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Quality of Life of Children With Spinal Muscular Atrophy: Parents' Perspectives in Light of New Treatments

Analyssa R. Tallas

QUALITY OF LIFE OF CHILDREN WITH SPINAL MUSCULAR ATROPHY: PARENTS' PERSPECTIVES IN LIGHT OF NEW TREATMENTS

by

Analyssa R. Tallas

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Accepted by:

Debera Zvejnieks, Director of Thesis

Sylvia Brook, Reader

Kristin Engelstad, Reader

Cheryl L. Addy, Vice Provost and Dean of the Graduate School

DEDICATION

For my family with gratitude.

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ABSTRACT

Purpose: To directly compare parents' perspectives of the quality of life of their children with Spinal Muscular Atrophy (SMA) who received supportive care, nusinersen (Spinraza®), onasemnogene abeparvovec-xioi (Zolgensma®), or both nusinersen and onasemnogene abeparvovec-xioi. Methods: The parents of children with SMA were recruited to complete anonymous online surveys. All surveys included qualitative questions about quality of life. Surveys regarding children in the 1-12-month and 13-24-month age groups included the Pediatric Quality of Life Infant Scales assessment. Surveys regarding children in the 2-4-year age group included the Pediatric Quality of Life Inventory 4.0 Generic Core Scales and the Pediatric Quality of Life 3.0 Neuromuscular Module assessments. The >4-year age group did not include a quantitative quality of life assessment. Results: The 1-12-month age group average physical quality of life summary score was increased for children treated with a combination of both nusinersen and onasemnogene abeparvovec-xioi and also those treated with onasemnogene abeparvovec-xioi only. The 1-12-month- age group average psychosocial quality of life summary score was increased for children treated with nusinersen only. Physical and psychosocial quality of life data regarding the 13-24-month age group was not statistically significant. All surveys regarding the 2-4-year age group and one survey from the >4-year age group were excluded to eliminate the possibility of identifying participants. Conclusion: It was not possible to identify and associate a single treatment with conferring a statistically higher quality of life; however, the quantitative

and qualitative responses collected allowed for an inference that parents believe their children with SMA have a greater quality of life when provided treatment over having only supportive care. Before the FDA approval of the available treatments, healthcare providers who shared the diagnosis of SMA with parents had to also share that there was no known effective treatment. However, today when families hear the diagnosis of SMA, they can be hopeful for their child and family's future because of the treatments available and the proven increase in quality of life with these treatments. Knowing how quality of life perspectives differ based on the type of treatment received can help in the education of parents of children with SMA.

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LIST OF ABBREVIATIONS

ACOG ..... American College of Obstetricians and Gynecologists

CPA.....Caregiver proxy assessment

FDA..... Food and Drug Administration

GSF .....Gwendolyn Strong Foundation

mRNA .....Messenger ribonucleic acid

PSA .....Patient self-assessment

PedsQL GCS ..... Pediatric Quality of Life Inventory 4.0 Generic Core Scales

PedsQL IS .....Pediatric Quality of Life Infant Scales

PedsQL NMM..... Pediatric Quality of Life 3.0 Neuromuscular Module

RUSP.....Recommended Uniform Screening Panel

SMA..... Spinal muscular atrophy

SMN..... Survival motor neuron (protein)

SMN1..... Survival motor neuron 1 (gene)

SMN2..... Survival motor neuron 2 (gene)

snRNP ..... Small nuclear ribonucleoproteins

CHAPTER 1

INTRODUCTION

Spinal Muscular Atrophy

Spinal Muscular Atrophy (SMA) is the leading genetic cause of mortality in infants with an incidence of approximately one in every eleven thousand livebirths (Kolb et al., 2017; Vaidya & Boes, 2018). SMA is an autosomal recessive disease characterized by alpha motor neuron degeneration in the anterior horn of the spinal cord, skeletal muscle atrophy, and generalized weakness involving the limbs, bulbar and respiratory muscles (Chiriboga et al., 2016; Wirth, Karakaya, Kye, & Mendoza-Ferreira, 2020).

There are five types of SMA that can be historically classified based on age of symptom onset and achieved motor abilities (Rao, Kapp, & Schroth, 2018; Vaidya & Boes, 2018; Wirth et al., 2020). SMA type zero is the most severe and is characterized by symptom onset in utero and death soon after birth. SMA type I, also known as Werdnig-Hoffman disease, is the most common type with symptom onset before six months of age and without substantial treatment, a two-year life expectancy. Individuals with SMA type I typically have severe hypotonia, difficulty breathing, poor suck, and are unable to sit independently (Lunn & Wang, 2008). Individuals with SMA type II typically have onset of symptoms between six to eighteen months of age. They are able to sit without support, although they may not retain this skill, and they are not able to walk, have generalized muscle weakness, and many develop kyphoscoliosis (Lunn & Wang, 2008). SMA type III, also known as Kugelberg-Welander disease, is characterized by the onset of

symptoms after eighteen months of age. Individuals with SMA type III may be able to sit and walk independently, although they may not retain these skills, and many develop scoliosis (Lunn & Wang, 2008). Individuals with SMA type IV have onset of symptoms in adulthood and typically have mild motor impairment and respiratory problems (Lunn & Wang).

Genetic Basis of SMA

SMA is caused by homozygous loss of function mutations in the survival motor neuron one (*SMN1*) gene that encodes the survival motor neuron (SMN) protein (Finkel at al., 2016). The function of the SMN protein is not completely understood; however, its primary role is thought to be in snRNP biogenesis and splicing (Wirth et al., 2020). A similar gene, survival motor neuron two (*SMN2*), has a coding sequence identical to that of the *SMN1* gene, except for five nucleotides (Wirth et al, 2020). Specifically, a C to T substitution within exon seven of *SMN2* (c.840C>T) causes this exon to be spliced out of *SMN2* mRNA transcripts 90% of the time, resulting in an unstable SMN protein that is rapidly degraded instead of the full-length SMN protein. It is estimated that a full-length SMN protein results from *SMN2* approximately 10% of the time as about 10% of *SMN2* mRNA transcripts include exon seven (Helmken et al., 2003; Lefebvre et al., 1995). The number of copies of *SMN2* generally explains the phenotypic variability between the different types of SMA. Approximately 80% of type I individuals have one or two *SMN2* copies, 82% of type II individuals have three copies, and about 50%-61% of individuals with type III and 75% of individuals with type IV have four copies (Calucho et al., 2018; Feldkötter, Schwarzer, Wirth, Weinker, & Wirth, 2002; Wirth et al., 2006). The more copies of *SMN2* an individual has, the more SMN protein they produce. Those with a

small amount of full-length SMN protein typically have more severe symptoms, and those with more full-length SMN protein typically have less severe symptoms (Chiriboga et al., 2016; Feldkötter et al., 2002; Finkel et al., 2016; Mailman et al., 2002; Wirth et al., 2006).

Medical Management for Individuals with SMA

Treatment with Nusinersen

On December 23, 2016 the Food and Drug Administration (FDA) approved nusinersen (Spinraza®) as the first treatment for individuals with all types of SMA (Hoy, 2017). Nusinersen is an antisense oligonucleotide delivered through repeated intrathecal injections (Finkel et al., 2016). Treatment with nusinersen includes three 12mg loading doses given fourteen days apart with a fourth 12mg dose given thirty days after the third loading dose. Continued treatment with nusinersen includes an additional 12mg dose every four months for life (Hoy, 2017). Nusinersen functions by altering the splicing of *SMN2* to promote the inclusion of exon seven in *SMN2* mRNA transcripts, thereby increasing the amount of full-length SMN protein produced (Kolb et al., 2017). Treatment with nusinersen costs approximately $400,000-500,000 in the first year and $250,000-300,000 per year thereafter for the duration of the treated individual's lifetime (Wirth et al., 2020).

In a randomized, double-blind clinical trial (ENDEAR), 122 infants with SMA type I aged 210 days or younger with two *SMN2* copies were treated with 12mg nusinersen or a sham-procedure. Those treated with nusinersen had a lower risk of death and were more likely to reach a motor milestone (i.e., head control, ability to roll, sitting without assistance, and standing) than those who received the sham-procedure. Adverse

reactions reported (i.e., constipation, lower and upper respiratory tract infections) were present for both the group treated with nusinersen and the group given the sham-procedure (Finkel et al., 2017). From this data it was concluded that early treatment with nusinersen may be necessary to maximize response outcomes. In a separate randomized, double-blind clinical trial (CHERISH), 12mg nusinersen or a sham-procedure was given to 126 children with SMA types II and III with onset of symptoms after six months of age. In this study, children treated with nusinersen showed definite motor improvement and higher probability of survival than the children given the sham-procedure (Mercuri et al, 2018a). Individuals who participated in ENDEAR and CHERISH clinical trials were enrolled in an open-label phase III clinical trial designed to evaluate the long-term safety and tolerability of 12mg of nusinersen (SHINE). An interim evaluation of SHINE data showed that treatment with nusinersen is safe and well tolerated (Maharshi & Hasan, 2017; Wirth et al., 2020).

In an open-label clinical trial (NURTURE), 25 infants six weeks or younger with genetically diagnosed presymptomatic SMA and two or three *SMN2* copies were treated with 12mg nusinersen. All of these infants were living, and none needed respiratory intervention after day 64 of treatment. Infants from this trial who were treated with nusinersen but then passed away were found on autopsy to have increased *SMN2* mRNA exon seven inclusion and increased SMN protein in the spinal cord compared to individuals with SMA who did not receive nusinersen (De Vivo et al, 2019; Finkel et al., 2016). Published interim efficacy and safety outcomes from this clinical trial showed that the infants (now children) treated with nusinersen were living past the age of expected symptom onset. Additionally, 100% could sit without support, 92% could walk without

assistance, and 88% could walk independently. From this data it was concluded that treatment with nusinersen as soon as possible after a genetic diagnosis of SMA is established is of extreme importance (De Vivo et al., 2019).

Treatment with Onasemnogene abeparvovec-xioi

On May 24, 2019 the FDA approved onasemnogene abeparvovec-xioi (Zolgensma®) as a second treatment for patients with SMA type I under two years of age (Hoy, 2019). It consists of adeno-associated virus nine, which is modified to include a functional copy of the *SMN1* gene (Hoy, 2019). Introducing a functional copy of the *SMN1* gene into an affected person's motor neuron cells addresses the genetic cause of SMA and increases the amount of SMN protein present in the body (Mendell et al., 2017). The dosing of onasemnogene abeparvovec-xioi is 1.1×10^{14} vector genomes/kg body weight administered over 60 minutes as a single intravenous infusion. Treatment with a single injection of onasemnogene abeparvovec-xioi costs two million US dollars (Wirth et al., 2020).

Fifteen infants with confirmed SMA type I and two copies of *SMN2* under the age of six months were enrolled in a phase I open-label clinical trial (START) where 12 infants were treated with a high dose of onasemnogene abeparvovec-xioi (2.0×10^{14} vector genomes/kg body weight) and three infants were treated with a lower dose (6.7×10^{13} vector genomes/kg body weight). Compared to historical cohorts of untreated infants with SMA, infants in this study treated with onasemnogene abeparvovec-xioi showed improved motor function and improved achievement of motor milestones such as sitting without support, rolling over, feeding orally, speaking, and walking independently. Additionally, it was shown that infants who received the higher dose of onasemnogene

abeparvovec-xioi before three months of age had improved motor function and improved motor milestone achievement earlier than those who also received the higher dose, but not until they were three months of age or older. A side effect observed was that infants' liver transaminase levels were increased significantly, a finding which was hypothesized to be a consequence of a massive immune response against viral peptides; however, this was successfully controlled by daily glucocorticoid administration for one-month post treatment (Mendell et al., 2017). At 24 months follow-up, infants in this study showed a reduced amount of pulmonary interventions, stable or improved swallow function, sustainment of achieved motor function and milestones, and decreased hospitalization rate compared to historical cohorts. It was suggested that the reduction in healthcare utilization observed with onasemnogene abeparvovec-xioi treatment might alleviate patient and caregiver burden and could be associated with an improved quality of life (Al-Zaidy et al., 2019; Shell et al., 2019; Mendell et al., 2019). The long-term follow-up START results are supported by the open-label phase III clinical trial (STR1VE) where 22 infants under the age of six months with SMA type I and one or two copies of *SMN2* were treated with onasemnogene abeparvovec-xioi and found to have rapid improvements in motor function that suggested future improvements in achievement of motor milestones and survival (Shell et al., 2019).

In an open-label phase I dose-escalation clinical trial (STRONG), individuals with SMA type II and three copies of *SMN2* were treated with onasemnogene abeparvovec-xioi. In total, three patients aged ≥6 to <24 months were treated with 6.0 X 10^13 vector genomes/kg body weight onasemnogene abeparvovec-xioi and thirteen patients aged ≥6 to <24 months were treated with 1.2 X 10^14 vector genomes/kg body weight of

onasemnogene abeparvovec-xioi. An additional five patients aged ≥24 to <60 months were treated with 1.2 X 10^14 vector genomes/kg body weight of onasemnogene abeparvovec-xioi. All treated individuals showed a gain in motor milestones achieved (i.e., rolling from back to sides, standing without support, walking without support) and there were no safety or tolerability concerns regarding the onasemnogene abeparvovec-xioi (Finkel et al., 2019).

