.50, -6.48) [2.81] P < 0.001	5.01 (-1.26, 11.28) [3.20] P = 0.12
Emotional	33	74.85 (18.31) [40-100]	83	66.4 (21.5)	400	80.9 (19.6)	-6.05 (-12.98, 0.88) [3.53] P = 0.09	8.45 (0.12, 16.78) [4.25] P = 0.05
Social	33	66.52 (17.57) [30-100]	83	63.3 (18.3)	399	87.4 (17.2)	-20.88 (-27.00, -14.76) [3.12] P < 0.001	3.22 (-4.08, 10.52) [3.72] P = 0.39
School	33	68.33 (18.10) [30-100]	81	66.7 (19.4)	386	78.6 (20.5)	-10.27 (-17.50, -3.05) [3.69] P = 0.006	1.63 (-6.08, 9.34) [3.93] P = 0.68
Neuromuscular Module Total Score	33	65.77 (16.04) 67.00 [31.25-100]	83	72.0 (13.5)	-	NA	-	-6.23 (-11.98, -0.48) [2.93] P = 0.04
About my neuromuscular disease	33	63.38 (17.91) 66.18 [27.94-100]	82	71.7 (13.9)	-	NA	-	-8.32 (-15.13, -1.51) [3.12] P = 0.009

Communication	28	72.32 (24.43) 75.00 [0-100]	64	63.9 (26.4)	-	NA	-	8.42 (-3.05, 19.90) [5.85] P = 0.15
About our family resources	28	73.57 (20.68) 77.50 [35-100]	64	74.9 (20.1)	-	NA	-	-1.33 (-10.33, 7.67) [4.59] P = 0.77
Fatigue Module Total Score	33	74.86 (15.12) [44.44-100]	66	71.6 (15.2)	209	81.8 (12.5)	-6.94 (-11.67, -2.21) [2.41] P = 0.004	3.26 (-3.08, 9.60) [3.24] P = 0.32
General Fatigue	33	74.74 (17.50) [33.33-100]	66	70.2 (19.7)	209	86.1 (13.6)	-11.36 (-17.61, -5.11) [3.19] P = 0.001	4.54 (-3.40, 12.48) [4.05] P = 0.27
Sleep/Rest Fatigue	33	73.23 (16.86) [37.5-100]	66	74.0 (17.5)	209	76.8 (16.3)	-3.57 (-9.58, 2.44) [3.07] P = 0.25	-0.77 (-8.00, 6.46) [3.69] P = 0.84
Cognitive Fatigue	33	76.26 (21.76) [20.83-100]	65	70.9 (23.0)	209	82.4 (16.5)	-6.14 (-13.89, 1.61) [3.96] P = 0.13	5.36 (-4.11, 14.83) [4.83] P = 0.27

Note: NA = Not applicable because the NM module is a disease specific HRQL measure, thus would not be applied to healthy controls

Table 4-5 Mean parent reported PedsQL score in children with SMA, children with DMD, and healthy children

	N	SMA Mean (SD)	N	DMD (Wei et al 2016, El-Aloul et al 2019)(59, 60) Mean (SD)	N	Healthy (Varni et al 2001)(63) Mean (SD)	SMA and Healthy Comparison Mean Difference (MD) 95% CI Standard Error (SE) P-Value	SMA and DMD comparison Mean Difference (MD) 95% CI Standard Error (SE) P-Value
Generic Core Total Score	42	54.48 (13.85) 52.17 [27.78-100]	95	51.9 (16.5)	717	87.6 (12.3)	-33.12 (-36.98, -29.27) [1.97] P < 0.001	2.58 (-3.14, 8.30) [2.92] P = 0.38
Physical summary	39	34.48 (26.50) 25.00 [0.00-100]	95	42.8 (25.7)	717	89.3 (16.4)	-54.82 (-63.32, -46.42) [4.29] P < 0.001	-8.32 (-17.99, 1.35) [4.93] P = 0.09
Psychosocial summary	42	64.67 (13.03) 65.00 [45-100]	95	57.2 (15.7)	717	86.6 (12.8)	-22.13 (-26.12, -18.14) [2.03] P < 0.001	7.47 (2.04, 12.90) [2.77] P = 0.008
Emotional	43	71.16 (18.09) 70.00 [35-100]	95	62.2 (18.0)	718	82.6 (17.5)	-11.44 (-16.84, -6.05) [2.75] P < 0.001	8.96 (2.47, 15.45) [3.31] P = 0.008
Social	42	57.98 (17.43) 57.50 [30-100]	95	50.0 (20.0)	716	91.6 (14.2)	-33.62 (-38.99, -28.25) [2.74] P < 0.001	7.98 (1.04, 14.91) [3.54] P = 0.026
School	39	61.41 (19.70) 60.00 [15-100]	95	58.7 (19.5)	611	85.5 (17.6)	-24.09 (-29.83, -18.35) [2.93] P < 0.001	2.71 (-4.58, 10.00) [3.72] P = 0.47
Neuromuscular Module Total Score	43	54.19 (17.70) 53.00 [17-100]	96	67.3 (17.0)	-	NA	-	-13.11 (-19.30, -6.92) [3.16] P < 0.001
About my neuromuscular disease	43	54.51 (19.76) 55.88 [13.24-100]	96	69.2 (17.3)	-	NA	-	-14.69 (-21.20, -8.18) [3.32] P < 0.001
Communication	43	61.05 (27.68)	96	58.0 (28.6)	-	NA	-	3.05 (-7.14, 13.24)

		66.67 [0-100]						[5.20] P= 0.56
About our family resources	43	48.95 (22.77) 50.00 [0-100]	96	66.7 (23.9)	-	NA	-	-17.75 (-26.22, -9.28) [4.32] P < 0.001
Fatigue Module Total Score	44	75.50 (15.45) 73.61 [33.33-100.00]	69	70.8 (16.0)	259	88.2 (11.1)	-12.70 (-17.46, -7.94) [2.43] P < 0.001	4.70 (-1.27, 10.67) [3.05] P = 0.13
General Fatigue	44	67.42 (20.75) 66.67 [12.5-100]	69	64.2 (20.1)	259	88.8 (12.3)	-21.38 (-27.69, -15.07) [3.22] P < 0.001	3.22 (-4.48, 10.92) [3.93] P = 0.41
Sleep/Rest Fatigue	44	76.33 (14.92) 75.00 [33.33-100]	69	76.9 (18.0)	259	87.6 (13.5)	-11.27 (-15.65, -6.89) [2.24] P < 0.001	-0.57 (-6.95, 5.81) [3.26] P = 0.86
Cognitive Fatigue	44	82.77 (17.87) 89.58 [50.00-100]	69	69.7 (24.6)	259	88.2 (16.0)	-5.43 (-10.63, -0.23) [2.66] P= 0.042	13.07 (5.22, 20.92) [4.00] P = 0.001

Note: NA = Not applicable because the NM module is a disease specific HRQL measure, thus would not be applied to healthy controls

Table 4-6 Parent and Child Paired Samples Statistics

Module	Parent (N)	Parent Scores Mean (SD)	Child (N)	Child Scores Mean (SD)	Mean Difference (95%CI) [SD]	P-value (2-sided)
PedsQL 4.0 Generic Core Module						
Total Score	31	55.98 (13.99)	31	57.62 (13.50)	-1.64 (-6.53, 3.25) [13.33]	0.50
Physical Health Summary Score	28	36.64 (29.90)	28	32.46 (19.19)	4.18 (-8.21, 16.57) [31.95]	0.50
Psychosocial Health Summary Score	31	65.99 (13.85)	31	70.92 (14.94)	-4.93 (-10.00, 0.14) [-10.01]	0.06
Emotional Summary Score	31	70.65 (19.78)	31	74.52 (18.14)	-3.87 (-9.51, 1.77) [15.37]	0.17
Social Summary Score	31	60.00 (17.70)	31	67.42 (16.78)	-7.42 (-14.96, 0.13) [20.57]	0.05
School Summary Score	31	65.81 (17.03)	31	69.19 (17.18)	-3.34 (-9.99, 3.22) [18.00]	0.30
PedsQL 4.0 Neuromuscular Module						
Total Score	31	53.94 (18.99)	31	65.76 (15.57)	-11.82 (-17.56, -6.10) [15.59]	<0.001
About my Neuromuscular Disease	31	53.13 (21.16)	31	63.39 (17.83)	-10.26 (-15.90, -4.61) [15.38]	0.001
Communication	27	65.12 (26.25)	27	71.30 (24.28)	-6.17 (-16.74, 439) [26.71]	0.24
About our Family Resources	27	50.74 (23.64)	27	72.59 (20.40)	-21.85 (-31.31, -12.40) [23.91]	<0.001

PedsQL 4.0 Fatigue Module						
Total Score	32	75.95 (15.92)	32	75.03 (15.33)	0.93 (-2.92, 4.78) [10.67]	0.63
General Fatigue	32	67.84 (20.64)	32	75.00 (17.68)	-7.16 (-13.61, -0.72) [17.87]	0.03
Sleep/Rest Fatigue	32	76.95 (15.19)	32	72.92 (17.03)	4.04 (-1.13, 9.21) [14.34]	0.12
Cognitive Fatigue	32	83.07 (18.78)	32	76.82 (21.87)	6.25 (1.35, 11.51) [13.59]	0.01

Table 4-7 Agreement between parent and child report of child's health-related quality of life

Scale	Subscale	N (Parent-Child Pairs)	ICC (95% CI)	Rating
Generic Core Total Score		31	0.53 (0.23, 0.75)	Moderate
	Physical summary	28	0.19 (-0.19, 0.53)	Poor
	Psychosocial summary	31	0.52 (0.21, 0.73)	Moderate
	Emotional	31	0.67 (0.42, 0.82)	Moderate
	Social	31	0.27 (-0.06, 0.56)	Poor
	School	31	0.47 (0.15,0.71)	Poor
Neuromuscular Module Total Score		31	0.49 (0.07, 0.13)	Poor
	About my neuromuscular disease	31	0.61 (0.23, 0.81)	Moderate
	Communication	27	0.44 (0.9, 0.70)	Poor
	About our family resources	27	0.28 (-0.08, 0.59)	Poor
Fatigue Module Total Score		32	0.77 (0.58, 0.88)	Good
	General Fatigue	32	0.54 (0.24, 0.74)	Moderate
	Sleep/Rest Fatigue	32	0.59 (0.32, 0.78)	Moderate
	Cognitive Fatigue	32	0.75 (0.51, 0.87)	Good

Table 4-8 Variables Included in Regression: Literature References

	Covariate	Literature references
1	**Fatigue**	(32) Belter et al found that all PROMIS fatigue scores in the SMA population were worse than the general population. However, there didn't appear to be a trend of scores increasing or decreasing by SMA type or functional status (50)Montes et al assessed the comparison between the fatigue score to the PedsQL score and noted participants and their parents reported good quality of life overall (83, 86.5 – on a scale of 0–100), while children reported slightly lower levels of fatigue than their parents (85,74 – on a scale of 0–100) (35)Dunaway et al found that perceived fatigue was not associated with function, quality of life, or fatigability in ambulatory SMA patients. Neither age, type, nor ambulatory status influenced perceived fatigue
3	**Functional Measures/Ambulatory status**	(41) Vega et al showed the group with less motor disability showed slightly better overall HRQL scores, only in the communication domain (34, 36) De Oliveria and Frongia found no association between functional status and HRQL (35) Dunaway compared PedsQL and short form scores with fatigue and function scores, which showed the Peds QL NM child and parent report didn't correlate to the function tests (Hammersmith or six-minute walk test) (all correlations had alpha levels of $p > 0.05$). They also found no association between ambulatory status and perceived fatigue (51)Swoboda et al found that the QOL didn't improve as the MHFMS improved, but there was evidence of deterioration in QOL as the hammersmith score declined
4	**SMA Type**	(43)Weaver et al showed significant differences in PedsQL family impact module were found in Weaver et al between SMA type I and type II (36) Frongia reported only 4 out of 42 parents of children with SMA 2 and 3 out of 9 parents of SMA type 3 children reported scores >80 in PedsQL (37)Klug reported children with SMA III assessed their disease-specific HRQL as fairly high (self-reported), while SMA I children had a low proxy-assessed HRQL (69 vs. 34 on a scale with 0 = min. and 100 = max.; $p < 0.001$) (42)Wagner reported all child and parents reported PedsQL 4.0 Generic Core Scales and PedsQL 3.0 Neuromuscular Module scores decreased in all three types of SMA patients, with the most decreased scores seen in type 1 SMA patients (34, 41)De Oliviera and Vega both found no differences in QoL scores when comparing different types of SMA
5	**Ventilation Support**	(43) Weaver et al showed that ventilation support impacted proxy quality of life perspectives (32)Among caregivers, the greatest levels of activity were experienced among those caring for affected individuals on permanent ventilation, 83.1%).