Finally, in an open-label phase III clinical trial (SPR1NT) individuals with presymptomatic SMA and two or three copies of *SMN2* were treated with onasemnogene abeparvovec-xioi. These presymptomatic individuals showed age-appropriate achievement of motor milestones and motor function after treatment (Schultz et al., 2019).

Nusinersen vs. Onasemnogene abeparvovec-xioi

Dabbous et al. (2019) indirectly compared previously published data about infants with SMA Type I and two copies of *SMN2* treated with nusinersen in the ENDEAR clinical trial to data about infants with SMA Type I and two copies of *SMN2* treated with onasemnogene abeparvovec-xioi in the START clinical trial. Looking at the overall survival for these infants, Dabbous et al. concluded that the likelihood of preventing death was 20% higher for those treated with onasemnogene abeparvovec-xioi. They also concluded that infants treated with onasemnogene abeparvovec-xioi might have more independence from permanent ventilation, improved motor function, and an increase in the number of motor milestones achieved than infants treated with nusinersen. They recommend long-term monitoring of patients treated with onasemnogene abeparvovec-xioi to confirm these conclusions.

Supportive Care

If an individual with SMA is not treated with nusinersen or onasemnogene abeparvovec-xioi, supportive care may be used to manage the clinical course of the disease. Respiratory support involves medications and techniques that mechanically enhance a patient's cough for the clearance of respiratory secretions (Kolb et al., 2017). Additionally, hypoventilation is prevented with devices that increase ventilation during sleep or periods of illness (Kolb et al., 2017). Nutritional support includes interventions to control gastroesophageal reflux, improve digestion, and minimize constipation. For patients with poor suck and swallowing issues, in addition to speech and feeding therapy, the use of a nasogastric tube or surgically placed feeding tube may be necessary (DiVito & Konek, 2010; Mercuri et al., 2018b). Physical therapy, occupational therapy, and bracing are used to prevent and treat contractures and scoliosis. Furthermore, some patients require surgery for internal spinal fixation (Iannaccone, 2007; Mercuri et al., 2018b; Wang et al, 2007).

Quality of Life

Definition

Vaidya and Boes (2018) define quality of life as "an individual's 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" and state it is important to take into account when assessing a patient's overall health. They also define health-related quality of life as "the degree to which a medical condition impacts the physical, emotional, and social well-being of an individual" (Vaidya & Boes, 2018). For the

purpose of this literature review, quality of life and health-related quality of life are used as an interchangeable concept.

Evaluating Quality of Life Within SMA

The two instruments used most frequently in SMA quality of life research are the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL GCS) and the Pediatric Quality of Life 3.0 Neuromuscular Module (PedsQL NMM). Therefore, this review of the present literature excludes studies that evaluate quality of life of children with SMA using other measurement tools. Additionally, because the present study is about the quality of life of children treated with nusinersen, onasemnogene abeparvovec-xioi, both nusinersen and onasemnogene abeparvovec-xioi, or supportive care, studies that evaluate the quality of life of children with SMA treated with other experimental medications are excluded from this literature review. The PedsQL GCS measures health related quality of life in healthy populations and populations where patients have acute or chronic health conditions. It contains questions about physical, emotional, social, and school functioning. The PedsQL NMM measures health related quality of life in patients with neuromuscular diseases. It contains questions about the patient's neuromuscular disease and ability to communicate as well as questions regarding family resources. Both instruments allow for patient self-assessment (PSA) and caregiver proxy-assessment (CPA). Table 1.1 contains information about previous research completed regarding the quality of life of children with SMA that use the PedsQL GCS and/or the PedsQL NMM. These studies consistently show that children with SMA have an impaired quality of life.

Rationale

The quality of life of children with SMA has been investigated previously; however, there is no apparent literature published that directly compares parents' perspectives of the quality of life of their children with SMA who received supportive care, nusinersen, onasemnogene abeparvovec-xioi, and those treated with a combination of both nusinersen and onasemnogene abeparvovec-xioi.

Committee Opinion Number 691, "Carrier Screening for Genetic Conditions", published by the American College of Obstetricians and Gynecologists (ACOG) in conjunction with the addition of SMA to the Recommended Uniform Screening Panel (RUSP), which is used as a guideline for state universal newborn screening programs, is support for the present study. ACOG (2017) recommends the following:

> Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant. In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, *SMN1* deletion testing should be recommended for the low-risk partner. (p. 2)

It is important for genetic counselors, genetic professionals, and other healthcare providers to be knowledgeable regarding parents' perspectives of the quality of life of their children with SMA who have received supportive care, nusinersen, onasemnogene abeparvovec-xioi, and those treated with both nusinersen and onasemnogene abeparvovec-xioi. Knowing how quality of life perspectives differ based on the type of treatment received can help genetics professionals educate parents who are found to be

carriers for SMA and are at risk of having an affected child, or who have a child that has been diagnosed with SMA. Additionally, quality of life research helps to inform about the implications of disease on the patient and the patient's family.

Purpose

The aim of the present study is to directly compare parents' perspectives regarding the quality of life of their children with SMA, both living and deceased, who received or are currently receiving supportive care, nusinersen, onasemnogene abeparvovec-xioi, or treatment with both nusinersen and onasemnogene abeparvovec-xioi. We predict that parents of children with SMA who received or are currently receiving treatment with nusinersen and/or onasemnogene abeparvovec-xioi will score their children's quality of life higher than parents whose children received or are currently receiving only supportive care.

Table 1.1 Previous Research Investigating the Quality of Life of Individuals with SMA

Table adapted from (Landfeldt et al., 2019). Studies that used instruments other than the PedsQL GCS and PedsQL NMM and studies that evaluated experimental medications other than nusinersen and onasemnogene abeparvovec-xioi were excluded.

Authors (Year)	Patient Sample	Instrument(s) (PSA and CPA)	Main Finding(s)
Iannaccone, Hynan & Group, 2003	33 US patients	PedsQL NMM	Patients had impaired quality of life across all instrument domains.
Iannaccone et al., 2009	125 US patients	PedsQL NMM PedsQL GCS	Patients had impaired quality of life across all instrument domains. Agreement between PSAs and CPAs was moderate to poor.
Kaufmann et al., 2012	57 US patients with type II or III	PedsQL GCS	Patients had impaired quality of life across all instrument domains. Instrument scores were markedly different across SMA type.
Kocova, Dvorackova, Vondracek, & Haberlova, 2014	35 Czech patients; 11% type I, 66% type II, and 23% type III	PedsQL NMM	Patients had impaired quality of life across all instrument domains, and lower scores compared with US reference data.
Klug et al., 2016	189 German patients; 6% type I, 39% type II, and 55% type III	PedsQL NMM	Patient quality of life was impaired across all instrument domains and inversely associated with SMA type.
Chiriboga et al, 2016	28 US patients; 54% type II and 46% type III	PedsQL NMM PedsQL GCS	No statistically significant changes in quality of life scores observed for patients given nusinersen.

CHAPTER 2

QUALITY OF LIFE OF CHILDREN WITH SPINAL MUSCULAR ATROPHY: PARENTS' PERSPECTIVES IN LIGHT OF NEW TREATMENTS[1]

[1]Tallas, A. Zvejnieks, D., Brook, S., & Engelstad, K. To be submitted to *Journal of Genetic Counseling.*

Abstract

Purpose: To directly compare parents' perspectives of the quality of life of their children with Spinal Muscular Atrophy (SMA) who received supportive care, nusinersen (Spinraza®), onasemnogene abeparvovec-xioi (Zolgensma®), or both nusinersen and onasemnogene abeparvovec-xioi. Methods: The parents of children with SMA were recruited to complete anonymous online surveys. All surveys included qualitative questions about quality of life. Surveys regarding children in the 1-12-month and 13-24-month age groups included the Pediatric Quality of Life Infant Scales assessment. Surveys regarding children in the 2-4-year age group included the Pediatric Quality of Life Inventory 4.0 Generic Core Scales and the Pediatric Quality of Life 3.0 Neuromuscular Module assessments. The >4-year age group did not include a quantitative quality of life assessment. Results: The 1-12-month age group average physical quality of life summary score was increased for children treated with a combination of both nusinersen and onasemnogene abeparvovec-xioi and also those treated with onasemnogene abeparvovec-xioi only. The 1-12-month- age group average psychosocial quality of life summary score was increased for children treated with nusinersen only. Conclusion: It was not possible to identify and associate a single treatment with conferring a statistically higher quality of life; however, the quantitative and qualitative responses collected allowed for an inference that parents believe their children with SMA have a greater quality of life when provided treatment over having only supportive care. Before the FDA approval of the available treatments, healthcare providers who shared the diagnosis of SMA with parents had to also share that there was no known effective treatment. However, today when families hear the diagnosis of SMA,

they can be hopeful for their child and family's future because of the treatments available and the proven increase in quality of life with these treatments. Knowing how quality of life perspectives differ based on the type of treatment received can help in the education of parents of children with SMA.

Introduction

Spinal Muscular Atrophy (SMA) is the leading genetic cause of mortality in infants (Vaidya & Boes, 2018). SMA is an autosomal recessive disease characterized by spinal cord motor neuron degeneration, skeletal muscle atrophy, and generalized weakness involving the limbs, bulbar, and respiratory muscles (Chiriboga et al, 2016; Wirth et al., 2020). There are five types of SMA that can be historically classified based on age of symptom onset and achieved motor abilities (Rao et al., 2018; Vaidya & Boes, 2018; Wirth et al., 2020).

SMA is caused by homozygous loss of function mutations in the survival motor neuron one (*SMN1*) gene that encodes the survival motor neuron (SMN) protein (Finkel at al., 2016). A similar gene, survival motor neuron two (*SMN2*), has a coding sequence identical to that of the *SMN1* gene, except for five nucleotides (Wirth et al, 2020). Specifically, a C to T substitution within exon seven of *SMN2* (c.840C>T) causes this exon to be spliced out of *SMN2* mRNA transcripts 90% of the time, resulting in an unstable SMN protein that is rapidly degraded instead of the full-length SMN protein. It is estimated that a full-length SMN protein results from *SMN2* approximately 10% of the time as about 10% of *SMN2* mRNA transcripts include exon seven (Helmken et al., 2003; Lefebvre et al., 1995). The number of copies of *SMN2* generally explains the phenotypic variability between the different types of SMA. The more copies of *SMN2* an individual

has, the more SMN protein they produce. Those with a small amount of full-length SMN protein typically have more severe symptoms, and those with more full-length SMN protein typically have less severe symptoms (Chiriboga et al., 2016; Feldkötter et al, 2002; Finkel et al., 2016; Mailman et al, 2002; Wirth et al., 2006).

Treatments for SMA

Nusinersen (Spinraza®) was the first FDA approved treatment for individuals with all types of SMA (Hoy, 2017). Nusinersen is an antisense oligonucleotide delivered through repeated intrathecal injections (Finkel et al., 2016). Treatment with nusinersen includes three 12mg loading doses given fourteen days apart with a fourth 12mg dose given thirty days after the third loading dose. Continued treatment with nusinersen includes an additional 12mg dose every four months for life (Hoy, 2017). Nusinersen functions by altering the splicing of *SMN2* to promote the inclusion of exon seven in *SMN2* mRNA transcripts, thereby increasing the amount of full-length SMN protein produced (Kolb et al., 2017). Treatment with nusinersen costs approximately $400,000-500,000 in the first year and $250,000-300,000 per year thereafter for the duration of the treated individual's lifetime (Wirth et al., 2020).

Onasemnogene abeparvovec-xioi (Zolgensma®) was the second FDA approved treatment for patients with SMA type I under two years of age (Hoy, 2019). It consists of adeno-associated virus nine, which is modified to include a functional copy of the *SMN1* gene (Hoy, 2019). Introducing a functional copy of the *SMN1* gene into an affected person's motor neuron cells addresses the genetic cause of SMA and increases the amount of SMN protein present in the body (Mendell et al., 2017). The dosing of onasemnogene abeparvovec-xioi is 1.1×10^{14} vector genomes/kg body weight

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Dabbous et al. (2019) indirectly compared previously published data about infants with SMA Type I and two copies of *SMN2* treated with nusinersen in the ENDEAR clinical trial to data about infants with SMA Type I and two copies of *SMN2* treated with onasemnogene abeparvovec-xioi in the START clinical trial. Looking at the overall survival for these infants, Dabbous et al. concluded that the likelihood of preventing death was 20% higher for those treated with onasemnogene abeparvovec-xioi. They also concluded that infants treated with onasemnogene abeparvovec-xioi might have more independence from permanent ventilation, improved motor function, and an increase in the number of motor milestones achieved than infants treated with nusinersen. They recommend long-term monitoring of patients treated with onasemnogene abeparvovec-xioi to confirm these conclusions.

If an individual with SMA is not treated with nusinersen or onasemnogene abeparvovec-xioi, supportive care may be used to manage the clinical course of the disease. Respiratory support involves medications and techniques that mechanically enhance a patient's cough for the clearance of respiratory secretions (Kolb et al., 2017). Additionally, hypoventilation is prevented with devices that increase ventilation during sleep or periods of illness (Kolb et al., 2017). Nutritional support includes interventions to control gastroesophageal reflux, improve digestion, and minimize constipation. For patients with poor suck and swallowing issues, in addition to speech and feeding therapy, the use of a nasogastric tube or surgically placed feeding tube may be necessary (DiVito

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Quality of Life

Vaidya and Boes (2018) define quality of life as "an individual's 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" and state it is important to take into account when assessing a patient's overall health. They also define health-related quality of life as "the degree to which a medical condition impacts the physical, emotional, and social well-being of an individual" (Vaidya & Boes, 2018). For the purpose of this study, quality of life and health-related quality of life are used as an interchangeable concept.

The two instruments used most frequently in SMA quality of life research are the PedsQL GCS and the PedsQL NMM. The PedsQL GCS measures health related quality of life in healthy populations and populations where patients have acute or chronic health conditions. The PedsQL NMM measures health related quality of life in patients with neuromuscular diseases. Previous research completed regarding the quality of life of children with SMA using the PedsQL GCS and/or the PedsQL NMM consistently show that children with SMA have an impaired quality of life (Landfeldt et al., 2019).

Rationale

The quality of life of children with SMA has been investigated previously; however, there is no apparent literature published that directly compares parents'

perspectives of the quality of life of their children with SMA who received supportive care, nusinersen, onasemnogene abeparvovec-xioi, and those treated with a combination of both nusinersen and onasemnogene abeparvovec-xioi.

Committee Opinion Number 691, "Carrier Screening for Genetic Conditions", published by the American College of Obstetricians and Gynecologists (ACOG) in conjunction with the addition of SMA to the Recommended Uniform Screening Panel (RUSP), which is used as a guideline for state universal newborn screening programs, is support for the present study. ACOG (2017) recommends the following:

> Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant. In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, *SMN1* deletion testing should be recommended for the low-risk partner. (p. 2)

It is important for genetic counselors, genetic professionals, and other healthcare providers to be knowledgeable regarding parents' perspectives of the quality of life of their children with SMA who have received supportive care, nusinersen, onasemnogene abeparvovec-xioi, and those treated with both nusinersen and onasemnogene abeparvovec-xioi. Knowing how quality of life perspectives differ based on the type of treatment received can help genetics professionals educate parents who are found to be carriers for SMA and are at risk of having an affected child, or who have a child that has been diagnosed with SMA. Additionally, quality of life research helps to inform about the implications of disease on the patient and the patient's family.

Purpose

The aim of the present study is to directly compare parents' perspectives regarding the quality of life of their children with SMA, both living and deceased, who received or are currently receiving supportive care, nusinersen, onasemnogene abeparvovec-xioi, or treatment with both nusinersen and onasemnogene abeparvovec-xioi. We predict that parents of children with SMA who received or are currently receiving treatment with nusinersen and/or onasemnogene abeparvovec-xioi will score their children's quality of life higher than parents whose children received or are currently receiving only supportive care.

Methods

Participants and Recruitment

The aim of this research was to directly compare parents' perspectives regarding the quality of life of their children with SMA. Therefore, participation was limited to the parents of children with SMA. This study included parents of children who were deceased in order to incorporate data from a population whose children might have only received supportive care.

Recruitment for this study was conducted with the aid of the Gwendolyn Strong Foundation (GSF), a non-profit dedicated to advocating for individuals and families with SMA, supporting SMA research, and promoting inclusion for all people living with a disability or genetic condition. The survey used was advertised through social media postings on the GSF Facebook page and stories (https://www.facebook.com/endsma/), Instagram account and stories (https://www.instagram.com/nevergiveuporg/), Twitter account (https://twitter.com/nevergiveuporg), and website (https://nevergiveup.org)

(Appendix A & Figure 2.1). Survey responses were recorded from August 21st, 2019 to September 26th, 2019. To incentivize participation, individuals could enter a raffle to win a $50 Amazon gift card and t-shirt from the GSF. In order to enter the raffle, participants provided their email address that also served as their consent to be contacted if they were selected as the winner. At the end of the survey period, all raffle entries were entered into an online software which randomly selected a winner. To avoid coercion, we did not provide any direct financial or academic compensation for participation in this study.

Participation in this study was voluntary. The survey welcome page detailed the purpose of the study, eligibility requirements, and information addressing informed consent (Appendix B). It was stated that participants could withdraw from the study at any time by not completing all of the survey questions, and that informed consent was provided upon completion of the survey. To establish participant eligibility and for determination of the correct survey for participants to complete, there were several screening questions at the beginning of the survey. Individuals who did not meet participation eligibility were automatically directed to the end of the survey.

A total of 333 individuals attempted to complete the online survey. Thirty-four individuals were excluded because they indicated they were not the parent of a child with SMA. Two hundred ninety-nine individuals indicated that they were the parent of a child with SMA and were directed to the next question. The next question asked participants if their child with SMA was living or deceased in order to direct them to a tense appropriate survey. If participants declined to answer this question, they were not allowed to move forward to complete the survey. There were two participants that declined to answer this question and were manually excluded from the study. An additional two survey responses

were manually excluded because participants completed surveys that were not appropriate for their child's age. Furthermore, six surveys were also excluded because participants did not complete greater than 50% of the quality of life assessment questions that were necessary for the calculation of quality of life scores. Also, 58 incomplete surveys were manually excluded as a completed survey was required for informed consent. In total, 231 survey responses were included in the final analysis. Of the 231 responses, 206 were regarding living children, and 25 were regarding deceased children. The survey exclusion process is summarized in Figure 2.2.

Instrument

Participants completed web-based surveys developed through Qualtrics.comXM. Three quality of life instruments were used in this study. The first two instruments were the PedsQL GCS and the PedsQL NMM (Iannaccone et al., 2009; Varni, Burwinkle, Seid, & Skarr, 2003). They are quality of life instruments that have been validated with SMA populations and are used most frequently in SMA quality of life research (Iannaccone et al., 2009; Landfeldt et al., 2019). The PedsQL GCS contains questions about physical, emotional, social, and school functioning. The PedsQL NMM contains questions about the patient's neuromuscular disease and ability to communicate as well as questions regarding family resources. While both instruments allow for patient self-assessment (PSA) and caregiver proxy-assessment (CPA), they are only validated for individuals over two years of age (Landfeldt et al., 2019). Due to the fact that onasemnogene abeparvovec-xioi is only FDA approved for children under the age of two, it was important that this study included an instrument that measured the quality of life of children under the age of two. As there is no quality of life instrument validated for

children with SMA who are younger than two years old, the third quality of life instrument used in this study was the PedsQL Infant Scales (PedsQL IS) (Varni et al., 2011). The PedsQL IS uses CPAs to measure health related quality of life in healthy infants and infants who have acute or chronic health conditions. It contains questions about physical symptoms and physical, emotional, social, and cognitive functioning.

There were eight separate but similar surveys available for participants to complete (Appendices C-J). All of the surveys contained questions about the child's current age or age when he/she passed away, treatment(s) given, the number of copies of *SMN2* they have/had, etc. Surveys C, D, E, and F, regarding children ≤24 months of age, were created using the PedsQL IS with permission from eProvide. Surveys C and D had a reliability score of 0.894 and surveys E and F had a reliability score of 0.791. Surveys G and H, regarding children in the 2-4-year age group, were created using the PedsQL GCS and PedsQL NMM with permission from eProvide. Surveys I and J, regarding children >4-years of age, did not include a published quality of life instrument because onasemnogene abeparvovec-xioi is only FDA approved for children under the age of two and considering the timing of this study and the approval of onasemnogene abeparvovec-xioi it would be highly unlikely for children in this age group to have received this treatment. Table 2.1 details the instruments used in each survey as well as the intended participants for each survey.

Surveys utilized the appropriate tense for parents whose children were deceased. For example, parents of a child who died would read, "How old was your child when he/she passed away?" instead of reading, "How old is your child?". Skip logic was utilized to ensure participants received surveys that had the appropriate tense and were

for the correct age of their child. Figures 2.3 - 2.6 show how many surveys were taken about children in each age category and the type of treatments the children received.

Data Analysis

Qualtrics.comXM software was used to collect all data. The Scaling and Scoring of the PedsQL published instructions were used in the analysis of the PedsQL IS, PedsQL GCS, and PedsQL NMM instruments with permission from eProvide (Varni, 2017). Microsoft® Excel and Laerd Statistics were used in the analysis of data. Statistical analyses were reported in APA style. Alpha was calculated for scales C, D, E, and F. A grounded theory approach was used to analyze the qualitative data collected from open-ended questions.

Results

Parent Reported Quality of Life of Children Aged 1-12 Months

A one-way Welch ANOVA was conducted to determine if parent proxy scores regarding their children's physical quality of life was different for those in the 1-12-month age group treated with nusinersen, onasemnogene abeparvovec-xioi, both nusinersen and onasemnogene abeparvovec-xioi, or supportive care. Participants were classified into four groups: nusinersen only (n=10), onasemnogene abeparvovec-xioi only (n=12), both nusinersen and onasemnogene abeparvovec-xioi (n=4), and supportive care (n=17). The differences between the physical quality of life scores between these groups were statistically significantly different, Welch's $F(3, 39) = 12.222$, $p < .001$. Visual analysis revealed that the mean physical quality of life summary score increased for children treated with a combination of both nusinersen and onasemnogene abeparvovec-xioi ($M = 69.270$, $SD = 2.604$) and those treated with onasemnogene abeparvovec-xioi

only (*M* =70.937, *SD* = 1.145) compared to children treated with nusinersen only (*M* = 55.671, *SD* = 3.356), and those with supportive care (*M* = 55.458, *SD* = 11.916). The average physical summary scores regarding children aged 1-12-months who received different interventions is shown in Figure 2.7.

A second one-way Welch ANOVA was conducted to determine if parent proxy scores regarding their children's psychosocial quality of life was different for those in the 1-12-month age group treated with nusinersen, onasemnogene abeparvovec-xioi, both nusinersen and onasemnogene abeparvovec-xioi, or supportive care. Participants were classified into four groups: nusinersen only (n=10), onasemnogene abeparvovec-xioi only (n=12), both nusinersen and onasemnogene abeparvovec-xioi (n=4), and supportive care (n=17). The differences between the psychosocial quality of life scores between these groups were statistically significantly different, Welch's $F(3, 39) = 12.163$, $p < .001$. Visual analysis revealed that the mean psychosocial quality of life summary score increased for children treated with nusinersen only (*M* = 87.268, *SD* = 3.285) compared to those treated with onasemnogene abeparvovec-xioi only (*M* = 68.914, *SD* = 9.1333), both nusinersen and onasemnogene abeparvovec-xioi (*M* = 71.701, *SD* = 8.038), and supportive care (*M* = 74.137, *SD* = 7.596). The average psychosocial summary scores regarding children aged 1-12-months who received different interventions is shown in Figure 2.8.

Parent Reported Quality of Life of Children Aged 13-24 Months

A one-way Welch ANOVA was conducted to determine if parent proxy scores regarding their children's physical quality of life was different for those in the 13-24-month age group treated with nusinersen, onasemnogene abeparvovec-xioi, both

nusinersen and onasemnogene abeparvovec-xioi, or supportive care. Participants were classified into four groups: nusinersen only (n=12), onasemnogene abeparvovec-xioi only (n=11), both nusinersen and onasemnogene abeparvovec-xioi (n=11), and supportive care (n=5). The mean physical quality of life summary score increased for children treated with both a combination of nusinersen and onasemnogene abeparvovec-xioi (M = 62.739 , SD = 12.487) and those treated with onasemnogene abeparvovec-xioi only (M = 65.517, SD = 11.982) compared to children treated with nusinersen only (M = 58.492 , SD = 11.299) and those with supportive care (M = 54.444, SD = 9.305); however, the differences between these groups were not statistically significant, Welch's $F(3,35)$ = 1.345 , p = .276. The average physical summary scores regarding children aged 13-24-months who received different interventions is shown in Figure 2.9.