Table 4-9 Clinical and Demographic Factors Included in the Regression Model Predicting Child and Parent Reported Scores

Clinical Factors	Sources of support
• SMA type (Type 1,2,3 and 4)	Bivariate analysis, literature review
• Ambulatory status (yes/no)	Clinician opinion, bivariate analysis
• Fatigue (PedsQL 4.0 Fatigue module)	Clinician opinion, bivariate analysis, literature review
• Assisted ventilation (None, Tracheostomy/Ventilation, Non-invasive Bi-PAP, Other)	Clinician opinion, bivariate analysis, literature review

Table 4-10 Multivariable Linear Regression Analyses to Predict Parent Proxy-Reported HRQL

	Dependent Variables B (P-Value)			
	PedsQL 4.0 Generic Core Total (N = 42)	**PedsQL 4.0 Generic Core Physical (N = 39)**	**PedsQL 4.0 Generic Core Psychosocial (N =42)**	**PedsQL 3.0 Neuromuscular Total (N = 43)**
Fatigue	0.35 (0.01)	-0.03 (0.92)	0.50 (< 0.001)	0.56 (<0.001)
Ventilation				
Ventilation Tracheostomy	10.99 (0.22)	11.19 (0.64)	-0.03 (0.99)	-6.20 (0.53)
Ventilation Bi-PAP	-0.82 (0.85)	-7.67 (0.47)	0.27 (0.94)	-11.03 (0.03)
Ventilation None (ref)	-	-	-	-
Ambulation				
Ambulatory	-2.75 (0.76)	-0.99 (0.96)	-5.70 (0.47)	8.92 (0.37)
Non-Ambulatory (ref)	-	-	-	-
SMA Type				
SMA Type 1	-8.40 (0.13)	-9.88 (0.46)	-5.03 (0.30)	-8.04 (0.18)
SMA Type 2 (ref)	-	-	-	-
SMA Type 3	2.76 (0.75)	-0.91 (0.97)	6.22 (0.42)	0.94 (0.92)
SMA Type 4	39.18 (0.01)	63.92 (0.08)	28.33 (0.03)	17.99 (0.28)

Table 4-11 Multivariable Linear Regression Analyses to Predict Child Self-Reported HRQL

	Dependent Variables B (P-Value)			
	PedsQL 4.0 Generic Core Total (N= 33)	**PedsQL 4.0 Generic Core Physical (N = 32)**	**PedsQL 4.0 Generic Core Psychosocial (N =33)**	**PedsQL 3.0 Neuromuscular Total (N = 33)**
Fatigue	0.46 (0.0004)	0.22 (0.16)	0.71 (<0.0001)	0.56 (0.0007)
Ventilation				
Ventilation Tracheostomy	-16.94 (0.13)	-	-18.52 (0.16)	-36.54 (0.01)
Ventilation Bi-PAP	6.09 (0.12)	2.96 (0.55)	1.45 (0.75)	-2.44 (0.62)
Ventilation None (ref)	-	-	-	-
Ambulation				
Ambulatory	4.70 (0.54)	25.62 (0.02)	-4.36 (0.63)	5.05 (0.61)
Non-Ambulatory (ref)	-	-	-	-
SMA Type				
SMA Type 1	3.66 (-0.50)	8.75 (0.22)	3.08 (0.63)	6.52 (0.35)
SMA Type 2 (ref)	-	-	-	-
SMA Type 3	1.84 (0.81)	-7.68 (0.44)	-1.01 (0.91)	3.84 (0.69)
SMA Type 4	31.47 (0.02)	44.90 (0.01)	16.33 (0.29)	15.70 (0.34)

Chapter 5

5.0 Discussion

This chapter provides interpretations of the study findings and discusses them within the context of existing literature. The strengths and limitations of the study are also be discussed, in addition to the implications of the findings and the future directions.

Objective 1: To describe the HRQL in children with SMA from the patients' and parents' perspective

The first objective was to describe the HRQL in children with SMA from the patients' and parents' perspectives. The results show that, from both the child and parent perspectives, HRQL is lowest in the physical domains and highest in the fatigue domains.

As a reference, HRQL of children with SMA and the parent/caregiver proxy scores of children with SMA were compared to those of similar-aged healthy children and similar-aged children with another chronic NM disease (Duchenne Muscular Dystrophy) using published data. The results from this analysis showed that, compared to healthy children, children with SMA reported lower HRQL, with the largest difference being in the physical domains (which includes items such as walking, running, taking a bath etc.). Compared to children with DMD, children with SMA reported similar levels for overall HRQL, the neuromuscular domain, and fatigue. The largest differences were found in the physical and neuromuscular summaries, where children with SMA reported significantly lower levels. Despite also being a severe progressive NM disorder, children with DMD have greater independent mobility until more advanced stages of their disease which may explain this discrepancy. Parents of children with DMD reported significantly better HRQL in the neuromuscular domain, "About My NM Disease" and "About Our Family Resources" summary scores. This is in comparison to parents of children with SMA who reported significantly better emotional, social, psychosocial, and fatigue scores compared

to the parents of children with DMD. Given that DMD has a much higher burden of cognitive and mental health problems, this finding was expected.(73) It is important to note that although SMA and DMD are both common degenerative neuromuscular diseases found in children, there are some differences between them. First, DMD is an x-linked disease, thus it only occurs in males whereas SMA is in both males and females. Additionally, although those with DMD may have greater independent mobility early in their disease, the progression is quite rapid and males with DMD are unable to walk by the age of 12.

Our results are comparable to those of another study that also assessed the HRQL in children with SMA and their parent proxy with a much larger sample size (Iannaccone et al. 2009).(49) The Iannaccone et al 2009 study assessed the feasibility, reliability, and validity of the PedsQL Generic core module and the PedsQL NM module, in 176 similar-age children with SMA and their parents. For the child reported HRQL scores, the HRQL PedsQL scores were similar for the PedsQL Generic and PedsQL NM total and sub scores except for the PedsQL Generic physical summary score, where our score was substantially lower compared to the data published by Iannaccone et al. 2009 (**Table 5-1**).

For the parent proxy-report, the majority of the HRQL PedsQL scores were similar except for the psychosocial, emotional, and family resources score PedsQL Generic psychosocial summary score, the PedsQL Generic emotional summary score, and the PedsQL NM family resources summary score. The psychosocial and family resources scores were significantly lower in this study compared to Iannaccone, and the emotional summary score in this study was substantially higher compared to Iannaccone et al. 2009 (**Table 5-2**).

It was hard to assess the reasons for the difference in scores between our study and Iannaccone et al. 2009, since Iannaccone et al. 2009 did not describe the demographic and clinical characteristics of their sample. It may be because our sample size was much smaller than their sample size, thus our sample size may not have been as representative of the general SMA population.

Objective 2: To examine the agreement between child reported and parent/caregiver proxy scores in children with SMA

The second objective was to assess the agreement between the child reported (≥ 5 years) and parent/caregiver proxy scores. Both paired t-tests and ICC analyses were performed because they both provide different information on the relationship between the parent proxy and child self reports. The parent proxy consistently rated the HRQL as worse compared to the child report, for most of the general and neuromuscular summaries, however not all results were significantly different. The parent proxy and child scores were comparable for the fatigue summary, with the parent's reporting higher HRQL than the child for the "cognitive fatigue", but lower for the "general fatigue" summary score.

Overall, the parents' ratings tend to be lower than the child self-report across most measures of HRQL. This finding has been consistently reported across a number of different pediatric chronic conditions.(74-76) There may be a few explanations for this. First of all, children may have adapted to their illness better than their parents because they live with the condition daily and had to reconcile their health situation, or it may be due to the fact that they have never known any other health status. Therefore, they may be less likely to see the impact of their health on their quality of life as dramatically as their parents. Additionally, parents are better able to anticipate the future than their children, and therefore more likely to be burdened by thoughts and fears regarding their child's disease, which may influence their assessment of their child's HRQL score. Cremeens et al. 2006 suggested the poor agreement between parent and child PedsQL scores can also be due to other factors such as the statistical methods used, the domains of the PedsQL investigated, the age of the child, and the parents own QoL. (77)

The agreement between the child self-reported and parent proxy-reported scores ranged from "poor" to "good". Agreement was highest in the fatigue total score, the cognitive fatigue score, and the emtional summary score. However, agreement was lowest in the "social" and "physical" domains, and the "about my family resource" domains.

It is important to note that the results from the paired t-test did not always give the same result as the ICC analysis. For example, although the PedsQL Generic physical summary score had an ICC of 0.19 (-0.19, 0.53) showing no agreement between the parent and

child scores, the paired t-test for the physical summary score only showed a mean difference of 4.18 (P = 0.5). This could be due to the fact that the ICC takes the the inter-rater reliability of the ratings into account, whereas the paired t-test only takes mean difference into consideration.(72) ICC may be the more appropriate test for this analysis, given that one is comparing two raters on a construct, however much work still needs to be done in this field to understand the best way to integrate and understand parent-proxy in relation to child HRQL.

Previous studies have also shown a poor level of agreement between parents and children with other chronic neuromuscular conditions.(74, 76, 78) The results from the literature review reported five studies that assesed the correlation and agreement between the parent proxy and child reported questionnaires. (36-38, 43, 49) However, only Iannaccone et al. 2009 performed an ICC to test differences between the parent and child PedsQL Generic and NM scores. The results showed that the parent-child agreement ranged from poor to fair agreements.(49) Although, Iannccone did not report on the fatigue module, they had similar ICC results to our general and NM modules. Their greatest agreement is found on the Total Generic Core (0.49) and About my Nueormuscular Disease (0.48) domains, which was also rated with higher agreement in our study (Total Generic [0.53]; About my Neuromuscular Disease: [0.61]). Additionally, their lowest overall agreement is in the ”About our family resources” (0.33) domain which was also rated with lower agreement in our study (0.28). However, their “emotional” (0.37) domain had a low agreement, compared to ours which had a moderate agreement (0.67).

The original hypothesis for this objective stated that childeren’s self assessments of their HRQL and the parent proxy assessments would be more similar for HRQLdomains related to physical domains than emotional/social domains. Based on the paired t-tests, the domains with the largest descrepancy in scores between the child self-report and parent proxy-reports are the PedsQL NM total and summary scores (“about my neuromuscular disease”, “communication”, “about our family resources”), and the domains with the smallest descrepancies were PedQL Generic total score and the PedsQL generic fatigue total score.

Using the ICC analysis the domains with the lowest agreement appeared to be “About our family resources”, “social”, and “physical summary” domains, and those with the highest ICC were the total Fatigue score and “cognitive fatigue” summary score, along with the “emotional” summary score. Overall, the findings from this study were somewhat consistent with the original hypothesis. The child and parent proxy assessments for the HRQL domains related to most of the emotional/social domains were least similar. However, there was a not as clear a pattern of similarity on the physical domains.

Ultimately our results would suggest that it remains difficult to determine the best way to interpret the dynamics between parent and child ratings of child HRQL. Researchers should still use both child self-report and parent proxy-report to get a comprehensive understanding of HRQL, especially when measuring interventions that could have a potential impact on HRQL in children with SMA. There is a need for additional studies to be done in this area to determine the HRQL and subscale constructs that are most consistent between the parent and child.

Objective 3: To explore associations between both the child reported and parent/caregiver proxy HRQL scores to clinical and family characteristics in children with SMA

The third obective was to explore associations between both the child reported and parent/caregiver proxy HRQL scores and clinical and family characteristics in children (≥ 5 years) with SMA. Based on the exploratory nature of this objective, a combination of a literature review, clinical expertise, and bivariate analyses were used to determine the variables included in the regression model. The following variables were included in the regression model predicting the child and parent proxy-reported scores: Fatigue score, ventilation, ambulation, and SMA type. Based on the multivaribale regression analysis for both parent and child HRQL scores, the factor most consistently associated with HRQL outcomes was fatigue. Fatigue was significantly associated with most of the HRQL outcomes for both child and parent reports, where lower (less) fatigue levels were

associated with higher (better) HRQL. In addition to fatigue, other clinical factors such as SMA type, ventiltion and ambulation were also significantly associated with at least one of the HRQL scores.

The strong relationship between fatigue and HRQL in children with SMA has been a novel finding from this study. This finding is consistent with studies of other NM conditions, specifically boys with DMD, which have also shown fatigue to be significantly associated with HRQL.(59) The measurement of subjectve fatigue in SMA needs to be further elucidated and understood in the SMA population. Given that our results point to fatigue as an important factor, we recognize that understanding perceived fatigue in terms of the clarity of the constructs, how to best measure perceived fatigue, how to clinically improve perceived fatigue and how patients understand it are all compelling research questions. We hope that the findings from our study will prompt further research in this area.

There were three hypotheses for this objective. The first being children whose families have higher socio-economic status have better HRQL, as reported by both child and parent/caregiver, compared to children from families with lower socio-economic status. Second, children who have a lower level of functioning have poorer HRQL, as reported by both child and parent/caregiver. Lastly, children who are diagnosed with a more severe type of SMA have poorer HRQL, as reported by both child and parent/caregiver, compared to children who are diagnosed with a less severe type of SMA.

Based on the results from our regression analyses, the variables of total yearly income and parental education were not significantly associated with any of the HRQL scores in the bivariate analysis. This may have been due to the fact that parents in our sample have higher educational attainment and a higher total household income compared to the general Canadian population, thus distorting the relationship between SES and HRQL.

Secondly, the results show that children who have a lower level of functioning do in fact have worse HRQL scores, consistent with our hypothesis. For example, those who have a tracheostomy or use a Bi-PAP machine to assist with their ventilation have a lower neuromuscular score compared to those who do not, for both child and parent reported scores. Additionally, those who are ambulatory have a better physical summary score

compared to those who are not ambulatory, in the child reported scores. Third, the results also show that children who are diagnosed with a more severe form of SMA, tend to have worse HRQL scores compared to those with a less severe form. For example, those with SMA type 4 (less severe) tend to have better general, physical, and psychosocial HRQL scores compared to those diagnosed with SMA type 2 (more severe).

5.1 Strengths and Limitations

Strengths

There are a couple key strengths of our study. First, this study provides a comprehensive examination of HRQL in children with SMA, by capturing the HRQL from both the children's and parent's perspectives with both generic and disease specific measures. Secondly, this study is one of the first studies to use a national registry to recruit participants and therefore creates a more representative sample than studies which recruited participants from individual sites. Other single center studies are likely to come from research intensive centers with a specific interest in HRQL and therefore may not give the true picture of HRQL in the general SMA population. The value of real-world data such as the data that is collected in the CNDR can be very important for many SMA stakeholders for various reasons. These stakeholders include patient advocacy organizations, clinical care guidelines and health policy makers. The data we have described are relevant in the current environment of new therapies, as society grapples with health economic decisions for expensive drugs for rare disease. Additionally, although our sample was small, given that SMA is a relatively rare disease, the study was able to capture an adequate sample size of the Canadian population with SMA. Lastly, to our knowledge, this is the first North American study to examine the independent association of clinical and demographic factors with child and parent reported HRQL scores. Although other studies have performed a correlation to assess whether certain clinical and demographic factors were associated with the HQRL scores, this is the first study that performed a multivariable regression. A multivariable regression analysis is important for the assessment of multiple independent variables that subsequently allows for the assessment and adjustment for confounders that could distort the relationship

between the dependent and individual independent variables. Therefore, although we had a small sample size, the comprehensive process we used will be very valuable for others working in this area to build upon.

Limitations

There were also some limitations in our study. First, the study had a small sample size which impacted the types of analyses that were conducted, as well as the number of covariates included in the regression mode. Any interpretation of results must be done with caution, due to this small sample size. Secondly, although no statistical differences were found between the clinical and demographic characteristics for responders and non-responders, selection bias may have occurred because there could have been differences between potential confounders that we were did not measure between the two groups. Additionally, the responder information was taken from the returned questionnaires and the non-responder information was taken from their clinical database. This could result in some information bias since the questionnaire information from responders could be more current and the registry information could potentially be more correct since it's a health care worker who is filling it in as opposed to the parent. Furthermore, the respondents were taken from a clinic-based registry (CNDR) and only families who indicated they were interested in research were mailed a questionnaire. Therefore, there may be differences between the families who said they were interested in research compared to families who were not interested in research. Third, this was a cross-sectional study design; therefore, no causation or casual inferences can be made between the independent variables and the HRQL outcomes. This is particularly important for the concepts of HRQL and fatigue where they are likely interrelated constructs and separating them will be complex. This study is part of a longitudinal study to determine the temporal associations, which will be helpful in informing the question of causality. Additionally, there may be bias regarding how the questions were answered. The instructions specifically asked the parents to not guide the child when answering their questions, however there may still be bias from the parents when the children are filling out the forms. If the parents did influence the responses of the child, this may lead to both the parents and child having similar answers. However, considering the large discrepancy

and disagreement between the child and parent scores, we do not think this was an issue in our sample. Another limitation is that the PedsQL questionnaires was only designed for children ages 5 and up and of those children, only those who were cognitively abled responded to the questionnaire. This could have biased the results because those who were unable to answer the questionnaires given their age or cognitive ability, may have had worse HRQL scores compared to those who were able to answer the questionnaires. The final limitation is regarding the generalizability concerns because the parents in our sample have a higher educational attainment and total household income compared to the general Canadian population. Seventy-eight percent of the families obtained some type of post-secondary education, and 36% of families reported an income of over ≥$150,000 a year. This is in comparison to the median after-tax income of Canadian families of $62,900 in 2019, and only 54.0% of Canadians aged 25 to 64 had either college or university qualifications.(79, 80) Therefore, if the people who participated in the study differ from the general Canadian population, this may impact the generalizability of the study and study results.

5.2 Implications

This study examined HRQL in a sample of children with SMA in Canada using a national registry. Due to the clinic-based registry from the CNDR, this study was able to include a broad representative sample of patients from different clinics and regions. The results from this study replicated prior findings that children with SMA report worse HRQL scores, compared to healthy children from both the children's and parent's perspectives. We found the social and school aspects of the HRQL are more affected compared to the psychosocial and emotional aspect, as reported by both the children and parents. The social aspects of the questionnaires include questions such as "getting along with other children", "keeping up playing with other children", and "getting teased by other children". The school aspect of the questionnaires includes questions such as "paying attention in class" and "keeping up with schoolwork". In a study assessing the schools and families' perceptions of the needs of children with chronic illnesses, the barriers identified by families included the teachers' misunderstanding of the needs of the child and misinformation about the illness. The most common barriers identified by the

school district was lack of funding, and lack of public and staff awareness.(81) Given this knowledge, more supports should be in place to improve the social and school supports for children with SMA, where additional school services could be implemented to reduce barriers and stigma for children with chronic illnesses.

Similar to previous studies of children with chronic conditions, this study also showed that HRQL scores from the child and parent perspectives are usually not in agreement with each other, with the parent usually assessing the child's HRQL as lower than how the child scores their own. The implications of the discrepancy between child and parent HRQL assessments are important because it is usually the parents' perceptions of their child's HRQL that are used to inform their child's treatment decisions. Additionally, there are circumstances where the child is too young, cognitively impaired, or too ill to report on their own HRQL. Therefore, due to the discrepancy between parent and child HRQL, child self-report should be taken into careful consideration, to avoid potential negative implications of relying on the parent proxy ratings alone. At this point, given the unclear pattern of parent proxy and child self-report HQOL we would recommend the use of both perspectives for both generic and disease specific measures in future research and clinical settings, to understand the breadth of outcomes when examining HRQL

This study identified perceived fatigue as a factor associated with several HRQL outcomes. Although fatigue is commonly seen in adults with a neuromuscular condition, it is not well studied in children with neuromuscular conditions, such as children with SMA. The findings of our study suggest it should be taken into consideration when caring for children with SMA. Considering perceived fatigue may be a modifiable factor, unlike ambulation or ventilation, future research should be done on the specific aspects of fatigue that contribute to a patients HRQL. This would allow healthcare workers to target this area of fatigue and develop effective therapeutic strategies that may ultimately increase the patients HRQL. There have been previous studies conducted in adults with Rheumatoid Arthritis, Multiple Sclerosis, cancer, and other chronic conditions regarding strategies on how to effectively reduce their perceived fatigue. Some of these interventions include pharmacological interventions, exercise, and cognitive behavioral therapy.(82-87) Additionally, fatigue outcome measures ought to be included as a

secondary outcome in studies, in conjunction with HRQL questionnaires such as the PedsQL. This would allow us to determine whether the treatment/intervention improved the HRQL of the child, in addition to the other physical assessments and may help determine clinically meaningful benefit.

5.3 Conclusion and Future Directions

HRQL of domains related to physical function were more affected than domains related to fatigue and emotions, from both parent and child perspectives. The HRQL of children with SMA as reported by the child self-report and parent-report are worse compared to the healthy children in all domains, and worse in the physical domains compared to children with other chronic conditions such as DMD. The parent proxy consistently reported worse HRQL compared to the child report for most of the general and NM modules, however not all differences were statistically significant. Agreement between parents and their children with SMA on children's level of HRQL ranged from good to poor. Lastly, greater fatigue appeared to be associated with lower HRQL in most domains and warrants further attention from researchers and healthcare-workers.

This study is part of a 3-year longitudinal study. With a longitudinal study, we can start to establish a temporal relationship between the independent variables and the HRQL outcomes. Additionally, due to the recent medical and treatment advancements for children with SMA, there has been a large increase in the number of CNDR participants indicating they are interested in research. This may increase the sample size of the longitudinal study, allowing us to be more confident in our conclusions regarding the aspects of HRQL. This will be critical for the development of future research studies and most importantly, for the clinical care of children living with SMA.

Table 5-1 Mean Self-Reported PedsQL core in Children with SMA: Comparison to the Iannaccone et al 2009 Study

	N	Study results	N	Study results from Iannaccone et al 2009	Comparison to Iannaccone et al 2009 Mean Difference (MD) 95% CI Standard Error (SE) P-Value
Generic Core Total Score	32	57.35 (13.83)	125	58.7 (14.4)	-1.35 (-6.90, 4.20) [2.83] P = 0.63
Physical summary	32	31.63 (18.47)	123	43.4 (21.2)	-11.67 (-19.71, -3.63) [4.10] P = 0.01
Psychosocial summary	33	70.41 (15.66)	125	66.6 (16.3)	3.810 (-2.39, 10.01) [3.17] P = 0.23
Emotional	33	74.85 (18.31)	125	67.0 (23.0)	7.85 (-0.64, 16.34) [4.33] P = 0.07
Social	33	66.52 (17.57)	125	66.1 (19.5)	0.42 (-6.91, 7.75) [3.74] P = 0.91
School	33	68.33 (18.10)	124	66.2 (20.9)	2.13 (-5.68, 9.94) [3.99] P = 0.59
Neuromuscular Module Total Score	33	65.77 (16.04)	123	67.5 (15.6)	-1.73 (-7.76, 4.30) [3.08] P = 0.58
About my neuromuscular disease	33	63.38 (17.91)	123	65.9 (16.5)	-2.52 (-8.98, 3.94) [3.29] P = 0.45
Communication	28	72.32 (24.43)	80	70.8 (23.6)	1.52 (-8.73, 11.77) [5.23] P = 0.77
About our family resources	28	73.57 (20.68)	80	74.7 (22.2)	-1.13 (-10.52, 8.26) [4.79] P = 0.81

Table 5-2 Mean Parent Reported PedsQL Score in Children with SMA: Comparison to the Iannaccone et al 2009 Study