A final one-way Welch ANOVA was conducted to determine if parent proxy scores regarding their children's psychosocial quality of life was different for those in the 13-24-month age group treated with nusinersen, onasemnogene abeparvovec-xioi, both nusinersen and onasemnogene abeparvovec-xioi, or supportive care. Participants were classified into four groups: nusinersen only (n=12), onasemnogene abeparvovec-xioi only (n=11), both nusinersen and onasemnogene abeparvovec-xioi (n=11), and supportive care (n=5). The differences between the average psychosocial quality of life summary scores for children treated with nusinersen only (M = 68.773, SD = 7.261), onasemnogene abeparvovec-xioi only (M = 75.722, SD = 8.477), both nusinersen and onasemnogene abeparvovec-xioi (M = 73.512, SD = 8.504), and supportive care (M = 71.076, SD = 12.897) were not statistically significant, Welch's $F(3, 35) = 1.309$, p = .287. The average

psychosocial summary scores regarding children aged 13-24-months who received different interventions is shown in Figure 2.10.

Parent Reported Quality of Life of Children Aged 2-4 Years

Of the 28 surveys taken about children with SMA in the 2-4-year age group, 26 were regarding children who received only nusinersen, one was about a child who received onasemnogene abeparvovec-xioi only, and one was about a child who received both nusinersen and onasemnogene abeparvovec-xioi. To eliminate the possibility of identifying the one child who received onasemnogene abeparvovec-xioi only and the other child who received both nusinersen and onasemnogene abeparvovec-xioi, all quality of life data regarding children in the 2-4-year age group was not analyzed and is not reported.

Parent Reported Quality of Life of Children Aged >4 Years

Of the 121 surveys taken about children with SMA in the >4-year age group, 22 were regarding children who received supportive care, 98 were about children who received nusinersen, and one was about a child who received onasemnogene abeparvovec-xioi only. To eliminate the possibility of identifying the one child in this age group who received onasemnogene abeparvovec-xioi only, the survey about this child was excluded from the data analysis. Qualitative quality of life responses regarding the 22 children who received supportive care and the 98 children who received nusinersen were analyzed.

Qualitative Quality of Life Responses

In each survey parents were provided the opportunity to answer a free response question and provide information about their children's quality of life, the treatments, etc.

Listed below are a few quotes from parents regarding the quality of life of their children who received supportive care.

1. *"He was unable to nurse after birth and a g-tube was placed shortly after. He was excellent at following movements with his eyes, but shortly after birth lost his moro reflex. He would cry if he had been held too long. He used his accessory muscles to help breathe from birth and at 12 weeks had his first collapsed lung."*
2. *"SMA took its natural course as far as progression goes. Despite following dietary and respiratory protocols, she needed to be trached and lost all movement."*
3. *"My son passed away almost twelve years ago at nine months old. He was diagnosed at six months old with SMA Type 1. His diagnosis was devastating. The team of doctors at [hospital] said that he was showing symptoms for one of two illnesses: Botulism or SMA. The same week he was treated for botulism and we were told that if he were diagnosed with SMA, it would be unlikely for him to reach his first birthday. I didn't research the disease for those excruciating five weeks while we waited for diagnosis results. I believed I saw improvement with the help of physical therapy. Then we were given the grim diagnosis, no treatment. No options. We were sent home, we loved on sweet little [name] in big ways those next three months. Pneumonia became a chronic illness for him, and we were placed on hospice and palliative care as patients on the pediatric floor for just shy of three months. My son's brave spirit and joy he shared with those who knew him are forever cherished. Families today have hope with this diagnosis. They have choices and options to improve their children's quality of*

life and life expectancy. What a gift this research has been. From the bottom of my heart, thank you."

4. *"There was no treatment available. Doctors told us we had six months with her [and we should] take her home and love her. Regarding our genetic counseling experience, frankly, it was worthless. My daughter attended the session and there absolutely zero information gained from the appointment. It was a waste of time and very disappointing. Thank you for your efforts in trying to improve this area."*

Listed below are a few quotes from parents regarding the quality of life of their children who received nusinersen (Spinraza®).

5. *"Our child's natural disposition seems to be happy, social, [and] determined. Coupled with treatment, it has helped us all stay positive."*
6. *"[Name] has an excellent quality of life. [He] is a very positive child who loves life, has many friends, and truly believes he can do everything."*
7. *"My child has a wonderful quality of life and is one of the happiest persons I know."*
8. *"As parents, we can see improvement in his hands and arms after 4 doses."*
9. *"[Name's] quality of life has improved w[ith] Spinraza. He is able to sit up in his chair longer and breathes better. He is also able to hold things in his hands, move his legs, and move his head from side to side. He definitely tells us he feels like he has more energy since starting Spinraza."*
10. *"Before Spinraza we were in hospital a lot. Started Spinraza at 29 months and he's now 48 months old. Since 29 months of age, we have had only two hospital*

admissions lasting 1-2 days each, compared to two-week admissions before Spinraza. He has shown mostly respiratory improvements."

11. *"He has had 10 doses of Spinraza, and it has helped with lung function. Before Spinraza cough sessions would take 2+ hours, now they only take 20 minutes!"*
12. *"My child's quality of life has improved since starting Spinraza treatments. Her stamina has improved, her voice is louder, her hand now has the stamina and strength to play independently on her iPad for hours."*
13. *"[Name] has been taking Spinraza for [a] year and a half. Although it may seem like small gains, his voice is louder, his enunciation is better, he has a productive cough, he has more stamina and is better able to drive his power chair. There are many other feats that have improved as well."*
14. *"Not having accessible transportation makes it difficult for us. She can't be an active member of our community."*
15. *"Mobility, accessibility and acceptance are my biggest fears for [name]."*
16. *"With age I fear the lack of inclusiveness around her might not make her feel as content as she now."*
17. *"Dealing with her disease has been life-altering in every aspect I can think of. It has been incredibly and profoundly difficult and has changed our family in ways that are difficult to explain. [Name] has lived an incredible life...we have found ways around her disability every opportunity we can. It is also been very isolating. I feel that despite her physical limitations, she has lived a very happy and amazing life."*

18. *"[Name] is a very energetic 5-year-old boy who loves everything about life. Hates when people treat him like he is disabled! Loves aqua therapy, horses, dinosaurs, [and] most of all playing soccer with his brother. Since starting Spinraza [name] has been able to lift his legs off of the bed to do 'kissing knees' and has a new goal to be able to ride a bike very soon."*

Listed below are a few quotes from parents regarding the quality of life of their children who received onasemnogene abeparvovec-xioi (Zolgensma®).

19. *"Our child has maxed out the Chop-intend at 3 months of age and has met all milestones so far, some even early. She is able to sit unassisted briefly and roll in both directions. She is also able to pull herself toward objects. The only indication of SMA symptoms presenting this far is slight aspiration on formula if rice cereal is not added. She received treatment at 3 months old."*
20. *"[Name] was treated with Zolgensma 7 days ago! We are already seeing new strength in him!"*
21. *"He has an amazing quality of life. We keep him involved with anything an able-bodied person would do, just modified."*

Listed below are a few quotes from parents regarding the quality of life of their children who received both nusinersen (Spinraza®) and onasemnogene abeparvovec-xioi (Zolgensma®).

22. *"The treatments have been amazing for my child."*
23. *"Has made some movement gains."*

24. *"Since starting Spinraza in April and then receiving Zolgensma in July, my son is improving rapidly. He gained back the skills he lost and is now even starting to stand with his braces/support."*

Discussion

In this study we set out to directly compare parents' perspectives regarding the quality of life of their children with SMA, both living and deceased, who received or are currently receiving supportive care, nusinersen, onasemnogene abeparvovec-xioi, or treatment with both nusinersen and onasemnogene abeparvovec-xioi. While the quality of life of children with SMA has been investigated previously, there is no apparent literature published that directly compares parents' perspectives of the quality of life of their children with SMA who have received these interventions. We predicted that parents of children with SMA who received or are currently receiving treatment with nusinersen and/or onasemnogene abeparvovec-xioi would score their children's quality of life higher than parents whose children received or are currently receiving only supportive care. Considering the present data, it is not possible to identify and associate a single treatment with conferring a statistically higher quality of life; however, the quantitative and qualitative responses collected allow for an inference that parents believe their children with SMA have a greater quality of life when provided treatment over having only supportive care.

Physical Quality of Life

The physical quality of life summary scores regarding children in the 1-12-month and 13-24-month age groups were an average of parents' answers to questions about their children's physical symptoms and physical functioning. In the 1-12-month age group

physical summary scores were increased, indicating greater quality of life, for children treated solely with onasemnogene abeparvovec-xioi and for children treated with both nusinersen and onasemnogene abeparvovec-xioi. Interestingly, while clinical trials have proven the effectiveness of nusinersen on improving physical functioning and motor abilities, children in this age group treated with nusinersen received low physical quality of life summary scores that were equivalent to the scores regarding children who received supportive care. Furthermore, while the differences between the physical quality of life summary scores regarding children in the 13-24-month age group were not statistically significant, it is important to note that for children in this age group, physical quality of life scores followed the same pattern recorded for the 1-12-month age group (increased for those treated with solely onasemnogene abeparvovec-xioi and also those treated with both nusinersen and onasemnogene abeparvovec-xioi and low for children treated with nusinersen and supportive care).

Considering these results, it may be that parents of children treated with nusinersen in the 1-12-month and 13-24-month age groups were thinking about their children's adverse reactions to the treatment when completing the quality of life assessment. Finkel et al. (2017) observed adverse reactions such as constipation and respiratory tract infections in both patients treated with nusinersen and those given a sham-procedure. Furthermore, parents of children treated with nusinersen in the 1-12-month and 13-24-month age groups may believe their children have a lower physical quality of life because of the repeated intrathecal injections required in the administration of this treatment. It is important to consider that children treated with nusinersen in these age groups would either be in their first year or would have just finished their first year of

treatment that involves the highest number of intrathecal injections (three 12mg loading doses given fourteen days apart, a fourth 12mg dose given thirty days after the third loading dose, and continued treatment with a 12mg dose every four months). The repeated intrathecal injections may also be the reason why parents of children in these age groups treated with both nusinersen and onasemnogene abeparvovec-xioi scored their children's physical quality of life slightly lower than those treated with only onasemnogene abeparvovec-xioi, which does not involve any intrathecal injections.

The qualitative responses from parents of children in the 1-12-month and 13-24-month age groups treated with nusinersen are uninformative in terms of physical quality of life as participants detailed their children's diagnosis stories, their efforts for onasemnogene abeparvovec-xioi to be covered by their children's insurance, and their appreciation for this study giving attention to the SMA community. The qualitative responses from parents of children in the >4-year age group treated with nusinersen however contradict the low physical quality of life scores recorded in the 1-12-month and 13-24-month age groups. Many parents of children in the >4-year age group shared that since their children started nusinersen they had seen improvements in respiratory function, motor abilities, and energy. Several participants also commented on a decrease in the amount and length of hospitalizations their children had since starting nusinersen. Al-Zaidy et al (2019) hypothesized that decreased hospitalizations of patients treated with onasemnogene abeparvovec-xioi was associated with an alleviation of patient and caregiver burden and could be associated with an improved quality of life, therefore we hypothesize that decreased hospitalizations of children treated with nusinersen might also be associated with an alleviation of patient and caregiver burden and could also be

associated with an improved quality of life. The low physical quality of life scores regarding children in the 1-12-month and 13-24-month age group and the lack of qualitative responses regarding physical quality of life for these children leave us with the hypothesis that the intrathecal injections necessary in the first year of treatment with nusinersen is a large contributing factor in parents' perspectives of their children's physical quality of life.

Psychosocial Quality of Life

The psychosocial quality of life summary scores regarding children in the 1-12-month and 13-24-month age group were an average of parents' answers to questions about their children's social, emotional, and cognitive functioning. Differences between psychosocial summary scores regarding children in the 1-12-month age group were statistically significant. Those treated solely with nusinersen had increased scores, indicating greater quality of life, compared to those that received onasemnogene abeparvovec-xioi only, both nusinersen and onasemnogene abeparvovec-xioi, and supportive care. The differences between psychosocial summary scores regarding children in the 13-24-month age group were not statistically significant and showed no recognizable pattern.

At the time the survey became available to participants, onasemnogene abeparvovec-xioi only had FDA approval for 3 months, compared to nusinersen that had FDA approval for 32 months. Considering this difference, it is possible that parents of children treated with onasemnogene abeparvovec-xioi had only seen an initial physical improvement, because the treatment functions to directly increase the amount of SMN protein in the body, and they might not have seen a psychosocial improvement yet at the

time they completed the survey as psychosocial improvement may be related to one's ability to move and interact in the community and environment. This theory is supported by the result that children treated with both nusinersen and onasemnogene abeparvovec-xioi had slightly higher psychosocial quality of life scores compared to those that received onasemnogene abeparvovec-xioi only.