	N	Study results	N	Study results from Iannaccone et al 2009	Comparison to Iannaccone et al 2009 Mean Difference (MD) 95% CI Standard Error (SE) P-Value
Generic Core Total Score	42	54.48 (13.85)	174	53.4 (14.2)	1.08 (-3.68, 5.84) [2.43] P = 0.66
Physical summary	39	34.48 (26.50)	172	36.3 (24.6)	-1.82 (-10.50, 6.86) [4.43] P = 0.68
Psychosocial summary	42	64.67 (13.03)	174	74.8 (18.2)	-10.13 (-14.91, -5.35) [2.44] P < 0.001
Emotional	43	71.16 (18.09)	173	62.2 (17.6)	8.96 (3.05, 14.87) [3.02] P = 0.003
Social	42	57.98 (17.43)	174	57.4 (17.4)	0.58(-5.29, 6.45) [2.99] P = 0.85
School	39	61.41 (19.70)	154	63.8 (20.0)	-2.39 (-9.40, 4.62) [3.58] P = 0.51
Neuromuscular Module Total Score	43	54.19 (17.70)	172	59.7 (16.8)	-5.51 (-11.19, 0.17) [2.90] P = 0.06
About my neuromuscular disease	43	54.51 (19.76)	176	58.8 (17.7)	-4.29 (-10.33, 1.75) [3.08] P = 0.17
Communication	43	61.05 (27.68)	172	67.0 (31.1)	-5.95 (-16.13, 4.23) [5.19] P = 0.25
About our family resources	43	48.95 (22.77)	176	59.6 (22.2)	-10.65 (-18.09, -3.21) [3.80] P = 0.005

References

1. Lunn MR, Wang CH. Spinal muscular atrophy. Lancet. 2008;371(9630):2120-33.
2. Dowling JJ, H DG, Cohn RD, Campbell C. Treating pediatric neuromuscular disorders: The future is now. Am J Med Genet A. 2018;176(4):804-41.
3. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin. 2015;33(4):831-46.
4. D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6:71.
5. Health NIo. Spinal Muscular Atrophy Fact Sheet 2019 [updated 2021-11-15].
6. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med. 2018;378(7):625-35.
7. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017;377(18):1723-32.
8. De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord. 2019;29(11):842-56.
9. Food and Drug Administration. FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality 2019. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease.
10. Day JW, Finkel RS, Chiriboga CA, Connolly AM, Crawford TO, Darras BT, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20(4):284-93.
11. Darras BT, Masson R, Mazurkiewicz-Bełdzińska M, Rose K, Xiong H, Zanoteli E, et al. Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls. N Engl J Med. 2021;385(5):427-35.
12. Davis E, Waters E, Mackinnon A, Reddihough D, Graham HK, Mehmet-Radji O, et al. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. Dev Med Child Neurol. 2006;48(4):311-8.
13. World Health Organization. WHOQOL: Measuring Quality of Life 2021. Available from: https://www.who.int/tools/whoqol.
14. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118(8):622-9.
15. Puka K, Tavares TP, Anderson KK, Ferro MA, Speechley KN. A systematic review of quality of life in parents of children with epilepsy. Epilepsy Behav. 2018;82:38-45.
16. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health. 2004;7(1):79-92.
17. Megari K. Quality of Life in Chronic Disease Patients. Health Psychol Res. 2013;1(3):e27.

18. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. 1971. Milbank Q. 2005;83(4):731-57.
19. Centers for Disease Control and Prevention. HRQOL Concepts 2018. https://www.cdc.gov/hrqol/concept.htm.
20. Spieth LE, Harris CV. Assessment of health-related quality of life in children and adolescents: an integrative review. J Pediatr Psychol. 1996;21(2):175-93.
21. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. Arch Dis Child. 2001;84(3):205-11.
22. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med. 1996;334(13):835-40.
23. Puka K, Ferro MA, Camfield CS, Levin SD, Smith ML, Wiebe S, et al. Trajectories of quality of life 10 years following a diagnosis of epilepsy in childhood. Epilepsia. 2020;61(7):1453-63.
24. Ferro MA, Avery L, Fayed N, Streiner DL, Cunningham CE, Boyle MH, et al. Child- and parent-reported quality of life trajectories in children with epilepsy: A prospective cohort study. Epilepsia. 2017;58(7):1277-86.
25. Speechley KN. What if quality of life better expressed outcomes for epilepsy? In: W.F. Arts AA, O.F. Brouwer, C. Camfield, P.Camfield,.(Eds.) editor. Progress in Epileptic Disorders Volume 12 Outcome of Childhood Epilepsies Surrey, UK2013. p. 253-61.
26. EMA. Reflection Paper on the Regulatory Guidance for the use of Health-Related Quality of Life (HRQL) Measures in the evaluation of Medicinal Products. July 2005.
27. Food and Drug Administration. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.
28. Landgraf JM AL. Measuring health outcomes in pediatric populations: issue in psychometrics and application Quality of Life and Pharmacoeconomics in Clinical Trials. Philidelphia: Lippincott-Raven Publishers; 1996.
29. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res. 2001;10(4):347-57.
30. Drotar D. Measuring child health: scientific questions, challenges, and recommendations. Ambul Pediatr. 2004;4(4 Suppl):353-7.
31. Palermo TM, Long AC, Lewandowski AS, Drotar D, Quittner AL, Walker LS. Evidence-based assessment of health-related quality of life and functional impairment in pediatric psychology. J Pediatr Psychol. 2008;33(9):983-96.
32. Belter L, Cruz R, Jarecki J. Quality of life data for individuals affected by spinal muscular atrophy: A baseline dataset from the Cure SMA Community Update Survey. Orphanet Journal of Rare Diseases. 2020;15(1):217.
33. Chambers GM, Settumba SN, Carey KA, Cairns A, Menezes MP, Ryan M, et al. Prenusinersen economic and health-related quality of life burden of spinal muscular atrophy. Neurology. 2020;95(1):1-10.
34. De Oliveira CM, Araujo APDQC. Self-reported quality of life has no correlation with functional status in children and adolescents with spinal muscular atrophy. European Journal of Paediatric Neurology. 2011;15(1):36-9.

35. Dunaway Young S, Montes J, Kramer SS, Podwika B, Rao AK, De Vivo DC. Perceived fatigue in spinal muscular atrophy: A pilot study. Journal of Neuromuscular Diseases. 2019;6(1):109-17.
36. Frongia AL, Zschaeck I, Cornejo MMAA, De Benito DN, Carrera-Garcia L, Mata JF, et al. Perceived quality of life and motor scales outcomes in type 2 and 3 SMA patients: Are they related? Journal of Neuromuscular Diseases. 2018;5 (Supplement 1):S317-S8.
37. Klug C, Schreiber-Katz O, Thiele S, Schorling E, Zowe J, Reilich P, et al. Disease burden of spinal muscular atrophy in Germany. Orphanet Journal of Rare Diseases. 2016;11(1):58.
38. Kocova H, Dvorackova O, Vondracek P, Haberlova J. Health-related quality of life in children and adolescents with spinal muscular atrophy in the Czech republic. Pediatric Neurology. 2014;50(6):591-4.
39. Lopez-Bastida J, Pena-Longobardo LM, Aranda-Reneo I, Tizzano E, Sefton M, Oliva-Moreno J. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. Orphanet Journal of Rare Diseases. 2017;12(1):141.
40. Pena-Longobardo LM, Aranda-Reneo I, Oliva-Moreno J, Litzkendorf S, Durand-Zaleski I, Tizzano E, et al. The economic impact and health-related quality of life of spinal muscular atrophy. An analysis across europe. International Journal of Environmental Research and Public Health. 2020;17(16):1-12.
41. Vega P, Glisser C, Castiglioni C, Virginia Amezquita M, Quirola M, Barja S. Quality of life in children and adolescents with spinal muscular atrophy. Revista Chilena de Pediatria. 2020;91(4):512-20.
42. Wagner S, Wong B, Lambert J, Horn P, Bange J, Rybalsky I, et al. SMA: Registries, Biomarkers & Outcome Measures: Patient reported health-related quality of life in pediatric patients with spinal muscular atrophy type 1, 2 and 3. Neuromuscular Disorders. 2020;30 (Supplement 1):S100.
43. Weaver MS, Hanna R, Hetzel S, Patterson K, Yuroff A, Sund S, et al. A prospective, crossover survey study of child- and proxy-reported quality of life according to spinal muscular atrophy type and medical interventions. Journal of Child Neurology. 2020;35(5):322-30.
44. Montes J, Krasinski D, Foster R, Gambino G, Paradis A, Garafalo S, et al. SMA - Therapy: Impact of continued nusinersin treatment on caregiver experience and health-related quality of life in later-onset SMA: Results from the SHINE study. Neuromuscular Disorders. 2020;30 (Supplement 1):S125.
45. Bach JR, Vega J, Majors J, Friedman A. Spinal muscular atrophy type 1 quality of life. American Journal of Physical Medicine and Rehabilitation. 2003;82(2):137-42.
46. Bertini E, Dessaud E, Mercuri E, Muntoni F, Kirschner J, Reid C, et al. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(7):513-22.
47. Chiriboga CA, Swoboda KJ, Darras BT, Iannaccone ST, Montes J, De Vivo DC, et al. Results from a phase 1 study of nusinersen (ISIS-SMN Rx) in children with spinal muscular atrophy. Neurology. 2016;86(10):890-7.

48. Iannaccone ST, Hynan LS, American Spinal Muscular Atrophy Randomized Trials G. Reliability of 4 outcome measures in pediatric spinal muscular atrophy. Archives of Neurology. 2003;60(8):1130-6.
49. Iannaccone ST, Hynan LS, Morton A, Buchanan R, Limbers CA, Varni JW. The PedsQLTM in pediatric patients with Spinal Muscular Atrophy: Feasibility, reliability, and validity of the Pediatric Quality of Life InventoryTM Generic Core Scales and Neuromuscular Module. Neuromuscular Disorders. 2009;19(12):805-12.
50. Montes J, Garber CE, Kramer SS, Montgomery MJ, Dunaway S, Kamil-Rosenberg S, et al. A randomized, controlled clinical trial of exercise in patients with spinal muscular atrophy: Methods and baseline characteristics. Journal of Neuromuscular Diseases. 2014;1(2):151-61.
51. Swoboda KJ, Scott CB, Crawford TO, Simard LR, Reyna SP, Krosschell KJ, et al. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. PloS one. 2010;5(8):e12140.
52. Kissel JT, Scott CB, Reyna SP, Crawford TO, Simard LR, Krosschell KJ, et al. SMA Carnival trial part II: a prospective, single-armed trial of L-carnitine and valproic acid in ambulatory children with spinal muscular atrophy. PLoS ONE. 2011;6(7):e21296.
53. Davis E, Nicolas C, Waters E, Cook K, Gibbs L, Gosch A, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. Qual Life Res. 2007;16(5):863-71.
54. Davis E, Mackinnon A, Waters E. Parent proxy-reported quality of life for children with cerebral palsy: is it related to parental psychosocial distress? Child Care Health Dev. 2012;38(4):553-60.
55. Hodgkinson V, Lounsberry J, M'Dahoma S, Russell A, Jewett G, Benstead T, et al. The Canadian Neuromuscular Disease Registry 2010-2019: A decade of facilitating clinical research through a nationwide, pan-neuromuscular disease registry. J Neuromuscul Dis. 2021;8(1):53-61.
56. University of Calgary. The Canadian Neuromuscular Disease Registry 2018 Available from: https://www.ucalgary.ca/research/participate/study/13438/canadian-neuromuscular-disease-registry.
57. CNDR. Canadian Neuromuscular Disease Registry. Available from: https://cndr.org/
58. Koeks Z, Bladen CL, Salgado D, van Zwet E, Pogoryelova O, McMacken G, et al. Clinical Outcomes in Duchenne Muscular Dystrophy: A study of 5345 patients from the TREAT-NMD DMD global database. J Neuromuscul Dis. 2017;4(4):293-306.
59. Wei Y, Speechley KN, Zou G, Campbell C. Factors associated with health-related quality of life in children with Duchenne Muscular Dystrophy. J Child Neurol. 2016;31(7):879-86.
60. El-Aloul B, Speechley KN, Wei Y, Wilk P, Campbell C. Fatigue in young people with Duchenne muscular dystrophy. Dev Med Child Neurol. 2020;62(2):245-51.
61. Verhaart IEC, Robertson A, Leary R, McMacken G, König K, Kirschner J, et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol. 2017;264(7):1465-73.
62. Upton P, Eiser C, Cheung I, Hutchings HA, Jenney M, Maddocks A, et al. Measurement properties of the UK-English version of the Pediatric Quality of Life Inventory 4.0 (PedsQL) generic core scales. Health Qual Life Outcomes. 2005;3:22.

63. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001;39(8):800-12.
64. Viecili MA, Weiss JA. Reliability and validity of the Pediatric Quality of Life Inventory with individuals with intellectual and developmental disabilities. Am J Intellect Dev Disabil. 2015;120(4):289-301.
65. Varni JW, Burwinkle TM, Jacobs JR, Gottschalk M, Kaufman F, Jones KL. The PedsQL™ in type 1 and Type 2 diabetes. Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Type 1 Diabetes Module. 2003;26(3):631-7.
66. DeCarlo DK, Forte E, Gao L, McGwin G, Jr., Owsley C. Reliability and validity of the PedsQL 4.0 Generic Core Scales in pediatric vision impairment. J aapos. 2020;24(2):94.e1-.e7.
67. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory generic core scales, multidimensional fatigue scale, and cancer module. Cancer. 2002;94(7):2090-106.
68. Varni JW, Junger KF, Kellermann T, Grossman LB, Wagner J, Mucci GA, et al. PedsQL™ cognitive functioning scale in youth with epilepsy: Reliability and validity. Epilepsy Behav. 2020;103(Pt A):106850.
69. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999;37(2):126-39.
70. Varni JW, Burwinkle TM, Szer IS. The PedsQL Multidimensional fatigue scale in pediatric rheumatology: reliability and validity. J Rheumatol. 2004;31(12):2494-500.
71. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420-8.
72. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med. 2016;15(2):155-63.
73. Banihani R, Smile S, Yoon G, Dupuis A, Mosleh M, Snider A, et al. Cognitive and neurobehavioral profile in boys with duchenne muscular dystrophy. J Child Neurol. 2015;30(11):1472-82.
74. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. Qual Life Res. 2008;17(6):895-913.
75. Ingerski LM, Modi AC, Hood KK, Pai AL, Zeller M, Piazza-Waggoner C, et al. Health-related quality of life across pediatric chronic conditions. J Pediatr. 2010;156(4):639-44.
76. Campbell C, McColl E, McDermott MP, Martens WB, Guglieri M, Griggs RC. Health related quality of life in young, steroid-naïve boys with Duchenne muscular dystrophy. Neuromuscul Disord. 2021;31(11):1161-8.
77. Cremeens J, Eiser C, Blades M. Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life Inventory 4.0 (PedsQL) generic core scales. Health Qual Life Outcomes. 2006;4:58.
78. Bray P, Bundy AC, Ryan MM, North KN, Everett A. Health-related quality of life in boys with Duchenne muscular dystrophy: agreement between parents and their sons. J Child Neurol. 2010;25(10):1188-94.

79. Statistics Canada. Canadian Income Survey, 2019. https://www150.statcan.gc.ca/n1/en/daily-quotidien/210323/dq210323a-eng.pdf?st=9QXVCNer.
80. Statistics Canada. Education in Canada: Key results from the 2016 Census. 2017. https://www150.statcan.gc.ca/n1/en/daily-quotidien/171129/dq171129a-eng.pdf?st=tm-qRfvi.
81. Lynch EW, Lewis RB, Murphy DS. Educational services for children with chronic illnesses: perspectives of educators and families. Except Child. 1993;59(3):210-20.
82. Khan F, Amatya B, Galea M. Management of fatigue in persons with multiple sclerosis. Front Neurol. 2014;5:177.
83. Safari R, Van der Linden ML, Mercer TH. Effect of exercise interventions on perceived fatigue in people with multiple sclerosis: synthesis of meta-analytic reviews. Neurodegener Dis Manag. 2017;7(3):219-30.
84. Hewlett S, Ambler N, Almeida C, Cliss A, Hammond A, Kitchen K, et al. Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. Ann Rheum Dis. 2011;70(6):1060-7.
85. Hagstrom AD, Marshall PW, Lonsdale C, Cheema BS, Fiatarone Singh MA, Green S. Resistance training improves fatigue and quality of life in previously sedentary breast cancer survivors: a randomised controlled trial. Eur J Cancer Care. 2016;25(5):784-94.
86. Tarakci E, Yeldan I, Huseyinsinoglu BE, Zenginler Y, Eraksoy M. Group exercise training for balance, functional status, spasticity, fatigue and quality of life in multiple sclerosis: a randomized controlled trial. Clin Rehabil. 2013;27(9):813-22.
87. Vashistha V, Singh B, Kaur S, Prokop LJ, Kaushik D. The effects of exercise on fatigue, quality of life, and psychological function for men with prostate cancer: systematic review and meta-analyses. Eur Urol Focus. 2016;2(3):284-95.

Appendices

Appendix A. Search Strategy

EMBASE

1. Spinal muscular atrophy.mp.
2. SMA.mp.
3. 1 or 2
4. Healthy related quality of life.mp.
5. health-related quality of life.mp.
6. HRQL.mp.
7. HRQOL.mp.
8. Quality of life.mp.
9. QOL.mp.
10. 4 or 5 or 6 or 7 or 8 or 9
11. Pediatric.mp.
12. Paediatric.mp.
13. Child*.mp.
14. 11 or 12 or 13
15. 3 and 10 and 14

MEDLINE

1. Spinal muscular atrophy.mp.
2. SMA.mp.
3. 1 or 2
4. Healthy related quality of life.mp.
5. health-related quality of life.mp.
6. HRQL.mp.
7. HRQOL.mp.
8. Quality of life.mp.
9. QOL.mp.
10. 4 or 5 or 6 or 7 or 8 or 9
11. Pediatric.mp.
12. Paediatric.mp.
13. Child*.mp.
14. 11 or 12 or 13
15. 3 and 10 and 14

Cochrane

#1 MESH descriptor: [Muscular Atrophy] explode all trees

#2 SMA

#3 #1 or #2

#4 MESH descriptor: [Quality of Life] explode all trees

#5 Healthy related quality of life

#6 health-related quality of life

#7 HRQL

#8 HRQOL

#9 Quality of life

#10 QoL

#11 #4 or #5 or #6 or #7 or #8 or #9 or #10

#12 Pediatric

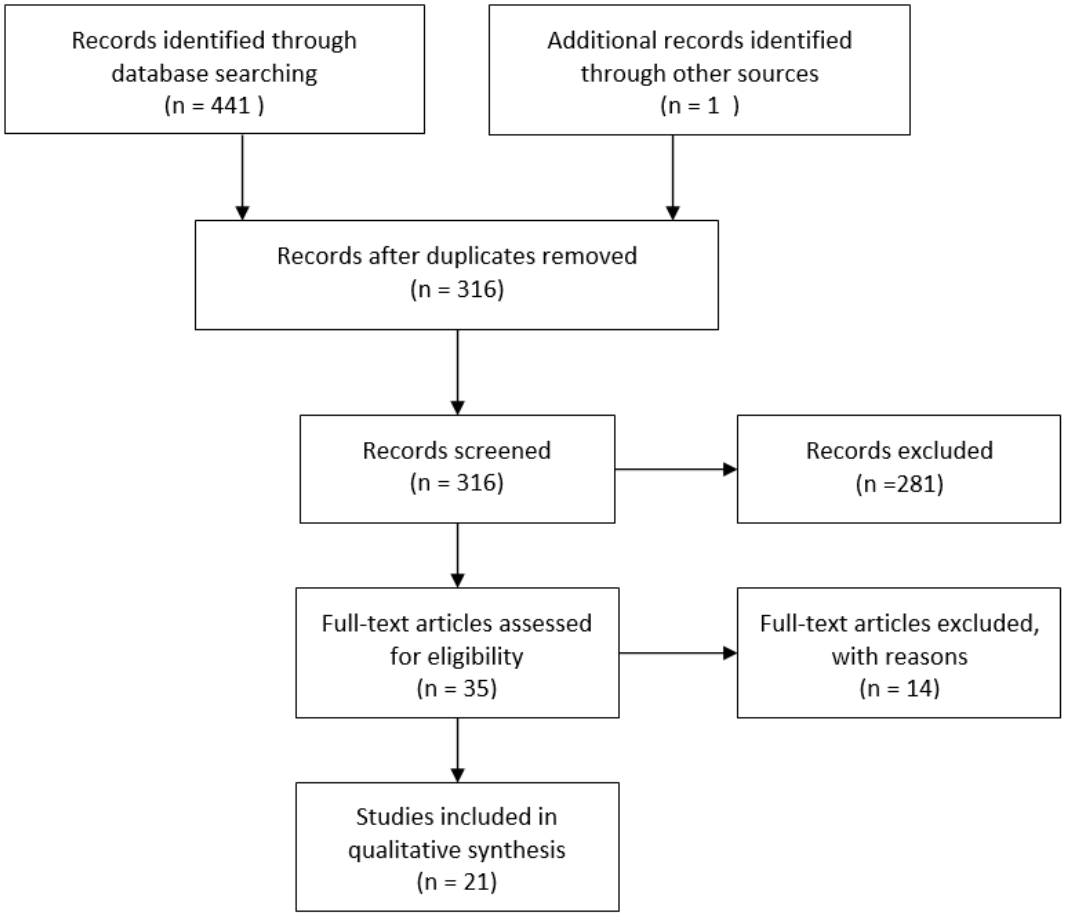
#13 Paediatric

#14 Child*

#15 #12 or #13 or #14

#14 #3 and #11 and #15

Appendix B. Prisma Diagram for literature review



Appendix C. Letter of Information and Assent Letter

Children's Hospital
London Health Sciences Centre

Project Title: Health related quality of life in children and adolescents with Spinal Muscular Atrophy: A longitudinal study in Canada

Investigators:

Dr. Craig Campbell
Dr. Eugenio Zapata Aldana
Sally Wei
Basmah El-Aloul
Research Coordinator: Rhiannon Hicks

Funding: Biogen has provided a grant to support this study.
Drs. Campbell and Zapata Aldana are members of the Biogen advisory committee.

Letter of information

You are being invited to participate in a research study looking at the quality of life and health related quality of life in children and adolescents with Spinal Muscular Atrophy (SMA) because you have indicated that you are interested in research opportunities through The Canadian Neuromuscular Disease Registry (www.CNDR.org). The purpose of this letter is to provide you with information required for you to make an informed decision regarding participation in this research.

The CNDR will call you in about a week to answer any questions you may have, and ask if you would like to participate in this study. If you indicate that you would like to participate a questionnaire package will be sent to you.

Why is this study being done?

Quality of life research allows healthcare workers to better understand the challenges children with SMA and their families face, and lead to better clinical care of these children.

What does my participation involve?

Patients between the ages of 0-18 with a confirmed diagnosis of SMA, who have been in the care of a parent for at least 6 months, are eligible for this study. Individuals with any significant medical problems not related to SMA, who are unable to complete the study protocol because of an inability to read and write English or French are not eligible to participate.

If you agree to participate, you and a parent will be asked to complete the set of questionnaires included with this letter. These questionnaires should take about 30 minutes to complete. There are some questionnaires that are for your parent to complete separately from you, some that you can complete together and some that you should complete on your own. If

you do require help with the questionnaires that you are to complete on your own, (e.g. you have trouble writing or do not understand how to fill out the forms) then, of course, you may ask your parents to help you. If you do get help please do your best to answer the question using your own feelings. There are no right or wrong answers for these questionnaires because they ask about how you feel about your life and your health. For the parent questionnaires we ask that all the forms be completed by the same parent, and it does not matter if this is your mother or father. Please note that some questions are similar or even identical to each other, we ask that you complete all of the questions on each page. We are trying to assess which questionnaire work best in the SMA population and thus it is important each questionnaire is complete. We would ask that once the questionnaires are complete that you place them in the included, pre-posted envelope and send them back to us.

Consent:

Consent for this study is implied consent, meaning that if you complete the questionnaires and submit them, you are agreeing to participate in the study.

Your participation in this study is voluntary. You may decide not to be in this study. Even if you consent to participate you have the right to not answer individual questions or to withdraw from the study at any time. If you choose not to participate or to leave the study at any time it will have no effect on your participation in the CNDR.

Are there any risks to participating?