It is important to note that two parent participants in the 1-12-month age group whose children received onasemnogene abeparvovec-xioi provided feedback that the quality of life assessment was difficult to complete. One parent stated that their child was young at one month and three weeks of age, so some of the assessment items were not applicable for them. They also stated that they did not realize they could skip questions and attempted to go backwards in the survey to deselect items but were unable to. The other parent stated that their child was six weeks old and received onasemnogene abeparvovec-xioi at four weeks of age, so they believed some of the questions did not apply to their child. After a review of the quality of life assessment these parents took, we conclude that the questions that contribute the physical quality of life summary scores apply equally to all children in the 1-12-month age group regardless of if they are 1 month or 12 months in age. Interestingly, we conclude that the questions that contribute to the psychosocial quality of life summary scores do not apply equally to children that are 1 month of age the same way that they apply to children that are 12 months of age. We believe these two parents of children treated with onasemnogene abeparvovec-xioi most likely scored their children lower on the psychosocial questions by indicating that their children have trouble completing skills that they might not be expected to achieve yet when considering their age and typical development (i.e. making eye contact,

laughing, not imitating caregiver's facial expressions and actions, etc.). Furthermore, it is possible that other parents participating in this study had this experience but did not provide feedback about it.

The Phrase "No Treatment" and Genetic Counseling

Nusinersen and onasemnogene abeparvovec-xioi were approved by the FDA as the first two treatments for SMA in 2016 and 2019 respectively. Before these treatments were available, individuals with SMA were provided supportive care for the management of disease progression and symptoms. Several parents of children who received supportive care shared about their heartbreak learning of the terminal diagnosis with no treatment, the natural disease progression SMA had on their child, and the fact that parents today are able to have hope because of the new treatments available. An example of one of these quotes from a parent whose child was in the 1-12-month age group is provided here:

> *My son passed away almost twelve years ago at nine months old. He was diagnosed at six months old with SMA Type 1. His diagnosis was devastating. The team of doctors at [hospital] said that he was showing symptoms for one of two illnesses: Botulism or SMA. The same week he was treated for botulism and we were told that if he were diagnosed with SMA, it would be unlikely for him to reach his first birthday. I didn't research the disease for those excruciating five weeks while we waited for diagnosis results. I believed I saw improvement with the help of physical therapy. Then we were given the grim diagnosis, no treatment. No options. We were sent home, we loved on sweet little [name] in big ways those next three months. Pneumonia became a chronic illness for him, and*

> *we were placed on hospice and palliative care as patients on the pediatric floor for just shy of three months. My son's brave spirit and joy he shared with those who knew him are forever cherished. Families today have hope with this diagnosis. They have choices and options to improve their children's quality of life and life expectancy.*

While the surveys available to take in this study did not include any questions regarding parents' genetic counseling experiences, one parent commented on the disappointing experience their family had:

> *"There was no treatment available. Doctors told us we had six months with her [and we should] take her home and love her. Regarding our genetic counseling experience, frankly, it was worthless. My daughter attended the session and there absolutely zero information gained from the appointment. It was a waste of time and very disappointing."*

Before the FDA approval of nusinersen and onasemnogene abeparvovec-xioi, genetic counselors, genetic professionals, and other healthcare providers who shared the diagnosis of SMA with parents had to also share about the natural history of the disease and that there was no known effective treatment. Yang et al. (2016) interviewed parents of children with SMA type I and II who received supportive care before FDA's approval of nusinersen and onasemnogene abeparvovec-xioi to learn their experiences with anticipatory loss. From these interviews it was found that parents of children with SMA felt completely helpless because there was no known effective treatment; however, they also felt pressure to provide their children the best care possible. They also learned that parents initially seized every opportunity for exploratory treatments to extend their

children's lives, however, as treatments consistently failed, they decided to spend more time cherishing their children's brief lives using supportive care. However, today when families hear the diagnosis of SMA, they will no longer be told that there is nothing they can do and that they should take their children home and love them. Now, when a family hears a diagnosis of SMA, they can be hopeful for their child and family's future because of the treatments available and the proven increase in quality of life with these treatments. It is important for genetic counselors, genetic professionals, and other healthcare providers to be knowledgeable about parents' perspectives of the quality of life of their children with SMA who have received the various treatments because knowing how quality of life perspectives differ based on the type of treatment received can help them educate parents who are found to be carriers for SMA and are at risk of having an affected child, or who have a child that has been diagnosed with SMA. Data collected in this study undoubtedly helps inform about parents' perspectives of the quality of life of their children with SMA who have received the various treatments.

Limitations and Future research

Due to the fact that onasemnogene abeparvovec-xioi is only FDA approved for children under the age of two, it was important that this study included an instrument that measured the quality of life of children in this age group, therefore the PedsQL IS was utilized. A limitation of this study is that the PedsQL IS assessment has not been used in SMA populations before, therefore we are not able to make a comparison of the data collected in this study using this assessment to previously published studies. An additional limitation of this study is that participants were only able to change, but not deselect items in the quantitative quality of life assessments. This technical issue is

important, because the questions in the PedsQL IS that contributed to the psychosocial quality of life summary scores do not apply equally to children that are 1 month of age the same way that they apply to children that are 12 months of age. We believe that at least two parents of children in the 1-12-month age group treated with onasemnogene abeparvovec-xioi scored their children lower on the psychosocial questions by indicating that their children have trouble completing skills that they might not be expected to achieve yet when considering their age and typical development (i.e. making eye contact, laughing, not imitating caregiver's facial expressions and actions, etc.). Another limitation of this study is that data regarding the 2-4-year age group, which used the PedsQL GCS and PedsQL NMM assessments previously used in SMA quality of life research, was excluded to eliminate the possibility of identifying participants and therefore comparisons to previously published quality of life data using these assessments could not be made. Another limitation of this study is that within the data that was statistically significant (the 1-12-month age group) there was a small sample size with ten parents whose children had nusinersen only, twelve parents whose children had onasemnogene abeparvovec-xioi only, four parents whose children had both nusinersen and onasemnogene abeparvovec-xioi, and seventeen parents whose children had supportive care. A greater sample size may have allowed for more robust data from the 1-12-month age group and statistically significant data from the 13-24-month age group and may have also allowed for inclusion of the data from the 2-4-year age group. Additionally, the free response qualitative quality of life question in each survey was too vague. If we included more specific qualitative quality of life questions such as, "please describe your child's physical quality of life" and "please describe your child's

psychosocial quality of life", we may have received more detailed information from parents about their children's quality of life. Furthermore, the quality of life of children without SMA was not assessed as a control group, therefore, the quality of life of children with SMA that received the various treatments could not be compared to the quality of life of unaffected, healthy children. Finally, although the aim of this study was to learn and directly compare parents' perspectives of their children's quality of life considering the various treatments, it is important to note that parents' perceptions may be different from their children's perceptions of their own quality of life as the affected individuals.

This study undoubtedly contributes to our knowledge of parents' perspectives of the quality of life of their children with SMA who have received the various interventions available. It also provides information about how quality of life perspectives differ based on the type of intervention received. Because the PedsQL IS assessment used in this study has not been used in SMA populations previously, we recommend this study be repeated with a larger sample size to 1) determine if this is an appropriate quality of life assessment for children with SMA and 2) provide replication data to compare with the data we collected. We suggest this larger follow-up study be conducted in approximately five years to allow for more time between when onasemnogene abeparvovec-xioi was approved by the FDA and data collection. Also, as SMA is considered a progressive disease, tracking how parent perspectives of their children's quality of life changes over time with the various treatments available may be informative. Finally, as more individuals are diagnosed and treated for SMA, it may be beneficial to investigate genetic

counselors', genetic professionals', and other health care providers' comfortability discussing the treatments and quality of life information with parents.

Conclusion

The purpose of this study was to directly compare parents' perspectives of the quality of life of their children with SMA who received supportive care, nusinersen, onasemnogene abeparvovec-xioi, or both nusinersen and onasemnogene abeparvovec-xioi. While the quality of life of children with SMA has been investigated previously, there is no apparent literature published that directly compares parents' perspectives of the quality of life of their children with SMA who have received these interventions. We predicted that parents of children with SMA who received or are currently receiving treatment with nusinersen and/or onasemnogene abeparvovec-xioi would score their children's quality of life higher than parents whose children received or are currently receiving only supportive care. Considering the present data, it was not possible to identify and associate a single treatment with conferring a statistically higher quality of life; however, the quantitative and qualitative responses collected allowed for an inference that parents believe their children with SMA have a greater quality of life when provided treatment over having only supportive care. Before the FDA approval of nusinersen and onasemnogene abeparvovec-xioi, genetic counselors, genetic professionals, and other healthcare providers who shared the diagnosis of SMA with parents had to also share that there was no known effective treatment. However, today when families hear the diagnosis of SMA, they can be hopeful for their child and family's future because of the treatments available and the proven increase in quality of life with these treatments. Knowing how quality of life perspectives differ based on the type of

treatment received can help in the education of parents who are found to be carriers for SMA and are at risk of having an affected child, or who have a child that has been diagnosed with SMA.

Table 2.1 Surveys Available for Participants to Take in the Present Study
The survey each participant took was dependent on if their child was living or deceased and the current age of their child or the child's age at death.

Survey	Child with SMA Living or Deceased	Current Age of Child or Age at Death	Instrument(s) (CPAs)
D	Living	1-12 Months	PedsQL IS
E	Deceased	1-12 Months	PedsQL IS
F	Living	13-24 Months	PedsQL IS
G	Deceased	13-24 Months	PedsQL IS
H	Living	2-4 Years	PedsQL GCS PedsQL NMM
I	Deceased	2-4 Years	PedsQL GCS PedsQL NMM
J	Living	Older than 4 Years	None
K	Deceased	Older than 4 Years	None

Figure 2.1 Participant Recruitment Social Media Image
This image was used in the social media post that recruited study participants.

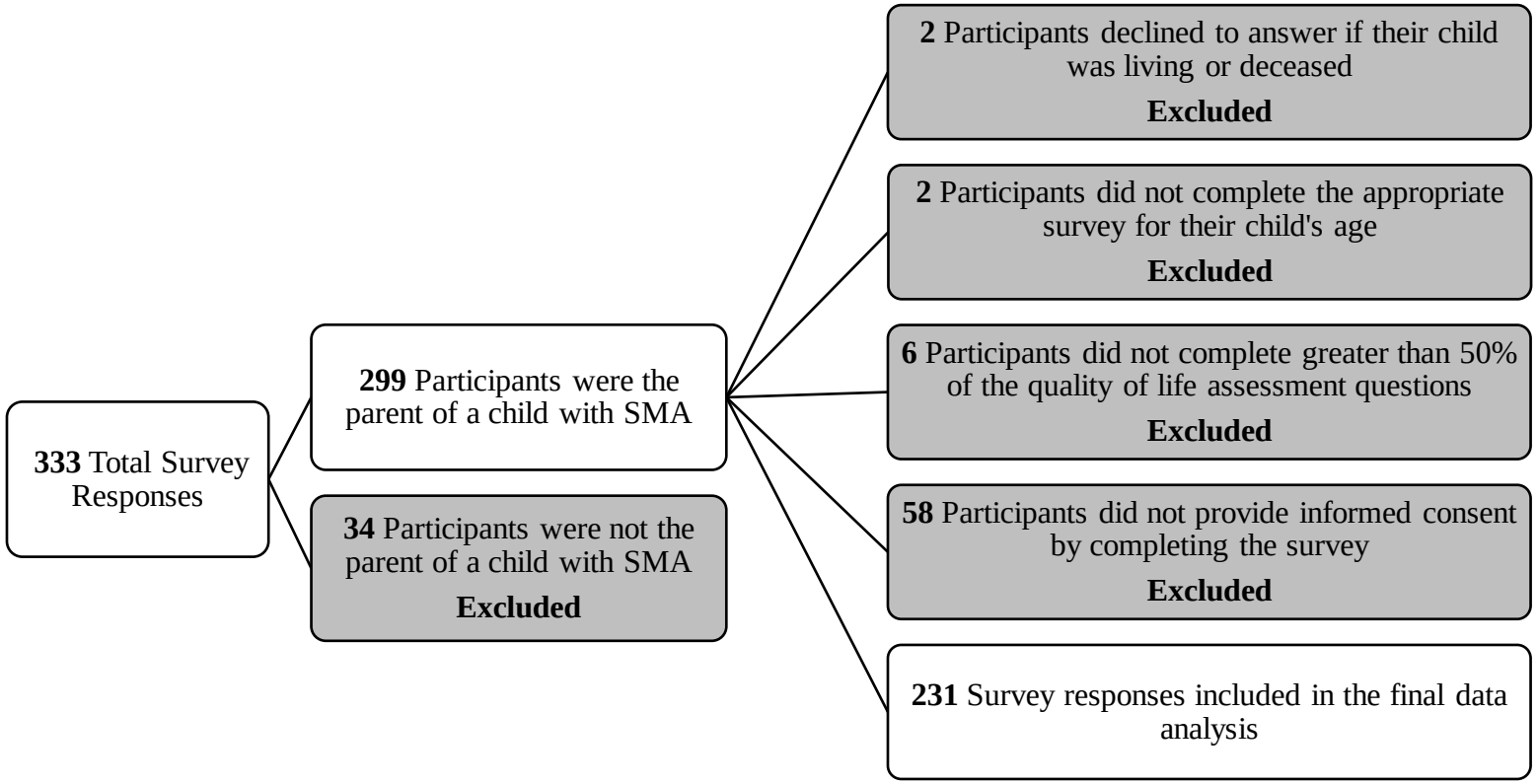

Figure 2.2 Survey Exclusion Process
Out of 333 total survey responses, 231 met the inclusion criteria and were included in the final data analysis.