There are no known risks or discomforts associated with participating in this study. However, if you do experience any problems or discomfort, you may discontinue the task at any time.

Are there any benefits to participating?

You may not directly benefit from participating in this study, but information from this study may provide benefits to the SMA community as a whole by allowing healthcare workers to better understand factors impacting quality of life in children with SMA. You will not be compensated for your participation in this research. Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care.

What will happen with my data? How will it be kept confidential?

All of the data collected will remain de-identified, confidential and accessible only by the investigators of this study. The data the study investigators receive will not contain any identifying information, you will notice on your questionnaire that there is a number, this will

Children's Hospital
London Health Sciences Centre

be your study number. The study information will only include your study number. The only people that will be able to link your study number and your name is the CNDR, this information will not be provided to the investigators of this study. If the results are published, your name or any identifying information will not be used.

Your questionnaires will be stored in a secure research office at London Health Sciences Centre. Study records will be kept for 15 years. All study data will be destroyed via the confidential disposal program at London Health Sciences Centre

What if I change my mind?

If you choose to withdraw from this study, you can choose to remove your data, or let the study keep the data already collected. If you choose to have your data removed, you will need to contact the CNDR so that they can let the site know your number so the study team can remove your data. Once this happens your data will be removed and destroyed from our database. . If you would like to have your data removed from this study, please contact the CNDR at [redacted]

If you require further information regarding this research project or your participation in the study you may contact Dr. Craig Campbell, [redacted]

If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Patient Experience Office at LHSC at [redacted] or access the online form at: [redacted] If you would like to receive a copy of any potential study results, please contact [redacted]

Please keep a copy of this Letter of Information for you records.

Children's Hospital
London Health Sciences Centre

Project Title: Health related quality of life in children and adolescents with Spinal Muscular Atrophy: A longitudinal study in Canada

Principal Investigator: Dr. Craig Campbell, Department of Neurology Paediatrics, Children's Hospital, London Health Sciences Centre

Assent Letter

1. **What this study is about?**
   Dr. Campbell and some researchers would like to find out about how you feel and what you think about your health. They want to see if you would like to be in this study. There will be another follow-up study next year.

2. **What will happen to you?**
   If you want to be in the study you will answer some questions about your life. The questions are not part of a test, and there are no right or wrong answers.

3. **Will the study help you?**
   No, this study will not help you directly but in the future it might help other children with Spinal Muscular Atrophy.

4. **What if you have any questions?**
   You can ask questions at any time, now or later. You can talk to the teachers, your family or someone else.

5. **Will there be any tests?**
   No, there will not be any tests or marks on the report card from this study

6. **Do you have to be in the study?**
   You do not have to be in the study. No one will be mad at you if you do not want to do this. If you do not want to be in the study, just say so. Even if you say yes, you can change your mind later. It is up to you. Also, if you say yes to participate in the study this year it does not mean you have to participate again next year.

By answering these questions, you give your consent to participate in this study.

Appendix D. Instructions for Young Child Reports

INSTRUCTIONS

TO PARENTS:

1. Due to the young age of your child, we ask that you act as an "interviewer" to your child. Please carefully follow the instructions for each section of the questionnaire. While helping your child complete the questionnaires, please indicate **his/her** answers, without your input. Do not interpret the question for him/her. Repeat the item to him exactly as written. Ask him/her to answer the item according to what *they think the question means*. If he/she has trouble deciding on an answer, ask him/her to choose the response that comes closest to how he/she feels.

2. Answer questions by checking the appropriate box (☐) or circling the appropriate number, unless otherwise instructed.

3. When answering questions, please consider the time-period indicated.

4. Certain questions may look alike or even identical to each other. Please try to answer all of the questions on each page.

5. If your child is unable to complete the questionnaire, even with some help from the parent, please indicate this by checking this box: ☐ and please return this booklet along with the parent questionnaire.

Appendix E. Instructions for Child and Teen Reports

INSTRUCTIONS

1. Please answer the questions in this booklet on your own.

2. There are no right or wrong answers. If you are unsure how to answer a question, please give the best answer you can. Write any comments you may have on the page beside the question or at the end of the questionnaire.

3. Answer questions by checking the appropriate box (☐) or circling the appropriate number, unless otherwise instructed.

4. When answering questions, please consider the time-period indicated.

5. Certain questions may look alike or even identical to each other. Please try to answer all of the questions on each page.

TO PARENTS:

1. If your child is unable to read the questions, you may read the questions to him/her. While helping your child complete the questionnaires, please indicate **his/her** answers, without your input. Do not interpret the question for him/her. Repeat the item to him/her exactly as written. Ask him/her to answer the item according to what t*hey think the question means*. If he/she has trouble deciding on an answer, ask him/her to choose the response that comes closest to how he/she feels.

2. If your child is unable to complete the questionnaire, even with some help from the parent, please indicate this by checking this box: ☐ and please return this booklet along with the parent questionnaire.

Appendix F. Instructions for Parent Reports

INSTRUCTIONS

1. Throughout this questionnaire when we refer to "your child", we are referring to your child with Spinal Muscular Atrophy. Please keep him/her in mind when responding to questions.

2. Most of the questions in this booklet ask about your child's health and wellbeing. A few questions ask about your own and your family's health and wellbeing. Your individual answers will remain strictly confidential.

3. Unless otherwise instructed, please complete the questionnaires independently of your child and avoid consulting with your child while completing the questionnaire. Feel free to discuss your answers with your child *after* completing of the questionnaires, but it is important for us to get your individual perspective.

4. Answer questions by checking the appropriate box (☐) or circling the appropriate number, unless otherwise instructed.

5. When answering questions, please consider the time-period indicated.

6. Certain questions may look alike or even identical to each other. Please try to answer all of the questions on each page.

7. There are no right or wrong answers. If you are unsure how to answer a question, please give the best answer you can. Write any comments you may have on the page beside the question or at the end of the questionnaire.

Appendix G. Reminder Postcard and Letter

March 1st, 2020

Last week a questionnaire was mailed to you from the Spinal Muscular Atrophy Quality of Life study.

If you have already completed and returned the questionnaire to us, please accept our sincere thanks. If not, please consider participating in our study today. We are especially grateful for your help because it is only by asking patients and parents like you to share your experiences that we can achieve our ultimate goal of optimizing health-related quality of life for children and families such as yours.

If you did not receive a questionnaire, or it was misplaced, please call us at [redacted] and we will get another one in the mail to you today.

Craig Campbell, MD
Paediatric Neurologist
Department of Paediatrics
Children's Hospital - LHSC
800 Commissioners Road East
London, Ontario, Canada N6C 2V5

Appendix H. Reminder Letter

January 4, 2019

About 4 weeks ago a questionnaire was sent to you from the Canadian Neuromuscular Disease Registry entitled: **"Health related quality of life in children and adolescents with Spinal Muscular Atrophy: A longitudinal study in Canada"**. To the best of our knowledge, it has not yet been returned.

The responses of participants who have already returned their questionnaires include a wide variety of experiences with Spinal Muscular Atrophy (SMA). We think the results are going to help us better understand the experiences of children living with SMA and their families to learn how we can best support children with SMA.

We are writing again because of the importance that your questionnaire has for helping us to get accurate results. Although we are sending questionnaires to people living all across Canada, it is only by hearing from nearly everyone in the sample that we can be sure the results are truly representative.

We would like to remind you that all information will be kept strictly confidential. Only a study number will identify information you give us. No personal information that could identify you will be left on the questionnaires once they are returned to the research office.

We hope that you will fill out and return the questionnaire soon, but if for any reason you prefer not to answer it, please let us know by returning a note or blank questionnaire in the enclosed stamped envelope.

Sincerely,

Craig Campbell, MD MSc FRCPC
Paediatric Neurologist
Head Department of Neurology Paediatrics
Children's Hospital, London Health Science Centre
800 Commissioner's Road East
London, Ontario N6C 2V5

Appendix I. Telephone Script

Script for phone call when call answered in person:

"Hello. May I please speak with _____?

My name is _____. I am with the CNDR. I'm phoning to let you know you'll be getting a package in the mail in about a week which relates to a Letter you should have received recently from Dr. Craig Campbell about a National SMA Quality of Life research study that you and your child are invited to participate in. I just wanted to introduce myself, give you the opportunity to ask questions and be sure you had my contact information should any questions come up when your package arrives.

Do you have any questions at this time?

If no: I won't take up any more of your time, please don't hesitate to contact me for any reason. I'm here for you and don't worry if you don't get to the package right away as I'll follow up with you and can walk you through the package.

If yes: Great! Let me tell you more about this study. Please interrupt me at any time if you have a question. For this study, we will be recruiting families across Canada to get detailed information to better understand what are the main issues that affect the Quality of Life of families and patients of any type of SMA.

To participate, we will send you a questionnaire for you and your child to complete, we are going to send you these questionnaires on three different occasions during the two years that this study lasts: the first questionnaire will be followed by the same questionnaire 12 and 24 months after the first time point. Each questionnaire takes around 30 minutes of your time, and can be either completed online or by pen and paper and returning via traditional mail, we will provide the stamps.

Does this information answer some of your questions?If yes: Great! Thank you for letting me take the time to tell you about this study.

If no: Can I help to answer any other questions or would you prefer to wait until you receive the package?

If you think of any other questions or would like to speak to me about this at any time, please call me at [PHONE #].

Take care and thank you.

Script for leaving a voice mail at 1st attempt to call:

My name is _____. I am with the CNDR. I'm phoning to let you know you'll be getting a package in the mail in about a week which relates to a Letter you should have received recently about a National study you and your child are invited to participate in. I was calling to introduce myself, give

Appendix J. Pediatric Quality of Life Inventory 4.0 Generic Core Module

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other children not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Appendix K. Pediatric Quality of Life Inventory 3.0 Neuromuscular Module

*In the **PAST MONTH**, how much of a **problem** has this been for your child …*

ABOUT MY CHILD'S NEUROMUSCULAR DISEASE (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for my child to breathe	0	1	2	3	4
2. My child gets sick easily	0	1	2	3	4
3. My child gets sores and/or rashes	0	1	2	3	4
4. My child's legs hurt	0	1	2	3	4
5. My child feels tired	0	1	2	3	4
6. My child's back feels stiff	0	1	2	3	4
7. My child wakes up tired	0	1	2	3	4
8. My child's hands are weak	0	1	2	3	4
9. It is hard for my child to use the bathroom	0	1	2	3	4
10. It is hard for my child to gain or lose weight when he or she wants to	0	1	2	3	4
11. It is hard for my child to use his or her hands	0	1	2	3	4
12. It is hard for my child to swallow food	0	1	2	3	4
13. It takes my child a long time to bathe or shower	0	1	2	3	4
14. My child gets hurt accidentally	0	1	2	3	4
15. My child takes a long time to eat	0	1	2	3	4
16. It is hard for my child to turn him or herself during the night	0	1	2	3	4
17. It is hard for my child to go places with his or her equipment	0	1	2	3	4

COMMUNICATION (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for my child to tell the doctors and nurses how he or she feels	0	1	2	3	4
2. It is hard for my child to ask the doctors and nurses questions	0	1	2	3	4
3. It is hard for my child to explain his or her illness to other people	0	1	2	3	4

ABOUT OUR FAMILY RESOURCES (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for our family to plan activities like vacations	0	1	2	3	4
2. It is hard for our family to get enough rest	0	1	2	3	4
3. I think money is a problem in our family	0	1	2	3	4
4. I think our family has a lot of problems	0	1	2	3	4
5. My child does not have the equipment he or she needs	0	1	2	3	4

Appendix L. Pediatric Quality of Life Inventory 2.0 Family IMPACT Module

THE FOLLOWING QUESTIONS ASK ABOUT YOU.

*In the past **ONE month**, as a result of your child's health, how much of a **problem** have **you** had with…*

PHYSICAL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. I feel tired during the day	0	1	2	3	4
2. I feel tired when I wake up in the morning	0	1	2	3	4
3. I feel too tired to do the things I like to do	0	1	2	3	4
4. I get headaches	0	1	2	3	4
5. I feel physically weak	0	1	2	3	4
6. I feel sick to my stomach	0	1	2	3	4

EMOTIONAL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. I feel anxious	0	1	2	3	4
2. I feel sad	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I feel frustrated	0	1	2	3	4
5. I feel helpless or hopeless	0	1	2	3	4

SOCIAL FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. I feel isolated from others	0	1	2	3	4
2. I have trouble getting support from others	0	1	2	3	4
3. It is hard to find time for social activities	0	1	2	3	4
4. I do not have enough energy for social activities	0	1	2	3	4

COGNITIVE FUNCTIONING (*problems with…*)	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4

Appendix M. Pediatric Quality of Life Inventory Fatigue Module

*In the past **one month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE *(PROBLEMS WITH…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(PROBLEMS WITH…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(PROBLEMS WITH…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

COMMUNICATION *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel that others do not understand my family's situation	0	1	2	3	4
2. It is hard for me to talk about my child's health with others	0	1	2	3	4
3. It is hard for me to tell doctors and nurses how I feel	0	1	2	3	4

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I worry about whether or not my child's medical treatments are working	0	1	2	3	4
2. I worry about the side effects of my child's medications/medical treatments	0	1	2	3	4
3. I worry about how others will react to my child's condition	0	1	2	3	4
4. I worry about how my child's illness is affecting other family members	0	1	2	3	4
5. I worry about my child's future	0	1	2	3	4

THE FOLLOWING QUESTIONS ASK ABOUT YOUR FAMILY.

*In the past **ONE month**, as a result of your child's health, how much of a **problem** has **your family** had with…*

DAILY ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Family activities taking more time and effort	0	1	2	3	4
2. Difficulty finding time to finish household tasks	0	1	2	3	4
3. Feeling too tired to finish household tasks	0	1	2	3	4

FAMILY RELATIONSHIPS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Lack of communication between family members	0	1	2	3	4
2. Conflicts between family members	0	1	2	3	4
3. Difficulty making decisions together as a family	0	1	2	3	4
4. Difficulty solving family problems together	0	1	2	3	4
5. Stress or tension between family members	0	1	2	3	4

Appendix N. Demographic and Medical Questionnaire

Household/Family information

1. Who currently lives with your son/daughter? Please do not use any people's names when completing the table below:

Person	Their relationship to your child (e.g. Mom, Dad, brother, sister, grandparent, aunt, uncle, friend, roommate, partner/spouse)	Their Age	Their Sex
1			☐ Male ☐ Female
2			☐ Male ☐ Female
3			☐ Male ☐ Female
4			☐ Male ☐ Female
5			☐ Male ☐ Female
6			☐ Male ☐ Female
7			☐ Male ☐ Female
8			☐ Male ☐ Female

2. Are you:
   ☐ Male
   ☐ Female

3. What is your age? ☐☐

4. What is your relationship to this person with spinal muscular atrophy? Check one box only.

☐ Biological parent ☐ Step parent ☐ Foster parent ☐ Adoptive parent ☐ Guardian ☐ Other (please explain on the line below)

5. What is the highest grade of school you have completed?

- ☐ Less than secondary school graduation
- ☐ Secondary school diploma or equivalent
- ☐ Some postsecondary education (no certificate, diploma or degree)
- ☐ Apprenticeship or trade's certificate or diploma
- ☐ College, CEGEP or other non-university certificate or diploma
- ☐ University certificate or diploma
- ☐ Bachelor's degree
- ☐ Master's degree
- ☐ Professional degree
- ☐ Doctoral degree
- ☐ Prefer not to disclose

6. Which of the following best describes your current work status? Check one box only.

☐ Not working due to my child's health	☐ Not working for "other" reasons	☐ Working full-time	☐ Working part-time	☐ Stay-at-home parent	☐ Student	☐ Retired

7. What is your current marital status? Check one box only.

☐ Married (and not separated)	☐ Living common law	☐ Widowed	☐ Separated	☐ Divorced	☐ Single

8. Are you currently living with a spouse or partner?

- ☐ No → If **no**, skip to question **11**.
- ☐ Yes → If **yes**, proceed to question **9**.

9. Which of the following best describes your spouse's/partner's current work status? Check one box only.

☐ Not working due to my child's health	☐ Not working for "other" reasons	☐ Working full-time	☐ Working part-time	☐ Stay-at-home parent	☐ Student	☐ Retired

10. What is the highest grade of school your spouse/partner has completed?

- ☐ Less than secondary school graduation
- ☐ Secondary school diploma or equivalent
- ☐ Some postsecondary education (no certificate, diploma or degree)
- ☐ Apprenticeship or trade's certificate or diploma
- ☐ College, CEGEP or other non-university certificate or diploma
- ☐ University certificate or diploma
- ☐ Bachelor's degree
- ☐ Master's degree
- ☐ Professional degree
- ☐ Doctoral degree
- ☐ Prefer not to disclose

The next two questions will allow us to compare your family's health to that of other people in the study who are similar to you.

11. In which category is your total yearly household income before taxes? Check one box only.

- ☐ Less than $20,000
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $59,999
- ☐ $60,000 to $ 69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $89,999
- ☐ $90,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 or more
- ☐ Prefer not to disclose

12. Thinking about your total family income, from which sources did your family receive income during the past year? Check all that apply.

- ☐ Wages and salaries
- ☐ Income from self-employment
- ☐ Family allowance (baby bonus)
- ☐ Unemployment insurance or strike pay
- ☐ Worker's compensation
- ☐ Old Age Security, Guaranteed Income Supplement, Canada or Quebec Pension Plan, Retirement Pension Plan, Superannuation
- ☐ Dividends and interest on bonds, deposits and saving certificates
- ☐ Other government sources such as welfare, mother's allowance, etc.
- ☐ Other source(s). Please specify: _____
- ☐ Prefer not to disclose

Your Child's Health Information

13. What type of SMA has your child been diagnosed with?

- ☐ Type 1
- ☐ Type 2
- ☐ Type 3
- ☐ Type 4

14. Is your child able to walk?

- ☐ Yes
- ☐ No

15. Does your child have scoliosis?

- ☐ Yes
- ☐ No

16. Does your child use assisted ventilation?

- ☐ None
- ☐ Trached/ventilation
- ☐ Non-invasive Bi-PAP
- ☐ Other _____

17. Is your child currently receiving Nusinursen/Spinraza?
    - ☐ Yes
    - ☐ No

If yes, Please indicate the duration of treatment: _____

18. Is your child currently receiving any investigational product?
    - ☐ Yes
    - ☐ No

If yes, please list: _____

19. Is your child currently taking salbutamol
    - ☐ Yes
    - ☐ No

20. Is your child currently taking Valproate
    - ☐ Yes
    - ☐ No

21. Is your child currently taking Gabapentin
    - ☐ Yes
    - ☐ No

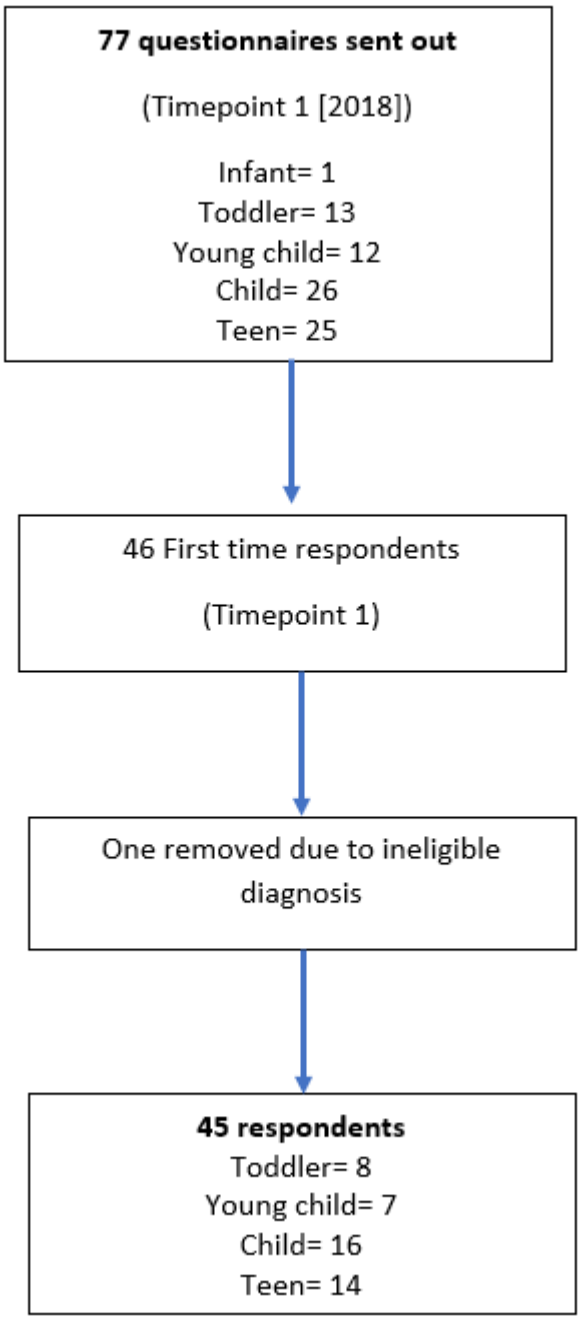
22. Is your child currently taking any nutritional supplements
    - ☐ Yes
    - ☐ No

If yes, please list: _____

23. Please list any additional medications or supplements your child is taking:

_____
_____
_____
_____

Appendix O. Responder Flow Diagram



Curriculum Vitae

Name Tran Nguyen

Post-secondary Education and Degrees

The University of Western Ontario
London, Ontario, Canada
2019-Present MSc. Candidate

The University of Western Ontario
London, Ontario, Canada
2016-2017 Diploma

The University of Western Ontario
London, Ontario, Canada
2012-2014 MSc.

The University of Western Ontario
London, Ontario, Canada
2008-2012 BSc.

Related Work Experience

Research Associate
Lawson Health Research Institute
2022-Present

Research Coordinator
London Health Sciences Centre
2021-2022

Associate Scientific Writer
Alimentiv Inc.
2019-2021

Assistant Managing Editor/Information Specialist
Cochrane
2016-2019

Medical Researcher
Legate & Associates
2014-2016

Research Assistant
The University of Western Ontario
2011-2013

Teaching Assistant
The University of Western Ontario
2013

Publications

Ma C, MacDonald JK, **Nguyen TM**, Chang J, Vande Casteele N, Feagan BG, Jairath V. *Systematic review: disease activity indices for immune checkpoint inhibitor-associated enterocolitis*. Aliment Pharmacol Ther. 2022 Jan;55(2):178-190.

Sedano R, Hogan M, **Nguyen TM**, Chang J, Zou GY, Macdonald JK, Vande Casteele N, Hanzel J, Crowley E, Battat R, Dulai PS, Singh S, D'Haens G, Sandborn W, Feagan BG, Ma C, Jairath V. *Systematic review and meta-analysis: clinical, endoscopic, histological and safety placebo rates in induction and maintenance trials of ulcerative colitis*. J Crohns Colitis. 2022 Feb 23;16(2):224-243.

Sedano R, **Nguyen TM**, Almradi A, Rieder F, Parker CE, Shackelton LM, D'Haens G, Sandborn WJ, Feagan BG, Ma C, Jairath V. *Disease activity indices for pouchitis: a systematic review*. Inflamm Bowel Dis. 2022 Mar 30;28(4):622-638.

Gordon IO, Bettenworth D, Bokemeyer A, Srivastava A, Rosty C, de Hertogh G, Robert ME, Valasek MA, Mao R, Li J, Harpaz N, Borralho P, Pai RK, Odze R, Feakins R, Parker CE, Guizzetti L, **Nguyen T**, Shackelton LM, Sandborn WJ, Jairath V, Baker M, Bruining D, Fletcher JG, Feagan BG, Pai RK, Rieder F; *Stenosis therapy and anti-fibrotic research (STAR) consortium. International consensus to standardise histopathological scoring for small bowel strictures in Crohn's disease*. Gut. 2022 Mar;71(3):479-486.

Ma C, MacDonald JK, **Nguyen TM**, Vande Casteele N, Linggi B, Lefevre P, Wang Y, Feagan BG, Jairath V. *Pharmacological interventions for the prevention and treatment of immune checkpoint inhibitor-associated enterocolitis: a systematic review*. Dig Dis Sci. 2022 Apr;67(4):1128-1155.