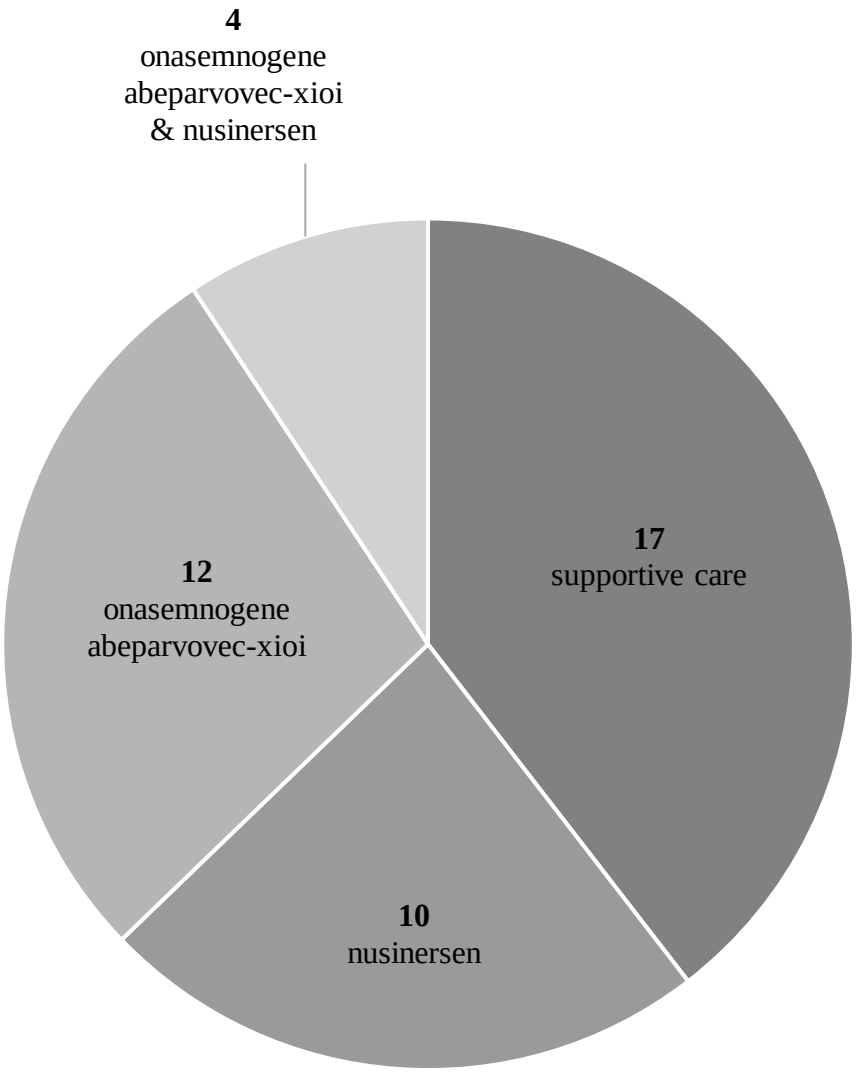

Figure 2.3 Interventions Received by Children with SMA Aged 1-12 Months
In total, 43 of the 231 surveys included in the final data analysis regarded children who were living and 1-12 months in age or deceased at 1-12 months of age.

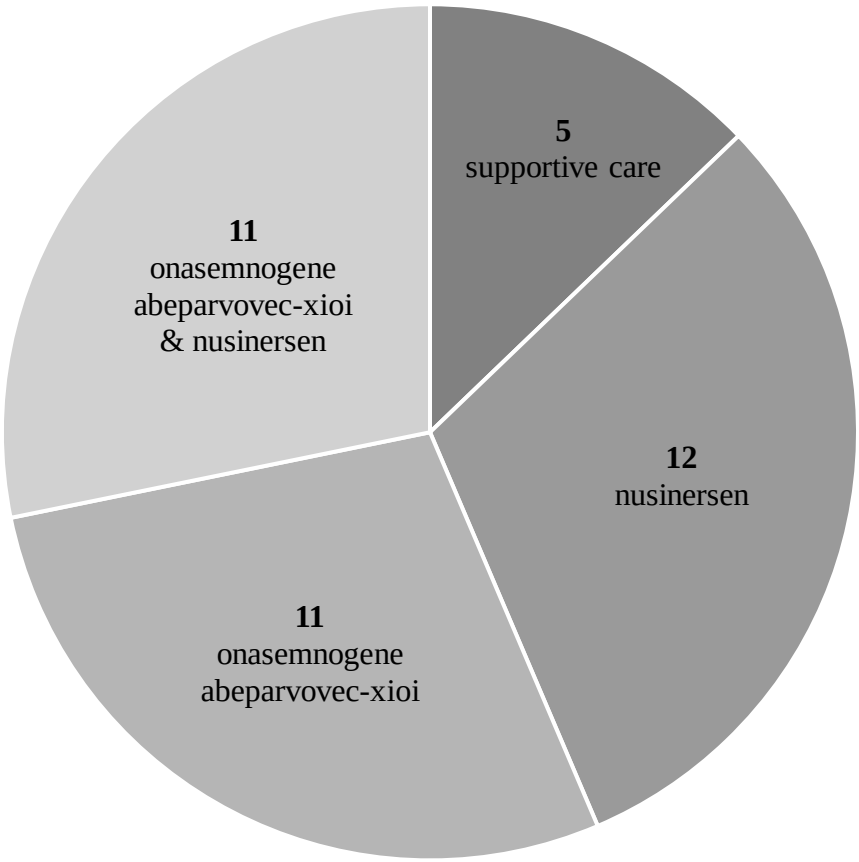

Figure 2.4 Interventions Received by Children with SMA Aged 13-24 Months
In total, 39 of the 231 surveys included in the final data analysis regarded children who were living and 13-24 months in age or deceased at 13-24 months of age.

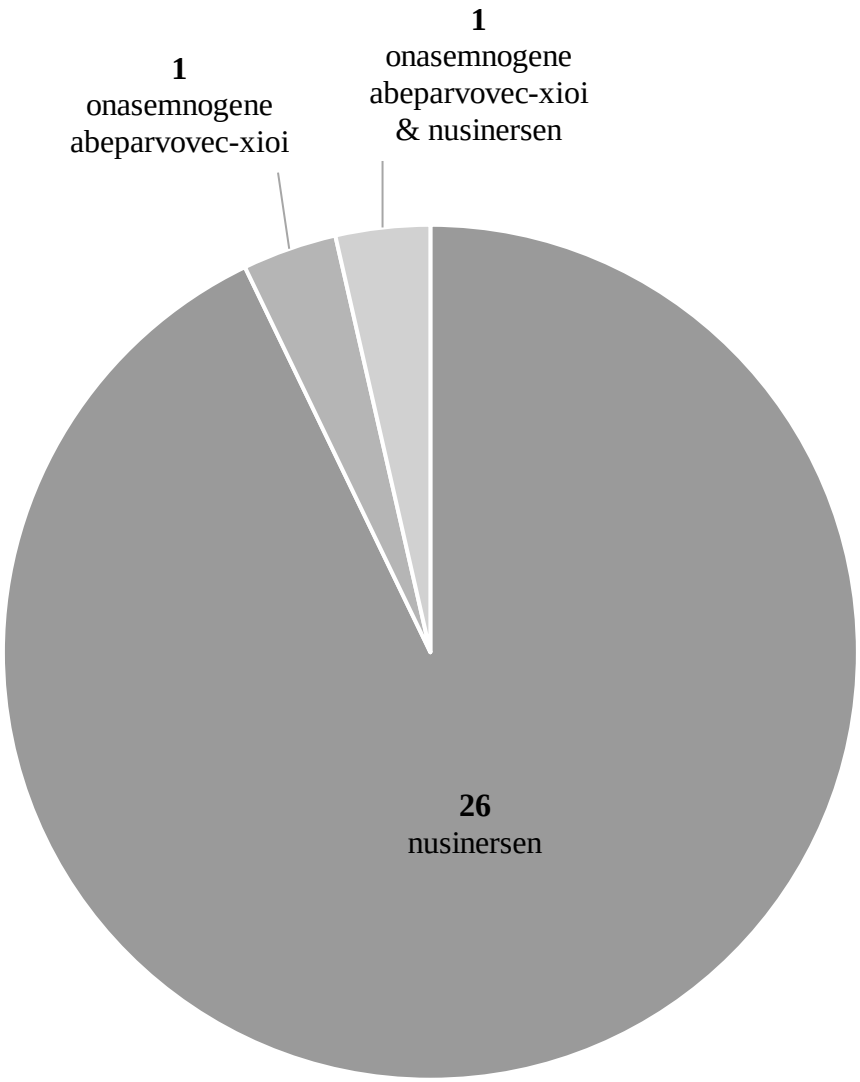

Figure 2.5 Interventions Received by Children with SMA Aged 2-4 Years
In total, 28 of the 231 surveys included in the final data analysis regarded children who were living and 2-4 years in age or deceased at 2-4 years of age.

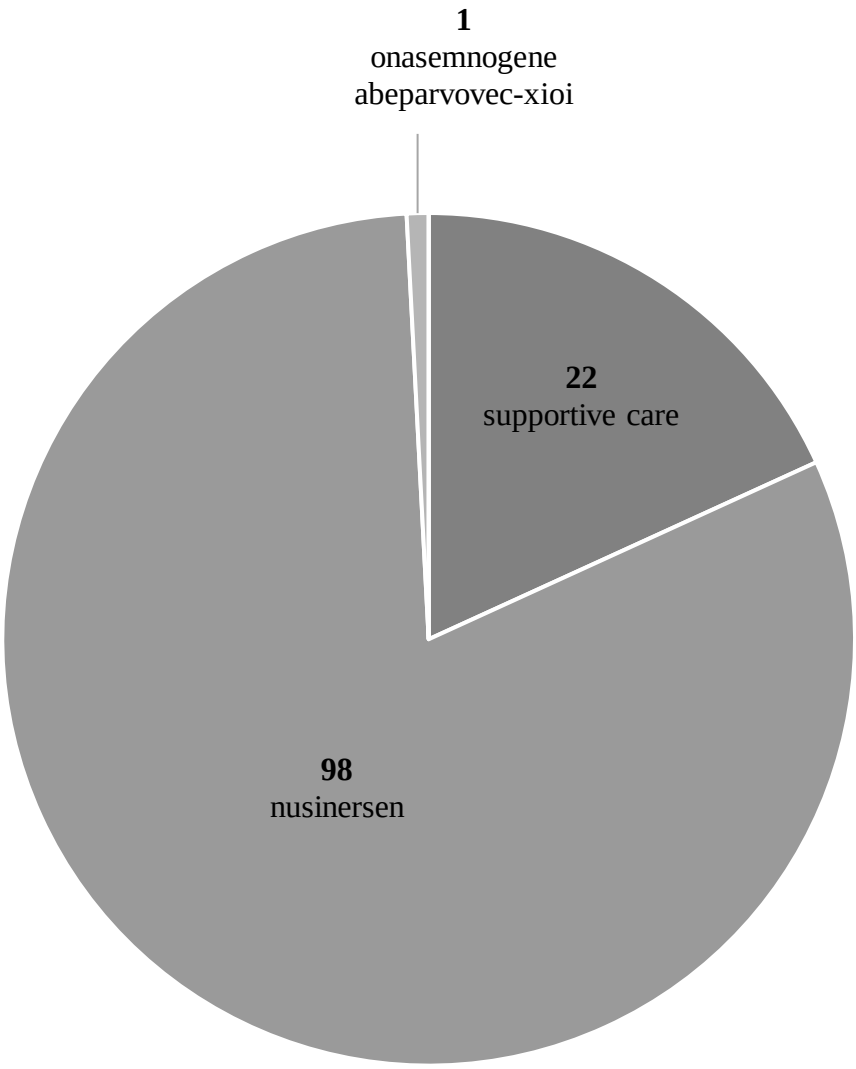

Figure 2.6 Interventions Received by Children with SMA Aged >4 years
In total, 121 of the 231 surveys included in the final data analysis regarded children who were living and >4 years in age or deceased at >4 years of age.

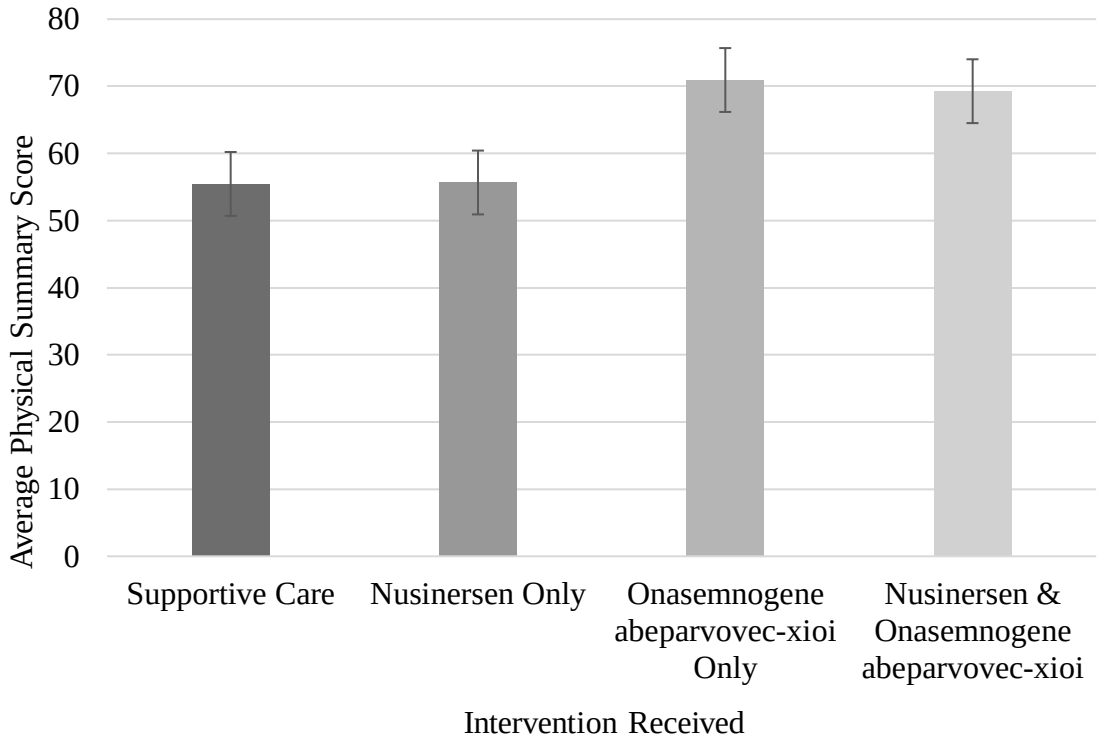

Figure 2.7 Average Physical Summary Scores Regarding Children with SMA Aged 1-12 Months

The average physical quality of life summary score increased for children treated with both nusinersen and onasemnogene abeparvovec-xioi and those treated with onasemnogene abeparvovec-xioi only compared to children treated with nusinersen only and those with supportive care.

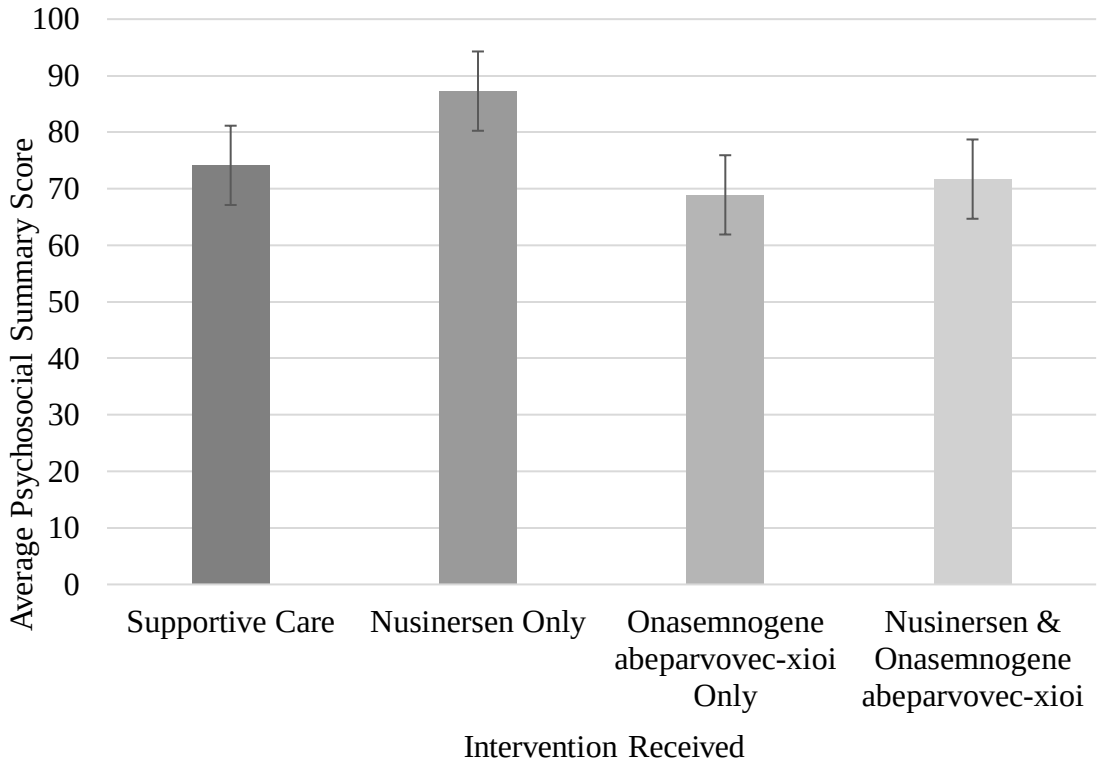

Figure 2.8 Average Psychosocial Summary Scores Regarding Children with SMA Aged 1-12 Months

The average psychosocial quality of life summary score increased for children treated with nusinersen only compared to those treated with onasemnogene abeparvovec-xioi only, both nusinersen and onasemnogene abeparvovec-xioi, or supportive care.

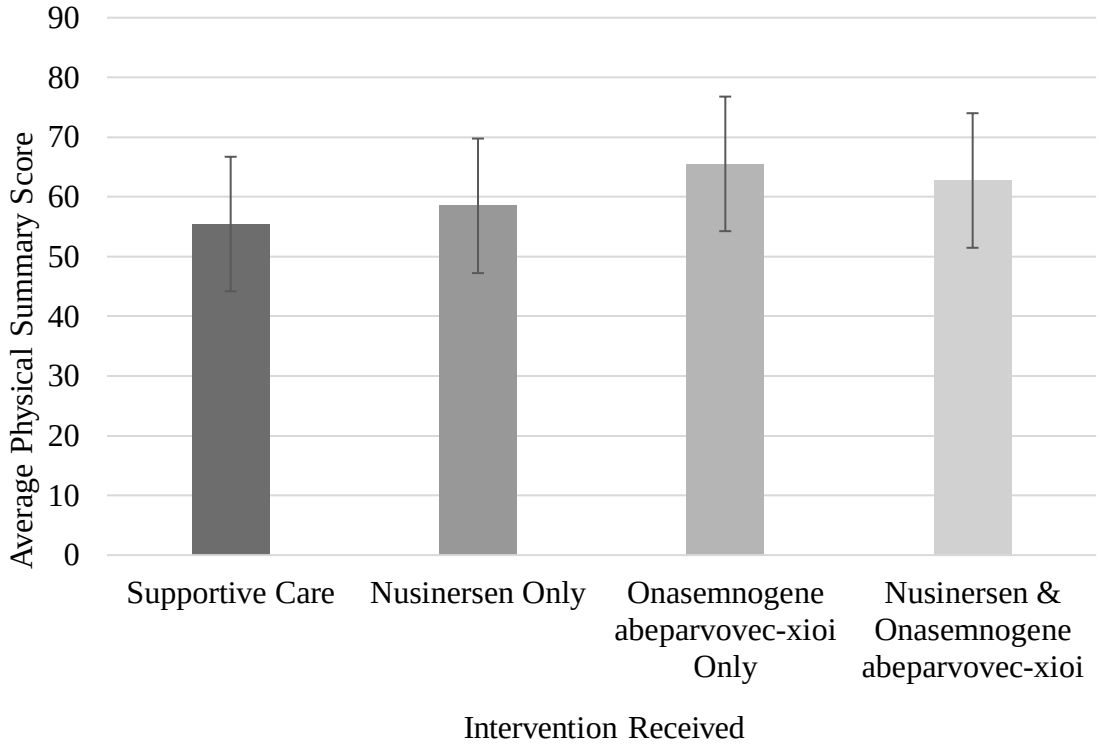

Figure 2.9 Average Physical Summary Scores Regarding Children with SMA Aged 13-24 Months

The differences between the average physical quality of life summary scores for children treated with nusinersen only, onasemnogene abeparvovec-xioi only, both nusinersen and onasemnogene abeparvovec-xioi, and supportive care was not statistically significant.

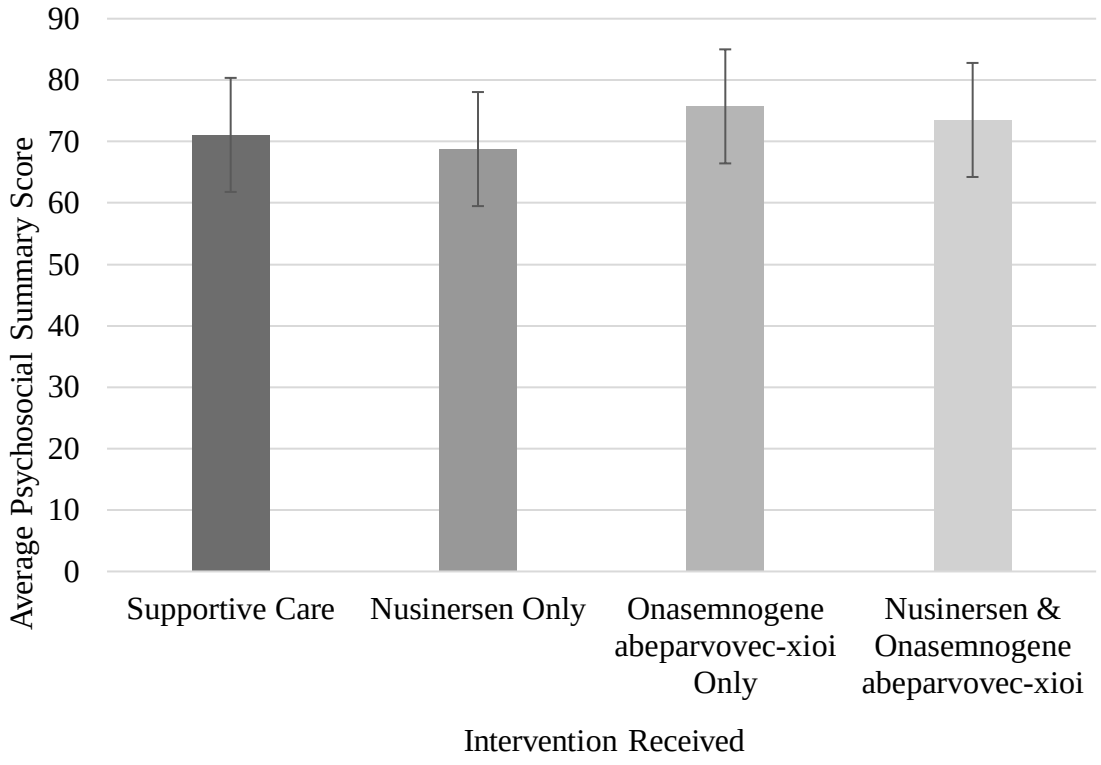

Figure 2.10 Average Psychosocial Summary Scores Regarding Children with SMA Aged 13-24 Months

The differences between the average psychosocial quality of life summary scores for children treated with nusinersen only, onasemnogene abeparvovec-xioi only, both nusinersen and onasemnogene abeparvovec-xioi, and supportive care was not statistically significant.

CHAPTER 3

CONCLUSIONS

The purpose of this study was to directly compare parents' perspectives of the quality of life of their children with SMA who received supportive care, nusinersen, onasemnogene abeparvovec-xioi, or both nusinersen and onasemnogene abeparvovec-xioi. While the quality of life of children with SMA has been investigated previously, there is no apparent literature published that directly compares parents' perspectives of the quality of life of their children with SMA who have received these interventions. We predicted that parents of children with SMA who received or are currently receiving treatment with nusinersen and/or onasemnogene abeparvovec-xioi would score their children's quality of life higher than parents whose children received or are currently receiving only supportive care. Considering the present data, it was not possible to identify and associate a single treatment with conferring a statistically higher quality of life; however, the quantitative and qualitative responses collected allowed for an inference that parents believe their children with SMA have a greater quality of life when provided treatment over having only supportive care. Before the FDA approval of nusinersen and onasemnogene abeparvovec-xioi, genetic counselors, genetic professionals, and other healthcare providers who shared the diagnosis of SMA with parents had to also share that there was no known effective treatment. However, today when families hear the diagnosis of SMA, they can be hopeful for their child and family's future because of the treatments available and the proven increase in quality of life with

these treatments. Knowing how quality of life perspectives differ based on the type of treatment received can help in the education of parents who are found to be carriers for SMA and are at risk of having an affected child, or who have a child that has been diagnosed with SMA.