Akhtar HJ, **Nguyen TM**, Ma C, Jairath V. *Vedolizumab for the treatment of noninflammatory bowel disease related enteropathy*. Clin Gastroenterol Hepatol. 2022 Mar;20(3): e614-e623.

Chande N, Singh S, Narula N, Gordon M, Kuenzig ME, **Nguyen TM**, MacDonald JK, Feagan BG. *Medical management following surgical therapy in inflammatory bowel disease: evidence from Cochrane reviews*. Inflamm Bowel Dis. 2021 Aug 19;27(9):1513-1524.

Goodsall TM, Jairath V, Feagan BG, Parker CE, **Nguyen TM**, Guizzetti L, Asthana AK, Begun J, Christensen B, Friedman AB, Kucharzik T, Lee A, Lewindon PJ, Maaser C, Novak KL, Rimola J, Taylor KM, Taylor SA, White LS, Wilkens R, Wilson SR, Wright EK, Bryant RV, Ma C. *Standardisation of intestinal ultrasound scoring in clinical trials for luminal Crohn's disease*. Aliment Pharmacol Ther. 2021 Apr;53(8):873-886.

Goodsall TM, **Nguyen TM**, Parker CE, Ma C, Andrews JM, Jairath V, Bryant RV. *Systematic Review: Gastrointestinal ultrasound scoring indices for inflammatory bowel disease*. J Crohns Colitis. 2021 Jan;15(1):125-142.

Al Draiweesh S, Ma C, Alkhattabi M, McDonald C, **Nguyen TM**, Beaton M, Chande N, Colquhoun P, Feagan BG, Gregor JC, Khanna R, Marotta P, Ponich T, Quan D, Qumosani K, Sandhu A, Sey M, Skaro A, Teriaky A, Wilson A, Yan B, Brahmania M, Jairath V. *Safety of combination biologic and antirejection therapy post-liver transplantation in patients with inflammatory bowel disease*. Inflamm Bowel Dis. 2020 May;26(6):949-959.

George J, Singh S, Dulai PS, Ma C, **Nguyen T**, Feagan BG, Sandborn WJ, Jairath V. *Corticosteroid-free remission vs overall remission in clinical trials of moderate-severe ulcerative colitis and Crohn's disease*. Inflamm Bowel Dis. 2020 Mar 4;26(4):515-523.

Murray A, **Nguyen TM**, Parker CE, Feagan BG, MacDonald JK. *Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis*. Cochrane Database Syst Rev. 2020 Aug;8:CD000544.

Murray A, **Nguyen TM**, Parker CE, Feagan BG, MacDonald JK. *Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis*. Cochrane Database Syst Rev. 2020 Aug;8:CD000543.

Davies SC, Hussein IM, **Nguyen TM**, Parker CE, Khanna R, Jairath V. *Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis*. Cochrane Database Syst Rev. 2020 Jan;1(1):CD012381.

Bettenworth D, Bokemeyer A, Baker M, Mao R, Parker CE, **Nguyen T**, Ma C, Panés J, Rimola J, Fletcher JG, Jairath V, Feagan BG, Rieder F; *Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium. assessment of Crohn's disease-associated small bowel strictures and fibrosis on cross-sectional imaging: a systematic review*. Gut. 2019 Jun;68(6):1115-1126.

Battat R, Duijvestein M, Guizzetti L, Choudhary D, Boland BS, Dulai PS, Parker CE, **Nguyen TM**, Singh S, Vande Casteele N, Pai RK, Feagan BG, Sandborn WJ, Jairath V. *Histologic healing rates of medical therapies for ulcerative colitis: A systematic review and meta-analysis of randomized controlled trials*. Am J Gastroenterol. 2019 May;114(5):733-745.

Ma C, Panaccione NR, **Nguyen TM**, Guizzetti L, Parker CE, Hussein IM, Vande Casteele N, Khanna R, Dulai PS, Singh S, Feagan BG, Jairath V. *Adverse events and nocebo effects in inflammatory bowel disease: A systematic review and meta-analysis of randomized controlled trials*. J Crohns Colitis. 2019 Sep;13(9):1201-1216.

Ma C, Lee JK, Mitra AR, Teriaky A, Choudhary D, **Nguyen TM**, Vande Casteele N, Khanna R, Panaccione R, Feagan BG, Jairath V. *Systematic review with meta-analysis: efficacy and safety of oral Janus kinase inhibitors for inflammatory bowel disease*. Aliment Pharmacol Ther. 2019 Jul;50(1):5-23.

Ma C, Guizzetti L, Cipriano LE, Parker CE, **Nguyen TM**, Gregor JC, Chande N, Feagan BG, Jairath V. *Systematic review with meta-analysis: high prevalence and cost of continued*

aminosalicylate use in patients with ulcerative colitis escalated to immunosuppressive and biological therapies. Aliment Pharmacol Ther. 2019 Feb;49(4):364-374.
Kafil TS, **Nguyen TM**, MacDonald JK, Chande N. *Cannabis for the treatment of ulcerative colitis*. Cochrane Database Syst Rev. 2018 Nov;11(11):CD012954.

Kafil TS, **Nguyen TM**, MacDonald JK, Chande N. *Cannabis for the treatment of Crohn's disease*. Cochrane Database Syst Rev. 2018 Nov;11(11):CD012853.

Bye WA, Ma C, **Nguyen TM**, Parker CE, Jairath V, East JE. *Strategies for detecting colorectal cancer in patients with inflammatory bowel disease: A cochrane systematic review and meta-analysis*. Am J Gastroenterol. 2018 Dec;113(12):1801-1809.

Ma C, Parker CE, **Nguyen TM**, Khanna R, Feagan BG, Jairath V. *Identifying outcomes in clinical trials of fistulizing Crohn's disease for the development of a core outcome set*. Clin Gastroenterol Hepatol. 2019 Aug;17(9):1904-1908.

Nelson SM, **Nguyen TM**, McDonald JW, MacDonald JK. *Natalizumab for induction of remission in Crohn's disease*. Cochrane Database Syst Rev. 2018 Aug;8(8):CD006097.

Ma C, van Rhijn BD, Jairath V, **Nguyen TM**, Parker CE, Aceves SS, Furuta GT, Gupta SK, Katzka DA, Safroneeva E, Schoepfer AM, Straumann A, Spergel JM, Pai RK, Feagan BG, Hirano I, Dellon ES, Bredenoord AJ. *Heterogeneity in clinical, endoscopic, and histologic outcome measures and placebo response rates in clinical trials of Eosinophilic Esophagitis: A systematic review*. Clin Gastroenterol Hepatol. 2018 Nov;16(11):1714-1729.

Ma C, Dutton SJ, Cipriano LE, Singh S, Parker CE, **Nguyen TM**, Guizzetti L, Gregor JC, Chande N, Hindryckx P, Feagan BG, Jairath V. *Systematic review with meta-analysis: prevalence, risk factors and costs of aminosalicylate use in Crohn's disease*. Aliment Pharmacol Ther. 2018 Jul;48(2):114-126.

Boyapati RK, Torres J, Palmela C, Parker CE, Silverberg OM, Upadhyaya SD, **Nguyen TM**, Colombel JF. *Withdrawal of immunosuppressant or biologic therapy for patients with quiescent Crohn's disease*. Cochrane Database Syst Rev. 2018 May;5(5):CD012540.

Ma C, Panaccione R, Fedorak RN, Parker CE, **Nguyen TM**, Khanna R, Siegel CA, Peyrin-Biroulet L, D'Haens G, Sandborn WJ, Feagan BG, Jairath V. *Heterogeneity in definitions of endpoints for clinical trials of ulcerative colitis: A systematic review for development of a core outcome set*. Clin Gastroenterol Hepatol. 2018 May;16(5):637-647.

Ma C, Guizzetti L, Panaccione R, Fedorak RN, Pai RK, Parker CE, **Nguyen TM**, Khanna R, Vande Casteele N, D'Haens G, Sandborn WJ, Feagan BG, Jairath V. *Systematic review with meta-analysis: endoscopic and histologic placebo rates in induction and maintenance trials of ulcerative colitis*. Aliment Pharmacol Ther. 2018 Jun;47(12):1578-1596.

Parker CE, **Nguyen TM**, Segal D, MacDonald JK, Chande N. *Low dose naltrexone for induction of remission in Crohn's disease*. Cochrane Database Syst Rev. 2018 Apr;4(4):CD010410.

Hindryckx P, Zou GY, Feagan BG, Garg SK, Singh JA, Lobaton T, Singh S, Parker CE, **Nguyen TM**, Silverberg OM, Khanna R, Jairath V. *Biologic drugs for induction and maintenance of remission in Crohn's disease: a network meta-analysis*. Cochrane Database Syst Rev. 2017 Aug;2017(8):CD012751.

Davies SC, **Nguyen TM**, Parker CE, MacDonald JK, Jairath V, Khanna R. *Anti-IL-12/23p40 antibodies for maintenance of remission in Crohn's disease*. Cochrane Database Syst Rev. 2019 Dec;12(12):CD012804.

Deol N, **Nguyen TM**, Parker CE, Khanna R, Feagan BG, MacDonald JK, Jairath V. *Infliximab for induction of remission in Crohn's disease*. Cochrane Database Syst Rev. 2017 Apr;2017(4):CD012623.

Chande N, Al Yatama N, Bhanji T, **Nguyen TM**, McDonald JW, MacDonald JK. *Interventions for treating lymphocytic colitis.* Cochrane Database Syst Rev. 2017 Jul;7(7):CD006096.

Kafil TS, **Nguyen TM**, Patton PH, MacDonald JK, Chande N, McDonald JW. *Interventions for treating collagenous colitis*. Cochrane Database Syst Rev. 2017 Nov;11(11):CD003575.

Bye WA, **Nguyen TM**, Parker CE, Jairath V, East JE. *Strategies for detecting colon cancer in patients with inflammatory bowel disease*. Cochrane Database Syst Rev. 2017 Sep;9(9):CD000279

Ma C, Panaccione R, Fedorak RN, Parker CE, **Nguyen TM**, Khanna R, Siegel CA, Peyrin-Biroulet L, D'Haens G, Sandborn WJ, Feagan BG, Jairath V. *Heterogeneity in definitions of endpoints for clinical trials of ulcerative colitis: A systematic review for development of a core outcome set*. Clin Gastroenterol Hepatol. 2018 May;16(5):637-647.

Nguyen TM, Macpherson EA. *The effects of diffuse noise and artificial reverberation on listener weighting of interaural cues in sound localization*. J Acoust Soc Am. 2017;141(5):3637.

MacDonald JK, **Nguyen TM**, Khanna R, Timmer A. *Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease*. Cochrane Database Syst Rev. 2016 Nov;11(11):CD007572.

Macpherson, E. A., **Nguyen TM.** *Weighting of interaural time difference and interaural level difference cues in wide-band stimuli with varying low and high frequency energy balance*. J Acoust Soc Am. 2014; 135(4): 2282.

Presentations

Nguyen TM. (November 2021). *Health-Related Quality of Life and Patient-Reported Outcomes in SMA*. Presented at the 2021 SMA Academy. Oral Presentation.

Nguyen TM, El Sherifc R, Bennett N, Matyushenko V, Nakamura H, Osredkar D, Wu Shiwen, Goemans Nathalie, Ambrosini A, Campbell C. (December 2019). *Academic productivity from*

rare neuromuscular disease registries: A systematic review. Presented at the TREAT-NMD meeting, Leiden, The Netherlands. Poster Presentation.
Nguyen TM & Macpherson EA. (May 2014). *Weighting of the interaural time difference and interaural level difference cues in wide-band stimuli with varying low and high frequency energy balance*. Presented at the American Society of Acoustics Conference, Providence, Rhode Island. Poster Presentation.

Nguyen TM & Macpherson EA. (February 2014). *Weighting of the interaural time difference and interaural level difference cues in wide-band stimuli with varying low and high frequency energy balance*. Presented at the Faculty of Health Sciences Conference, London, ON. Poster Presentation.

Nguyen TM. (February 2014). *The effects of noise and reverberation on auditory cue weighting during sound localization*. Presented at the Health and Rehabilitation Science Conference, London, ON. Oral Presentation.

Nguyen TM. (August 2014). *The effects of target spectrum, noise, and reverberation on auditory cue weighting during sound localization*. Presented at The National Centre for Audiology (Master's thesis public presentation), London, ON. Oral Presentation.