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APPENDIX A

PARTICIPANT RECRUITMENT SOCIAL MEDIA TEXT

Calling all SMA parents! We need your help with a new research study. This research could help inform doctors, genetic counselors, and other medical professionals about our children and their quality of life. With treatments such as Spinraza and gene therapy/Zolgensma, it's important that the medical community knows about our children's lives so that they can speak knowledgeably to parents facing a new diagnosis. This study is being done by Analyssa Tallas, a graduate student in the genetic counseling program at the University of South Carolina, who was inspired to go into this field because of Gwendolyn's SMA diagnosis. She is passionate about making a difference and has been an advocate for the SMA community for years. If you are the parent of a child with SMA, both living or deceased, treatment or no treatment or a combination of treatments, we hope you will participate. The survey will take approximately 15 minutes, and if you participate you will be entered to win a $50 Amazon gift card and a t-shirt from our NEVER GIVE UP. Shop! The link posted below will take you directly to Analyssa's survey. Thank you so much for helping to continue changing the future of SMA. http://uofsc.co1.qualtrics.com/jfe/form/SV_3EsTV2zveCSmr9X

APPENDIX B

PARTICIPANT RECRUITMENT LETTER

Dear Potential Participant,

You are invited to participate in a graduate research study focusing on parents' perspectives of the quality of life of children with Spinal Muscular Atrophy (SMA). I am a graduate student in the genetic counseling program at the University of South Carolina School of Medicine. My research investigates parents' perspectives of the quality of life of children with SMA. This research could help inform medical professionals so that they might be able to speak knowledgably about the parents' perspectives of their child's life. You are eligible to participate in this study if you are the parent of a child with SMA. You must be over 18 years of age and be able to read and write in English.

Your participation in this study is voluntary. By completing this survey, you are consenting that you have read and understand this information. At any time, you may withdraw from the study by not completing the survey. All responses gathered will be kept anonymous and confidential. The results of this study might be published or presented at academic meetings; however, participants will not be identified.

This survey should take approximately 15 minutes to complete. Participants who complete the survey will have the option to enter into a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation. If you win, your prize will be sent to you at a later date, after all data has been collected. The email you provide in order to

enter the raffle will not be used for any other purposes beyond to send you the raffle prize if you have won.

Thank you for your time and consideration to participate in this study. If you have any questions regarding this research, you may contact me directly using the contact information below. If you have any questions about your rights as a research participant, you may contact the Office of Research Compliance at the University of South Carolina at (803) 777-7095.

Sincerely,

Analyssa Tallas

Master's Candidate in Genetic Counseling

Analyssa.Tallas@uscmed.sc.edu

APPENDIX C

SURVEY FOR PARENTS WHOSE CHLD IS LIVING AND 1-12 MONTHS IN AGE

Are you the parent of a child with SMA?
If you are the parent of more than one child with SMA please take the survey 1 time for each child.

Yes

No

We would like to provide you with questions that use the appropriate tense; is your child with SMA living or deceased?

My child is living

My child is deceased

How old is your child? If your child is 24 months, please choose 13-24 months. If your child is older than 24 months but still 2, please choose the 2-4 option.

1-12 months

13-24 months

2-4 years

My child is older than 4 years

How many copies of the SMN2 gene does your child have? _____

Please select the treatments(s) your child has received.

Spinraza (nusinersen)

Zolgensma (onasemnogene abeparvovec-xioi)

None of the above

If your child has not received either of these treatments, please select “none of the above”.

The PedsQL IS assessment was utilized in this survey. Permission granted by eProvide.

To confirm that you have completed the correct questionnaire, please enter your child's age.____

If you have additional information you would like us to know about your child, his/her treatment(s), quality of life, etc. please use the space provided below. _____

As a token of our appreciation for taking this survey, we will have a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation.

If you are interested in entering the raffle, please enter your email below.

By providing your email you acknowledge that your answers to this survey may not be anonymous. _____.

APPENDIX D

SURVEY FOR PARENTS WHOSE CHILD IS DECEASED AT 1-12 MONTHS OF AGE

Are you the parent of a child with SMA?
If you are the parent of more than one child with SMA please take the survey 1 time for each child.

Yes

No

We would like to provide you with questions that use the appropriate tense; is your child with SMA living or deceased?

My child is living

My child is deceased

How old was your child when he/she passed away? If your child was 24 months, please choose 13-24 months. If your child was older than 24 months but still 2, please choose the 2-4 option.

1-12 months

13-24 months

2-4 years

My child was older than 4 years

How many copies of the SMN2 gene did your child have? _____

Please select the treatments(s) your child received.

Spinraza (nusinersen)

Zolgensma (onasemnogene abeparvovec-xioi)

None of the above

If your child did not receive either of these treatments, please select “none of the above”.

The PedsQL IS assessment was utilized in this survey. Permission granted by eProvide.

To confirm that you have completed the correct questionnaire, please enter how old your child was when he/she passed away. ____

If you have additional information you would like us to know about your child, his/her treatment(s), quality of life, etc. please use the space provided below. _____

As a token of our appreciation for taking this survey, we will have a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation.

If you are interested in entering the raffle, please enter your email below.

By providing your email you acknowledge that your answers to this survey may not be anonymous. _____.

APPENDIX E

SURVEY FOR PARENTS WHOSE CHILD IS LIVING AND 13-24 MONTHS IN AGE

Are you the parent of a child with SMA?
If you are the parent of more than one child with SMA please take the survey 1 time for each child.

Yes

No

We would like to provide you with questions that use the appropriate tense; is your child with SMA living or deceased?

My child is living

My child is deceased

How old is your child? If your child is 24 months, please choose 13-24 months. If your child is older than 24 months but still 2, please choose the 2-4 option.

1-12 months

13-24 months

2-4 years

My child is older than 4 years

How many copies of the SMN2 gene does your child have? _____

Please select the treatments(s) your child has received.

Spinraza (nusinersen)

Zolgensma (onasemnogene abeparvovec-xioi)

None of the above

If your child has not received either of these treatments, please select “none of the above”.

The PedsQL IS assessment was utilized in this survey. Permission granted by eProvide.

To confirm that you have completed the correct questionnaire, please enter your child's age. ____

If you have additional information you would like us to know about your child, his/her treatment(s), quality of life, etc. please use the space provided below. _____

As a token of our appreciation for taking this survey, we will have a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation.

If you are interested in entering the raffle, please enter your email below.

By providing your email you acknowledge that your answers to this survey may not be anonymous. _____.

APPENDIX F

SURVEY FOR PARENTS WHOSE CHILD IS DECEASED AT 13-24 MONTHS OF AGE

Are you the parent of a child with SMA?

If you are the parent of more than one child with SMA please take the survey 1 time for each child.

Yes

No

We would like to provide you with questions that use the appropriate tense; is your child with SMA living or deceased?

My child is living

My child is deceased

How old was your child when he/she passed away? If your child was 24 months, please choose 13-24 months. If your child was older than 24 months but still 2, please choose the 2-4 option.

1-12 months

13-24 months

2-4 years

My child was older than 4 years

How many copies of the SMN2 gene did your child have? _____

Please select the treatments(s) your child received.

Spinraza (nusinersen)

Zolgensma (onasemnogene abeparvovec-xioi)

None of the above

If your child did not receive either of these treatments, please select “none of the above”.

The PedsQL IS assessment was utilized in this survey. Permission granted by eProvide.

To confirm that you have completed the correct questionnaire, please enter how old your child was when he/she passed away. ____

If you have additional information you would like us to know about your child, his/her treatment(s), quality of life, etc. please use the space provided below. _____

As a token of our appreciation for taking this survey, we will have a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation.

If you are interested in entering the raffle, please enter your email below.

By providing your email you acknowledge that your answers to this survey may not be anonymous. _____.

APPENDIX G

SURVEY FOR PARENTS WHOSE CHILD IS LIVING AND 2-4 YEARS IN AGE

Are you the parent of a child with SMA?

If you are the parent of more than one child with SMA please take the survey 1 time for each child.

Yes

No

We would like to provide you with questions that use the appropriate tense; is your child with SMA living or deceased?

My child is living

My child is deceased

How old is your child? If your child is 24 months, please choose 13-24 months. If your child is older than 24 months but still 2, please choose the 2-4 option.

1-12 months

13-24 months

2-4 years

My child is older than 4 years

How many copies of the SMN2 gene does your child have? _____

Please select the treatments(s) your child has received.

Spinraza (nusinersen)

Zolgensma (onasemnogene abeparvovec-xioi)

None of the above

If your child has not received either of these treatments, please select “none of the above”.

The PedsQL GCS and PedsQL NMM assessments were utilized in this survey. Permission granted by eProvide.

To confirm that you have completed the correct questionnaire, please enter your child's age. ____

If you have additional information you would like us to know about your child, his/her treatment(s), quality of life, etc. please use the space provided below. _____

As a token of our appreciation for taking this survey, we will have a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation.

If you are interested in entering the raffle, please enter your email below.

By providing your email you acknowledge that your answers to this survey may not be anonymous. _____.

APPENDIX H

SURVEY FOR PARENTS WHOSE CHILD IS DECEASED AT 2-4 YEARS OF AGE

Are you the parent of a child with SMA?
If you are the parent of more than one child with SMA please take the survey 1 time for each child.

Yes

No

We would like to provide you with questions that use the appropriate tense; is your child with SMA living or deceased?

My child is living

My child is deceased

How old was your child when he/she passed away? If your child was 24 months, please choose 13-24 months. If your child was older than 24 months but still 2, please choose the 2-4 option.

1-12 months

13-24 months

2-4 years

My child was older than 4 years

How many copies of the SMN2 gene did your child have? _____

Please select the treatments(s) your child received.

Spinraza (nusinersen)

Zolgensma (onasemnogene abeparvovec-xioi)

None of the above

If your child did not receive either of these treatments, please select “none of the above”.

The PedsQL GCS and PedsQL NMM assessments were utilized in this survey. Permission granted by eProvide.

To confirm that you have completed the correct questionnaire, please enter how old your child was when he/she passed away. ____

If you have additional information you would like us to know about your child, his/her treatment(s), quality of life, etc. please use the space provided below. _____

As a token of our appreciation for taking this survey, we will have a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation.

If you are interested in entering the raffle, please enter your email below.

By providing your email you acknowledge that your answers to this survey may not be anonymous. _____.

APPENDIX I

SURVEY FOR PARENTS WHOSE CHILD IS LIVING AND OLDER THAN 4 YEARS OF AGE

Are you the parent of a child with SMA?

If you are the parent of more than one child with SMA please take the survey 1 time for each child.

Yes

No

We would like to provide you with questions that use the appropriate tense; is your child with SMA living or deceased?

My child is living

My child is deceased

How old is your child? If your child is 24 months, please choose 13-24 months. If your child is older than 24 months but still 2, please choose the 2-4 option.

1-12 months

13-24 months

2-4 years

My child is older than 4 years

How many copies of the SMN2 gene does your child have? _____

Please select the treatments(s) your child has received.

Spinraza (nusinersen)

Zolgensma (onasemnogene abeparvovec-xioi)

None of the above

If your child has not received either of these treatments, please select “none of the above”.

If you would like to share information about your child, his/her treatment(s), quality of life, etc. please use the space provided below. _____

As a token of our appreciation for taking this survey, we will have a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation.

If you are interested in entering the raffle, please enter your email below.

By providing your email you acknowledge that your answers to this survey may not be anonymous. _____.

APPENDIX J

SURVEY FOR PARENTS WHOSE CHILD IS DECEASED AT OLDER THAN 4 YEARS OF AGE

Are you the parent of a child with SMA?
If you are the parent of more than one child with SMA please take the survey 1 time for each child.

Yes

No

We would like to provide you with questions that use the appropriate tense; is your child with SMA living or deceased?

My child is living

My child is deceased

How old was your child when he/she passed away? If your child was 24 months, please choose 13-24 months. If your child was older than 24 months but still 2, please choose the 2-4 option.

1-12 months

13-24 months

2-4 years

My child was older than 4 years

How many copies of the SMN2 gene did your child have? _____

Please select the treatments(s) your child received.

Spinraza (nusinersen)

Zolgensma (onasemnogene abeparvovec-xioi)

None of the above

If your child did not receive either of these treatments, please select “none of the above”.

If you would like to share information about your child, his/her treatment(s), quality of life, etc. please use the space provided below. _____

As a token of our appreciation for taking this survey, we will have a raffle for a $50 amazon gift card and a t-shirt from The Gwendolyn Strong Foundation.

If you are interested in entering the raffle, please enter your email below.

By providing your email you acknowledge that your answers to this survey may not be anonymous. _____.